Management of Early PD (Motor)

Francisco Cardoso MD PhD FAAN
Professor of Neurology
UFMG
Belo Horizonte, Brazil
President - MDS

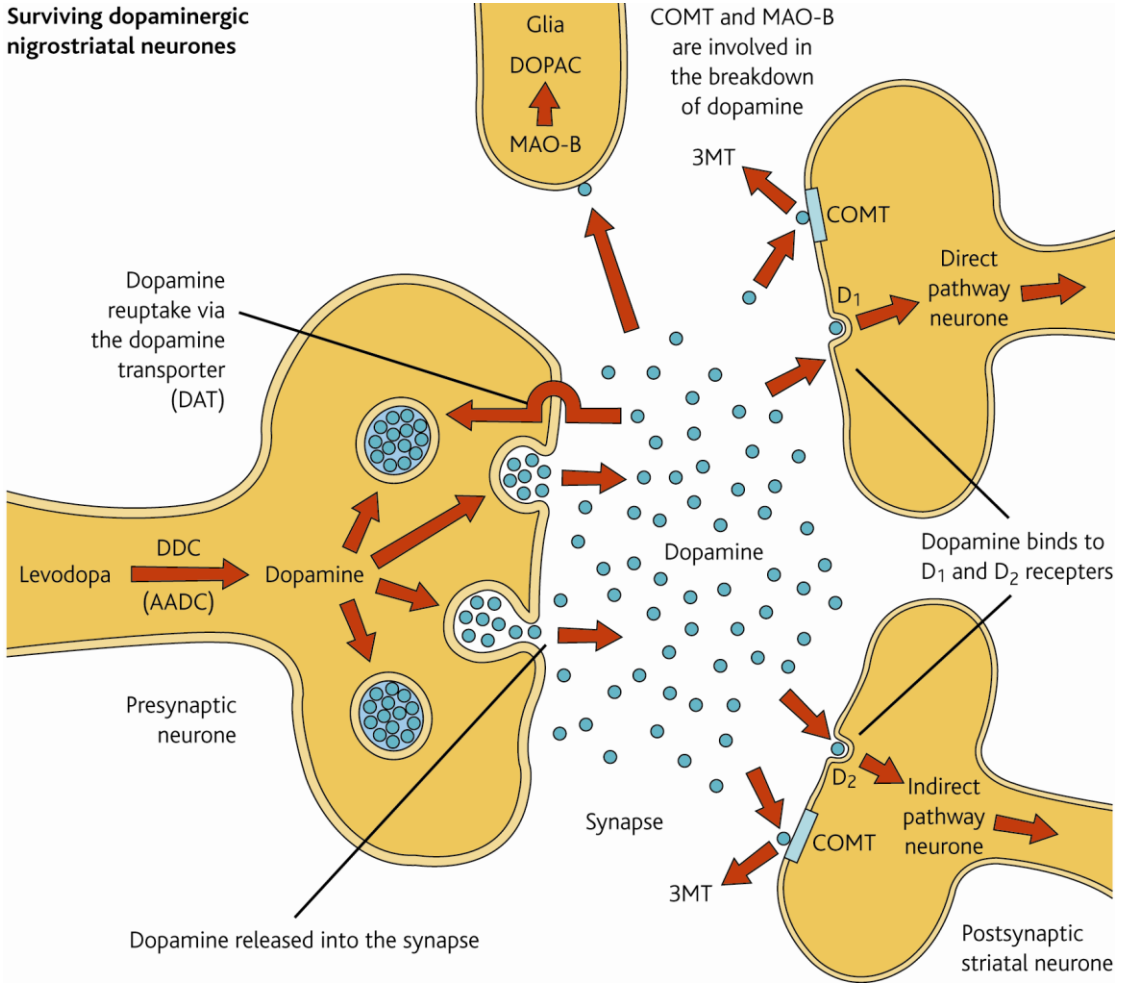
Disclosures

- None

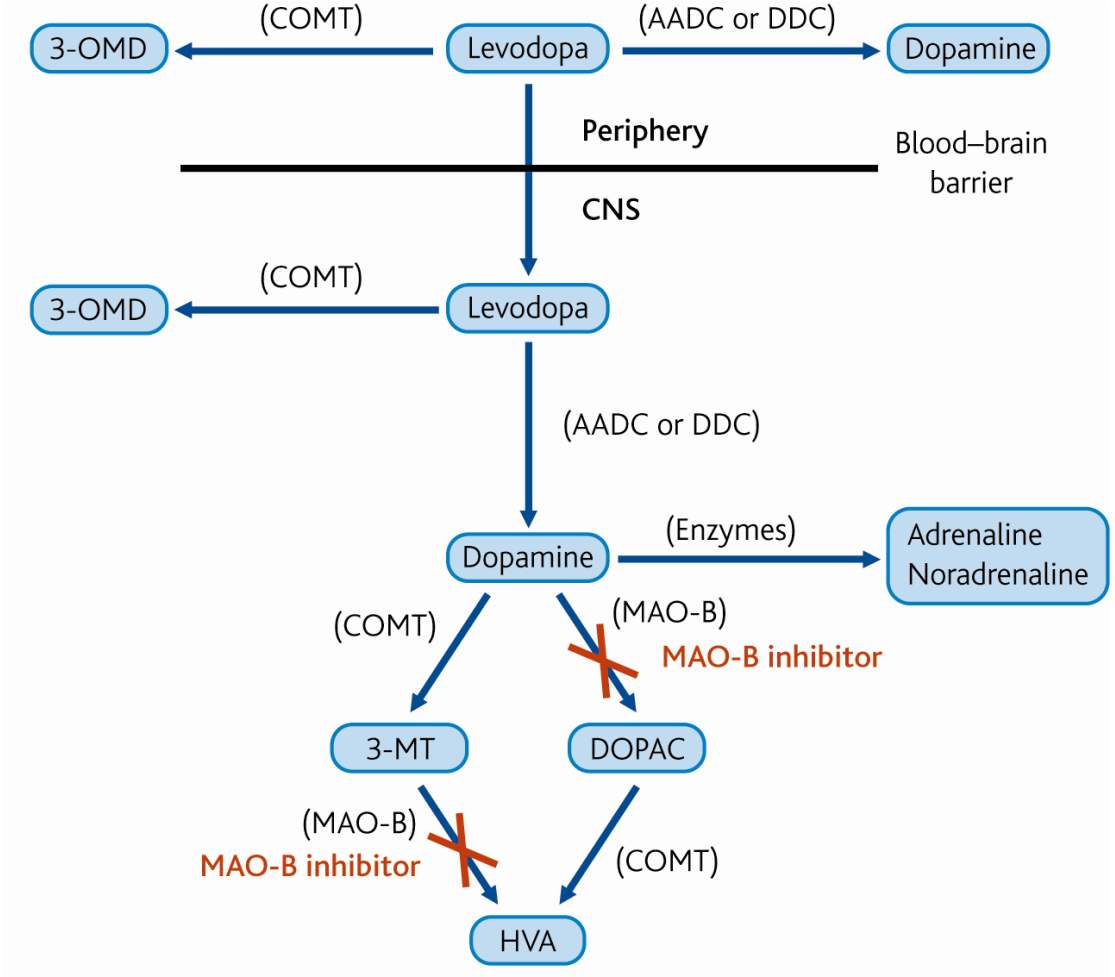
Pharmacological Options

- MAOB Inhibitors
  - Selegiline
  - Rasagiline
- Anticholinergics
- Amantadine
- Dopamine Agonists
- Levodopa

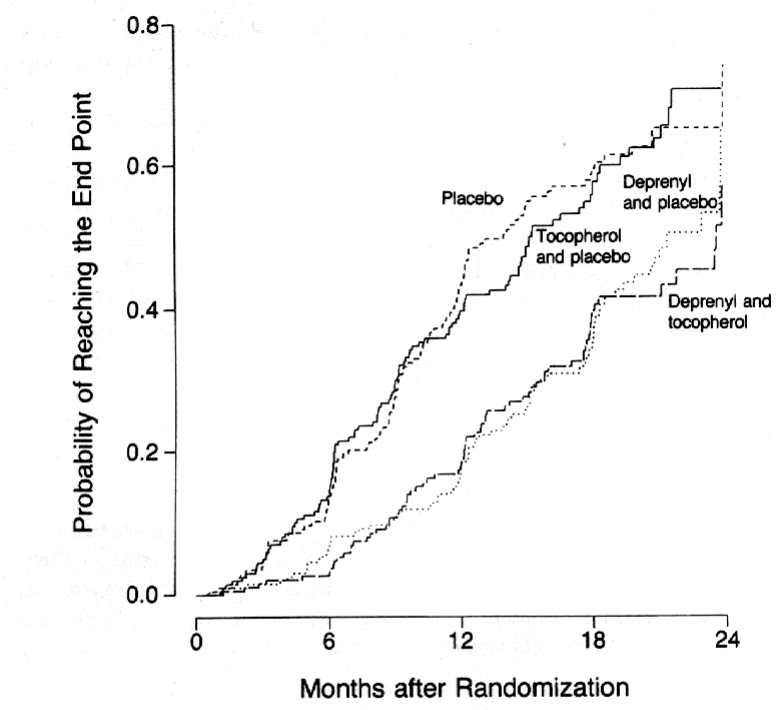
Nigro-Striatal Synapse



MAOB Inhibitors



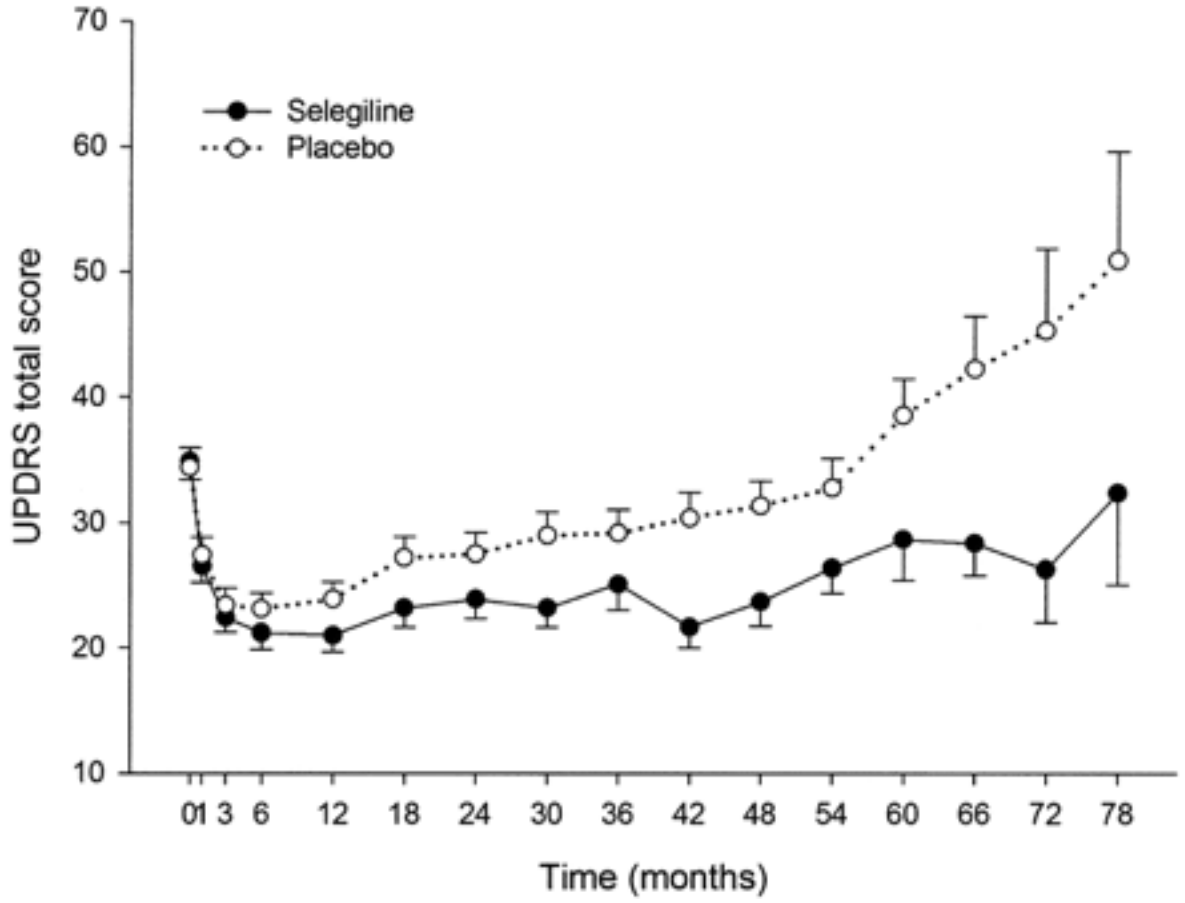
Selegiline



Placebo	199	164	102	50	3
Tocopherol and placebo	202	165	109	48	0
Deprenyl and placebo	202	181	153	81	3
Deprenyl and tocopherol	197	184	143	72	8

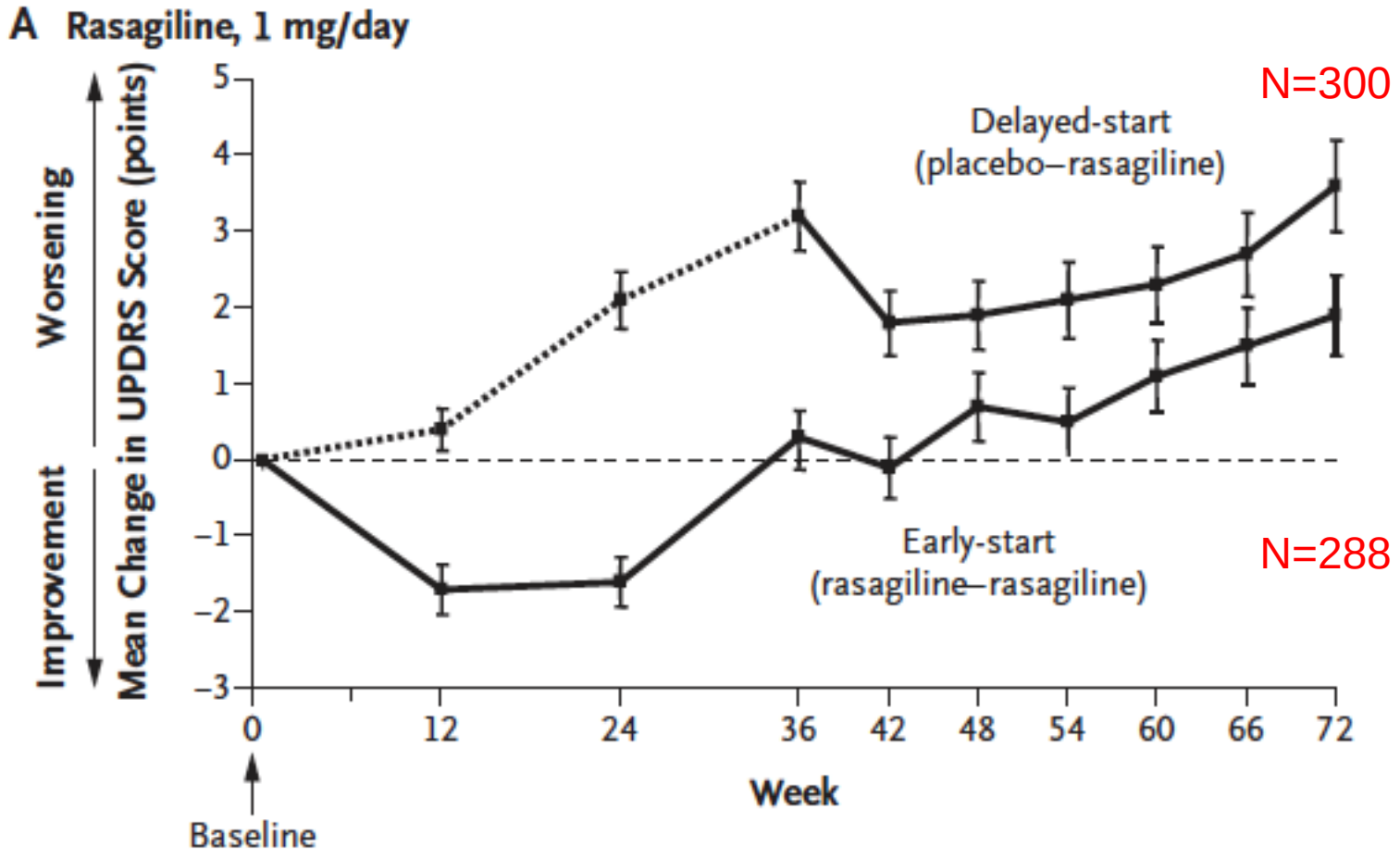
PSG. NEJM 1993;328:176

Selegiline



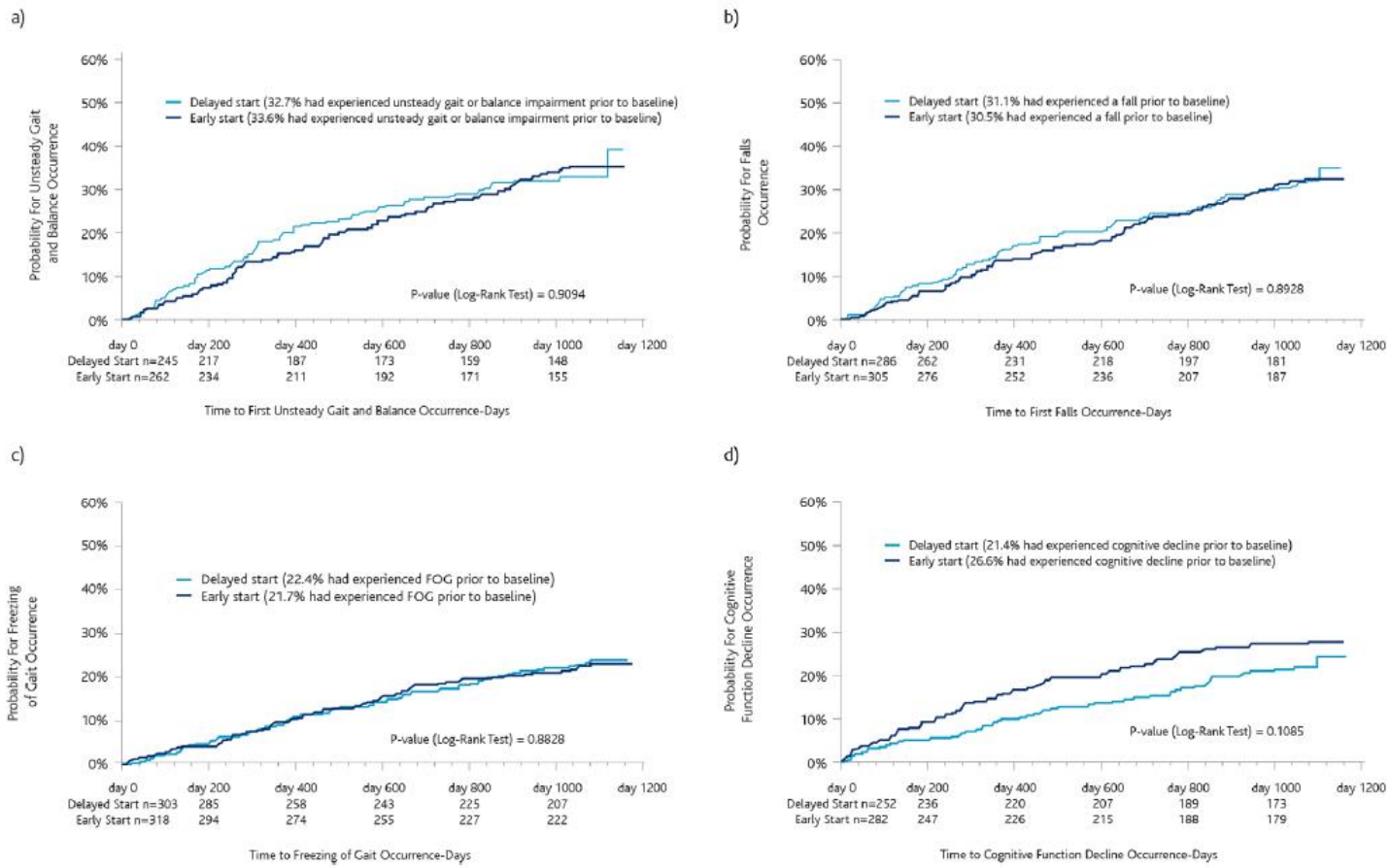
Palhagen et al. Neurology 2006;66:1200

Rasagiline



Olanow et al. NEJM 2009

Rasagiline



Rascol et al. Mov Disord 2016;31:1489

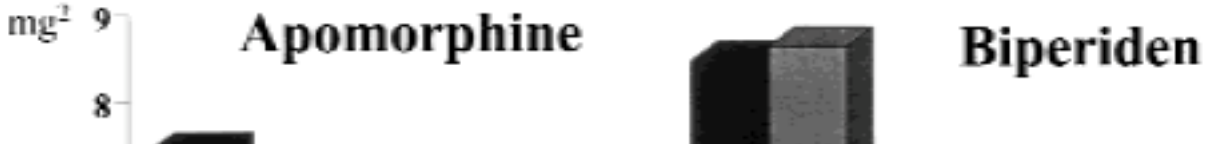
MDS EBM Conclusions - 1

TABLE 1. Treatments that prevent/delay disease progression

Intervention	Drug	Efficacy conclusions	Safety[a]	Implications for clinical practice
Dopamine agonists	Ropinirole	Insufficient evidence		Investigational
	Pramipexole	*Nonefficacious*		*Not useful*
	Pergolide	Unlikely efficacious	Acceptable risk with specialized monitoring	*Not useful*
Levodopa/peripheral decarboxylase inhibitor	Standard IR formulation	Insufficient evidence		Investigational
MAO-B inhibitors	Selegiline	Insufficient evidence		Investigational
	Rasagiline	Insufficient evidence		Investigational
Supplements	Coenzyme Q_{10}	*Nonefficacious*		*Not useful*
	Creatine	*Nonefficacious*		*Not useful*
	Vitamin D	*Insufficient evidence*		*Investigational*
Exercise	Exercise	*Insufficient evidence*		*Investigational*

Fox et al. Mov Disord 2018;33:1248

Anticholinergics



	Rigidity	Bradykinesia
Baseline	2.07	13.27
On apomorphine	0.87*	6.87*
Baseline	2.07	13.27
On biperiden	1.87	12.60

UPDRS, Unified Parkinson's Disease Rating Scale.
*p <0.001.

Schrag et al. Mov Disord 1999;14:252

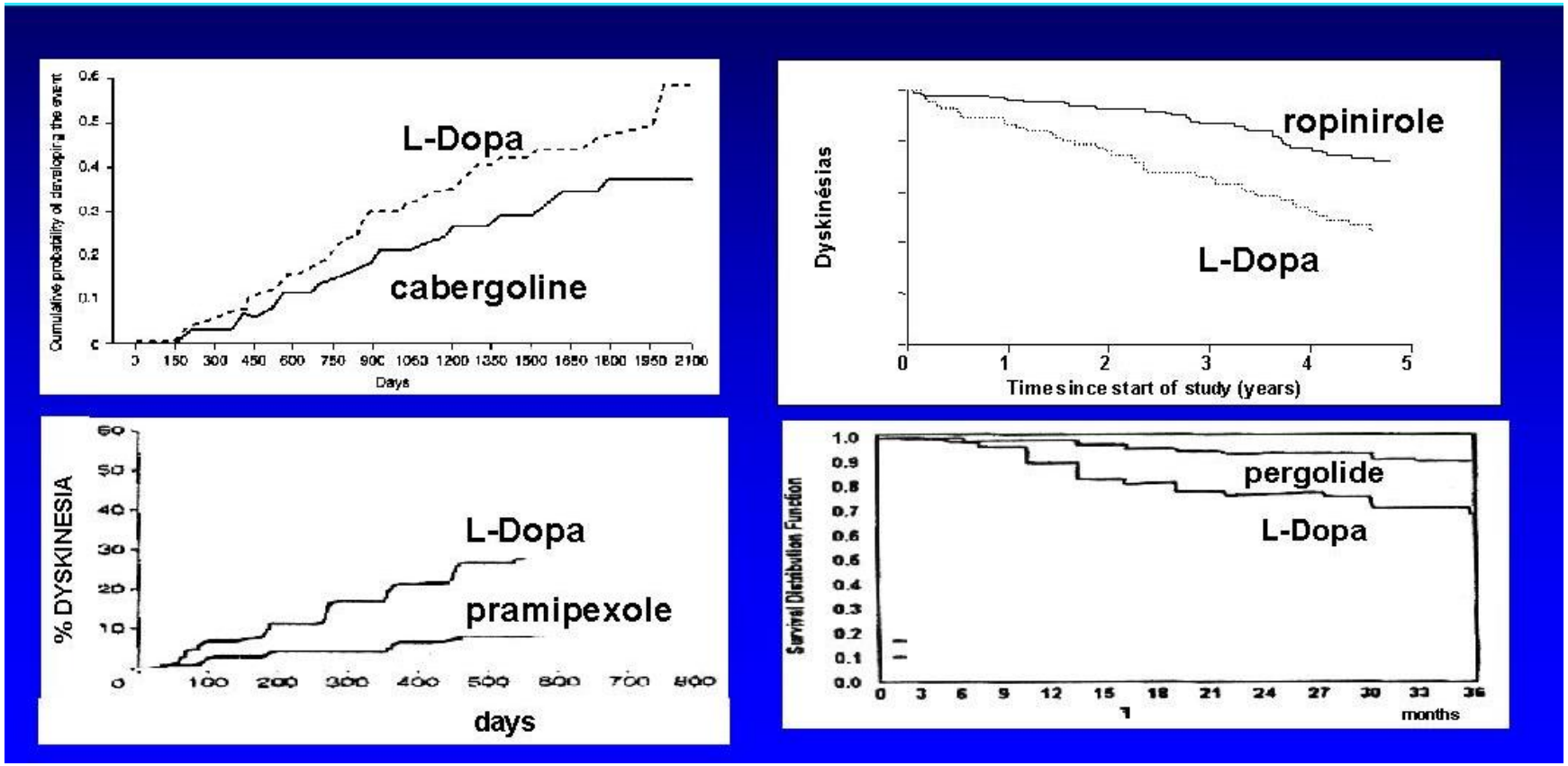
Dopamine Agonists

	D1	D2	D3	D4	D5	5HT	α1	α2
Bromocriptine*	+/-	+++	++	++	?	++	++	++
Lisuride*	+/-	+++	+++	+++	?	++	++	++
Pergolide*	+	+++	+++	+++	?	++	+	++
Cabergoline*	+	+++	+++	++	?	++	++	++
Pramipexole	0	++	+++	++	?	0	0	+
Ropinirole	0	++	+++	++	?	0	0	0
Piribedil	?	+++	++	++	?	?	0	0
Rotigotine	+	+	+					

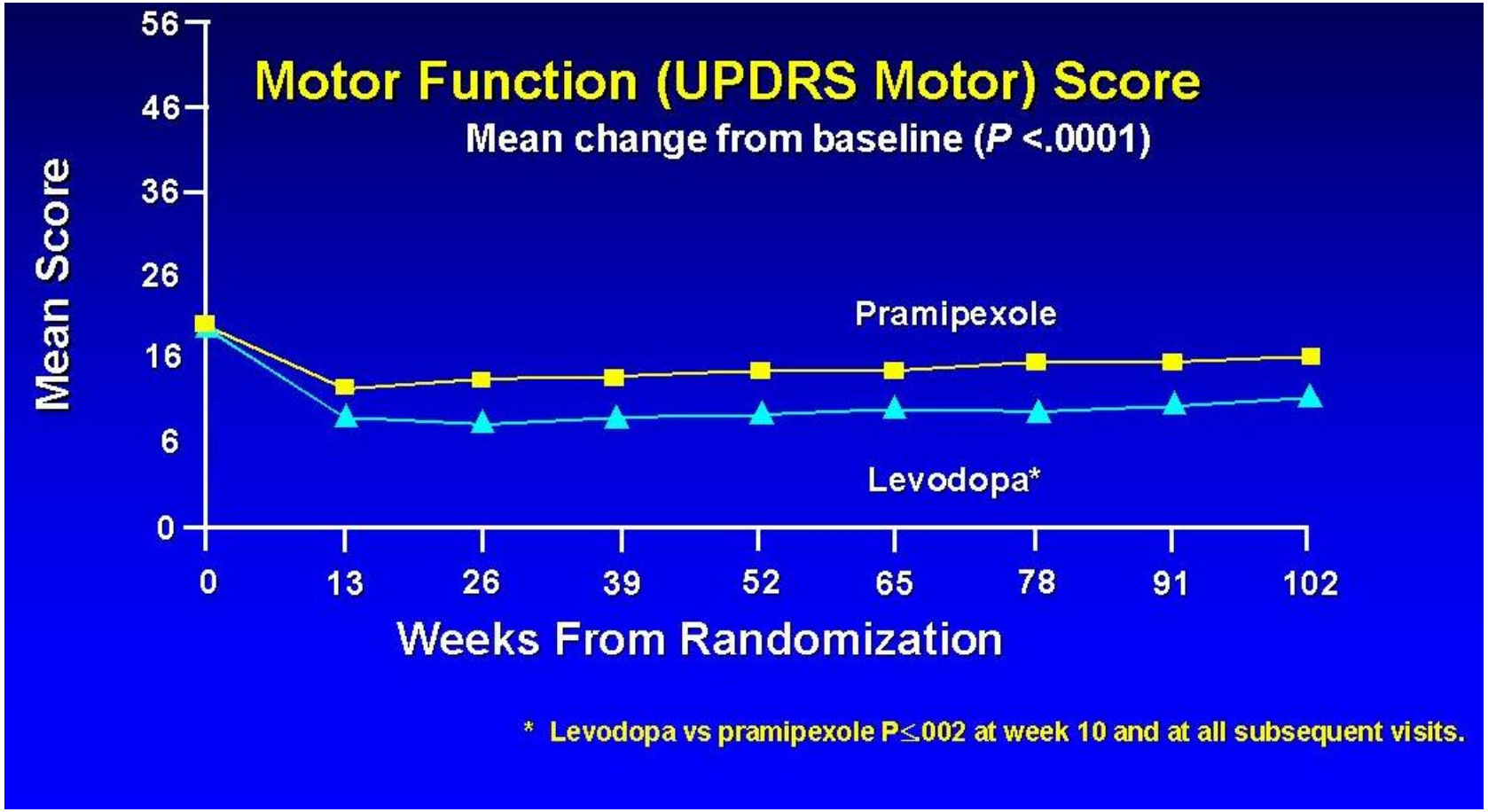
* Ergot derivatives

Piercy et al, 1996 ; Tulloch, 1997 ; Fariello, 1998 ; Perachon et al, 1998

Dopamine Agonists

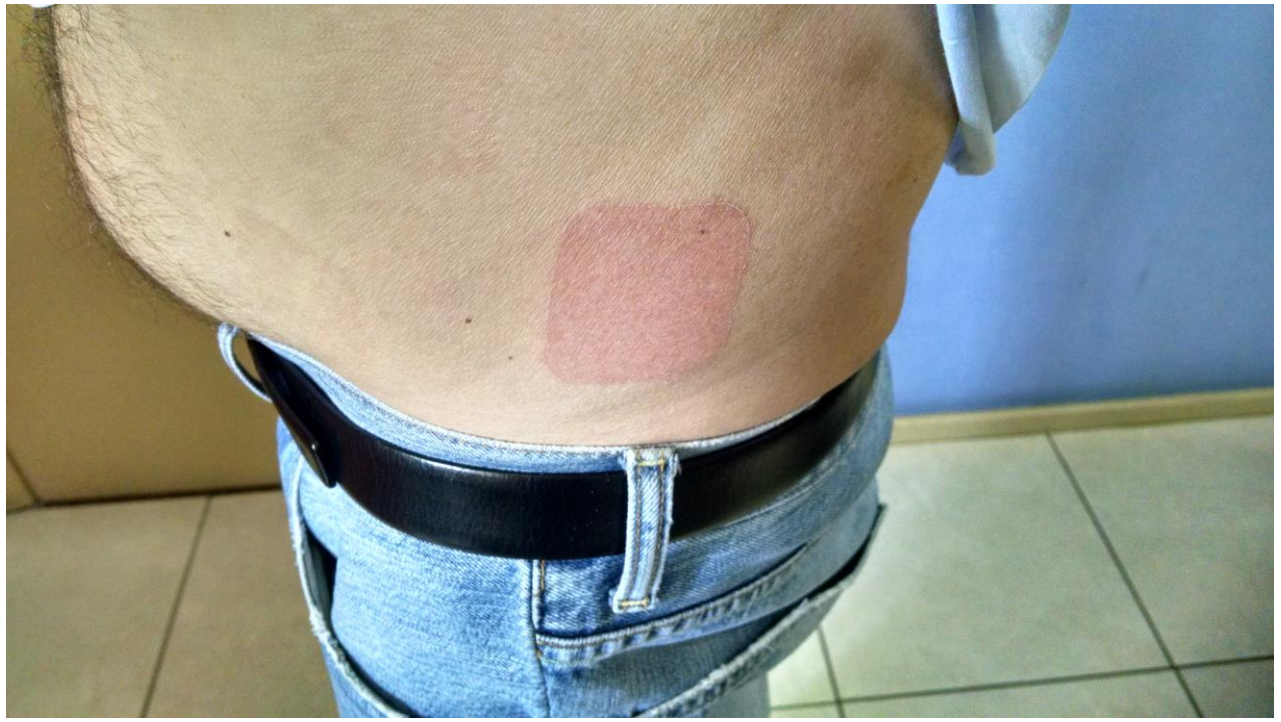


Dopamine Agonists



Parkinson Study Group. JAMA 2000;284:231.

Dopamine Agonists



Dopamine Agonists

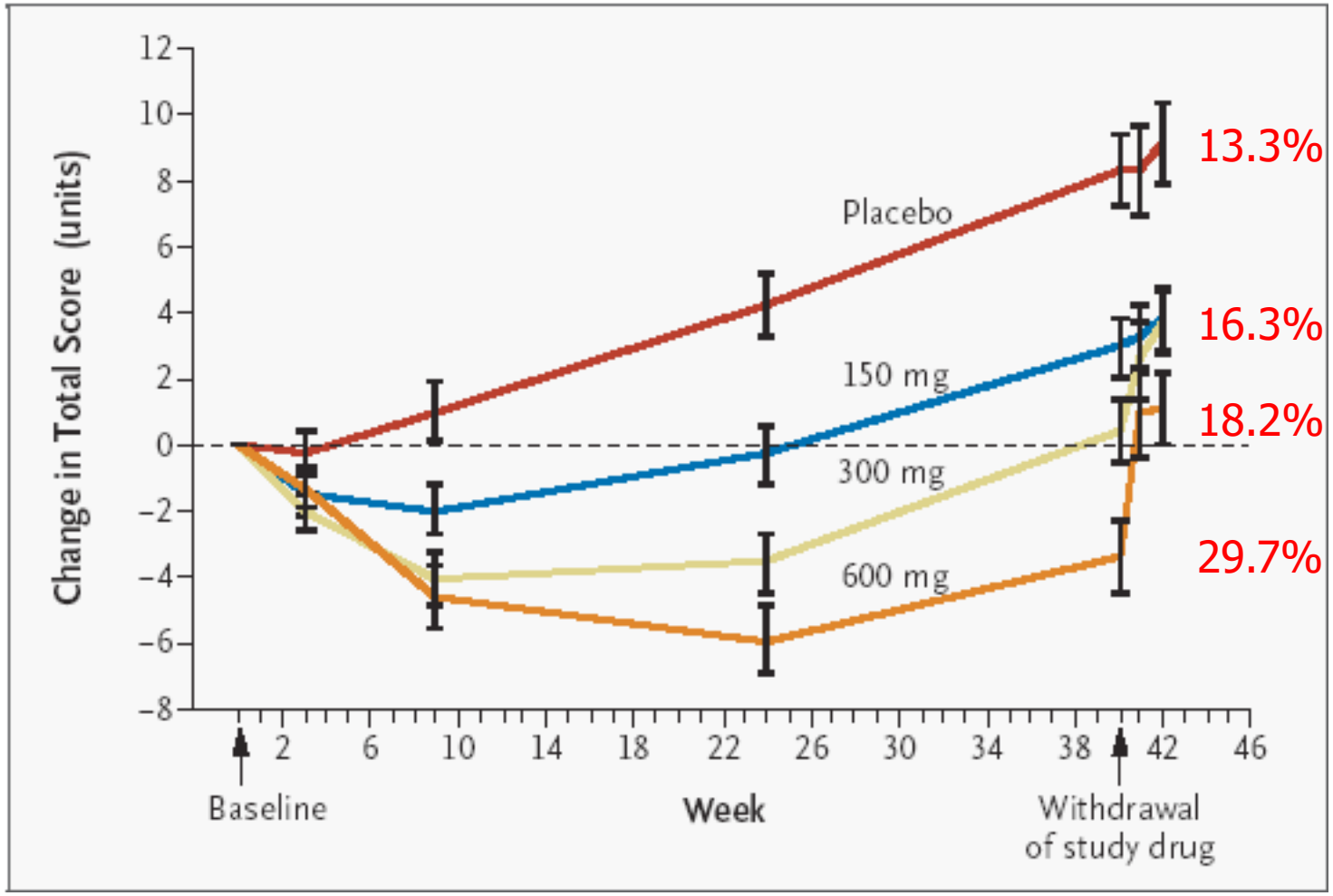
Impulse Control Disorder

Table 2. ICD Frequencies by Dopamine Agonist Treatment Status

ICD Type	Treatment Status (N=3090)[a]	No. (%) Current ICD	No. (%) No Current ICD	OR (95% CI)[b]	*P* Value[c]
Any ICD	No dopamine agonist	72 (6.9)	978 (93.1)	2.72 (2.08-3.54)	<.001
	Dopamine agonist	348 (17.1)	1692 (82.9)		
Problem/pathological gambling	No dopamine agonist	24 (2.3)	1026 (97.7)	2.82 (1.81-4.39)	<.001
	Dopamine agonist	130 (6.4)	1910 (93.6)		
Pathological gambling only	No dopamine agonist	17 (1.6)	1033 (98.4)	2.15 (1.26-3.66)	.004
	Dopamine agonist	72 (3.5)	1968 (96.5)		
Compulsive sexual behavior	No dopamine agonist	18 (1.7)	1032 (98.3)	2.59 (1.55-4.33)	<.001
	Dopamine agonist	90 (4.4)	1950 (95.6)		
Compulsive buying	No dopamine agonist	30 (2.9)	1020 (97.1)	2.53 (1.69-3.78)	<.001
	Dopamine agonist	147 (7.2)	1893 (92.8)		
Binge-eating disorder	No dopamine agonist	18 (1.7)	1032 (98.3)	3.34 (2.01-5.53)	<.001
	Dopamine agonist	114 (5.6)	1926 (94.4)		

Weintraub et al. Arch Neurol 2010;67:589

Levodopa



Fahn et al. NEJM 2004;351:2498-508

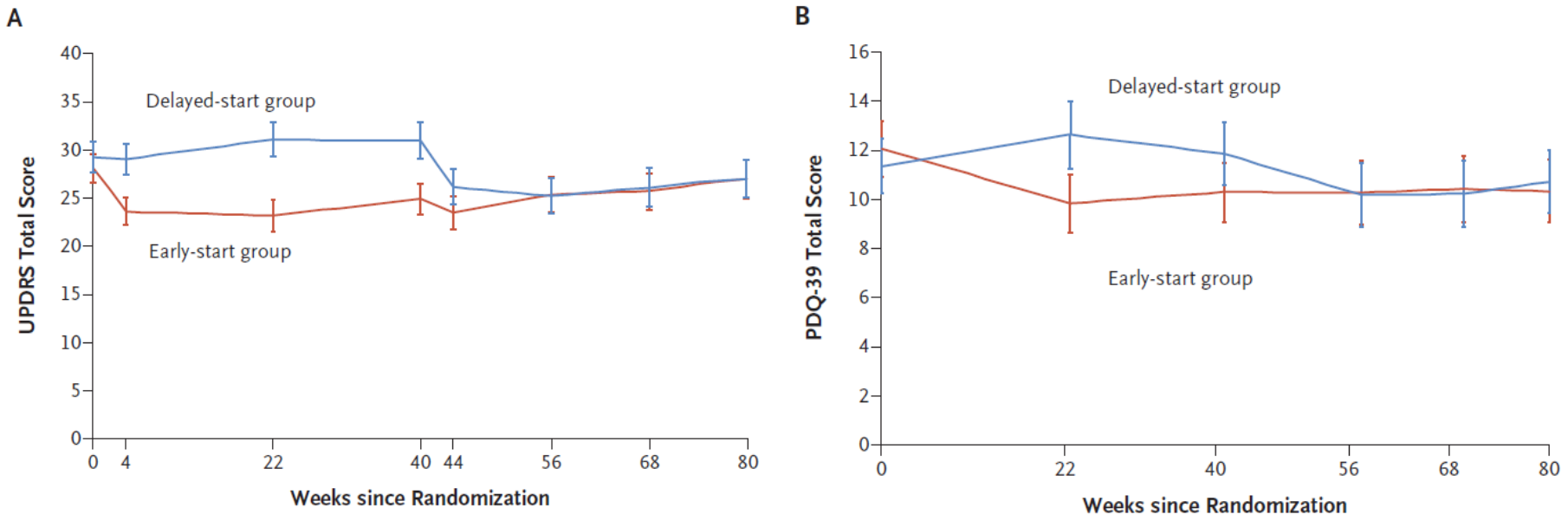
MDS EBM Conclusions - 2

TABLE 2. Treatments for symptomatic monotherapy

Intervention	Drug	Efficacy conclusions	Safety[a]	Implications for clinical practice
Dopamine agonists	Pramipexole IR	Efficacious		Clinically useful
Nonergot	Pramipexole ER	Efficacious		Clinically useful
	Rotigotine	Efficacious		Clinically useful
	Piribedil	Efficacious		Clinically useful
	Ropinirole IR	Efficacious		Clinically useful
	Ropinirole PR	Likely efficacious		Possibly useful
Ergot	Cabergoline	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	DHEC	Efficacious		Clinically useful
	Pergolide	Efficacious		Clinically useful
	Bromocriptine	Likely efficacious		Possibly useful
Levodopa/peripheral decarboxylase inhibitor	Standard (IR) formulation	Efficacious		Clinically useful
	Controlled release (CR)	Efficacious		Clinically useful
	Extended release	*Efficacious*		*Clinically useful*
MAO-B inhibitors	Selegiline	Efficacious		Clinically useful
	Rasagiline	Efficacious		Clinically useful
Others	Anticholinergics	Likely efficacious		Clinically useful
	Amantadine	Likely efficacious		Possibly useful
Adenosine A_{2A} antagonist	Istradefylline	*Nonefficacious*		*Not Useful*

Fox et al. Mov Disord 2018;33:1248

Neuroprotective Levodopa?



Verschuur et al. NEJM 2019;380:315

To delay Levodopa?

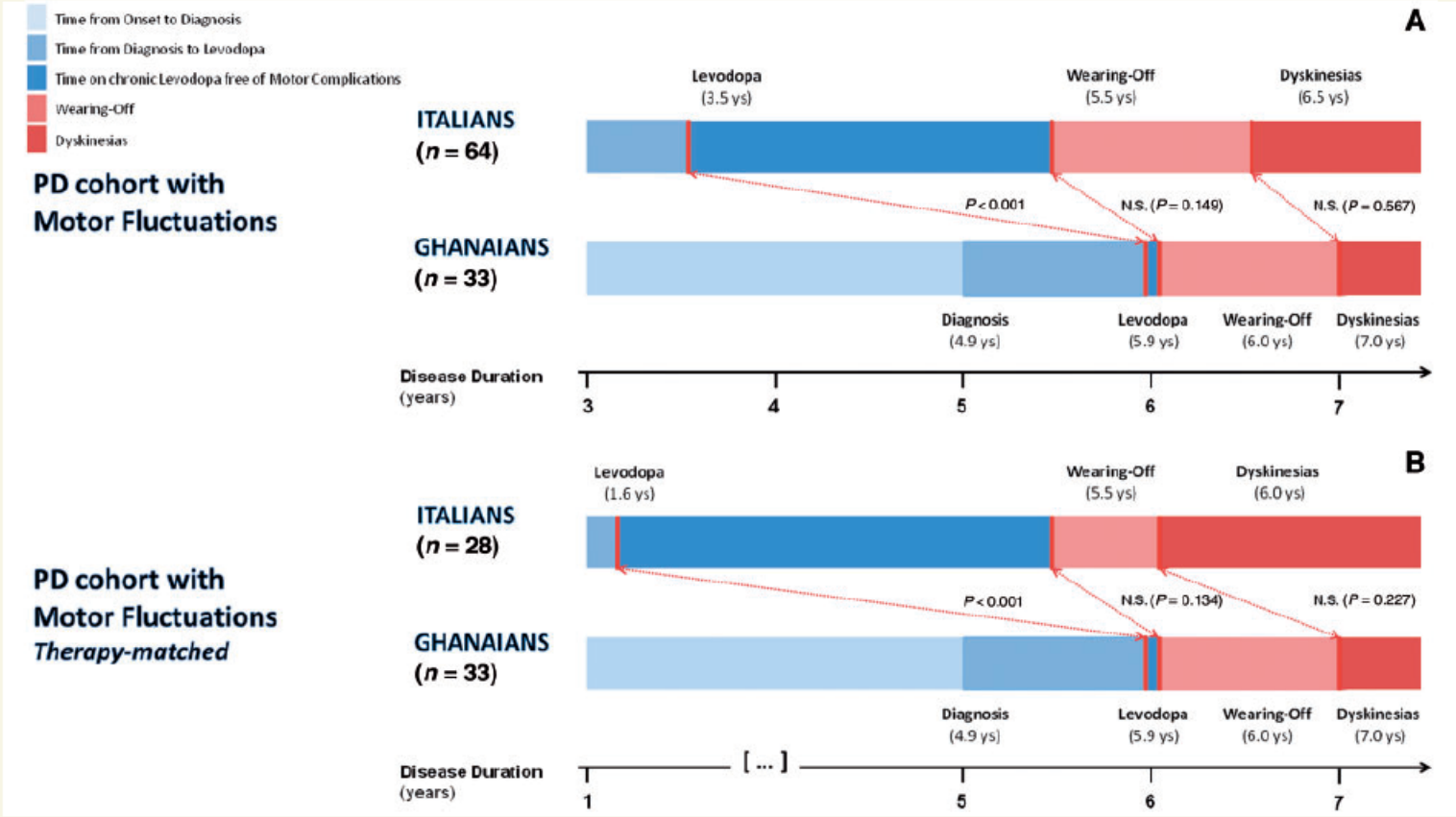


Figure 2 (A) Relationship between initiation of levodopa therapy and onset of motor fluctuations, and between initiation of levodopa therapy and onset of dyskinesias in Ghanaian patients with Parkinson's disease and Italian Parkinson's disease control subjects with motor fluctuations (Supplementary Table 1). (B) The Parkinson's disease control group has been additionally matched for therapy regimen (Table 3).

Cilia et al. Brain 2014;137:2731

Levodopa Versus Agonist

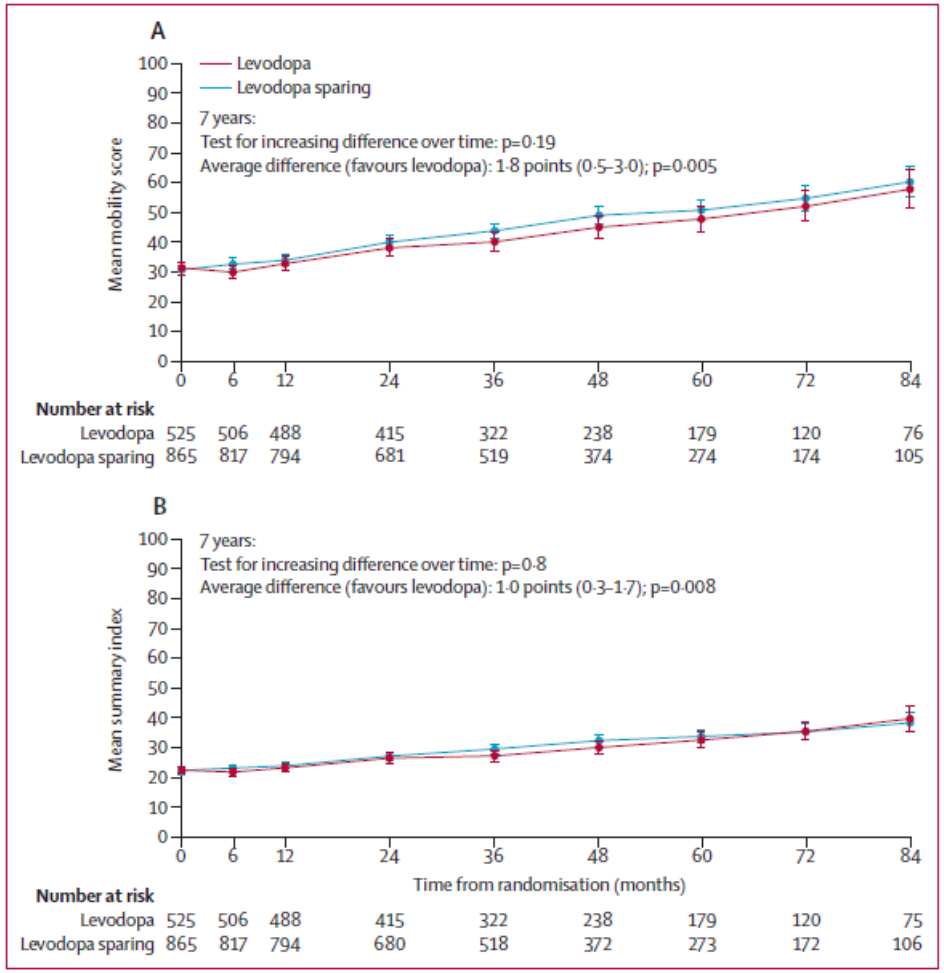
Table 2 Prevalence of motor complications at final follow-up

Prevalence at final follow-up	L-dopa arm (n = 42)	Bromocriptine arm (n = 63)	Difference* (95% CI)	p Value
Any dyskinesia	58%	56%	−5.3% (−25%, 15%)	0.61
Moderate/severe dyskinesia	39%	35%	−6.0% (−25%, 13%)	0.51
Any fluctuations	50%	56%	5.1% (−15%, 25%)	0.61
Moderate/severe fluctuations	33%	35%	0.01% (−19%, 19%)	0.94

*Adjusted for baseline characteristics (age, duration of disease, baseline Hoehn & Yahr, Northwestern University Disability, and Webster ratings).

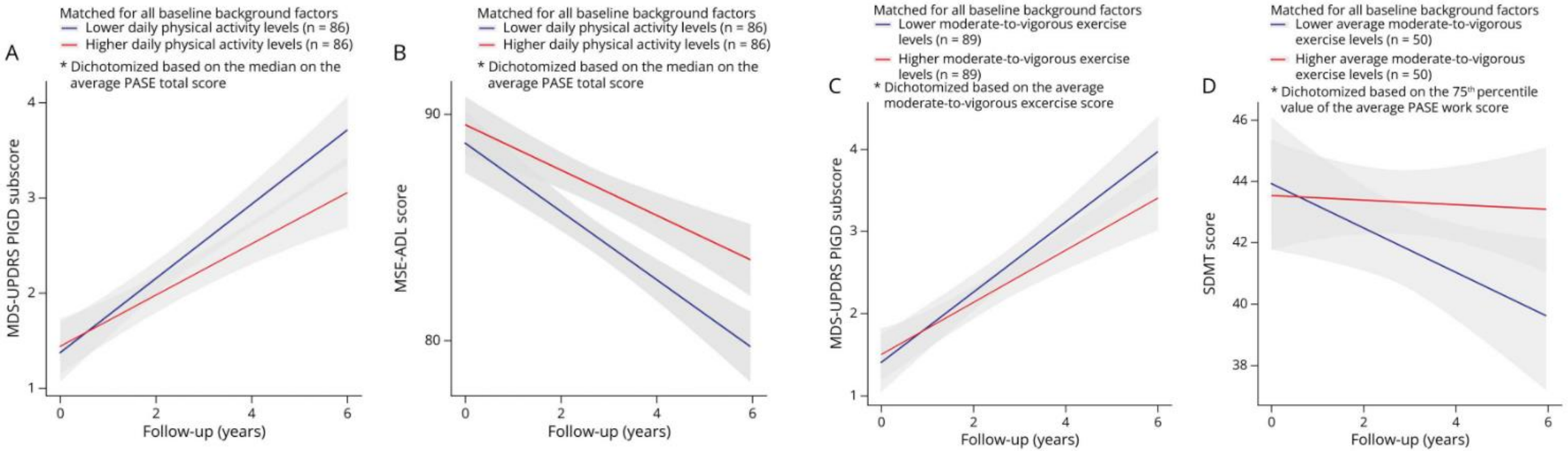
Katzenschlager et al. Neurology 2008;71:474

Levodopa Versus Levodopa-Sparing



PD Med Collaborative Group. Lancet 2014;384:1196

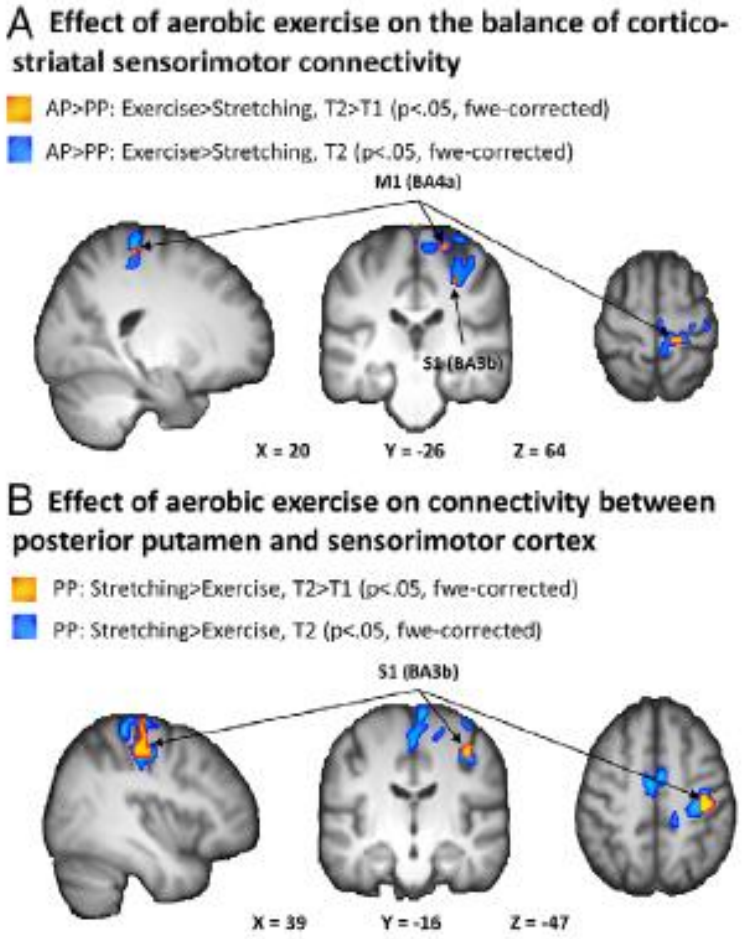
Physical Activity

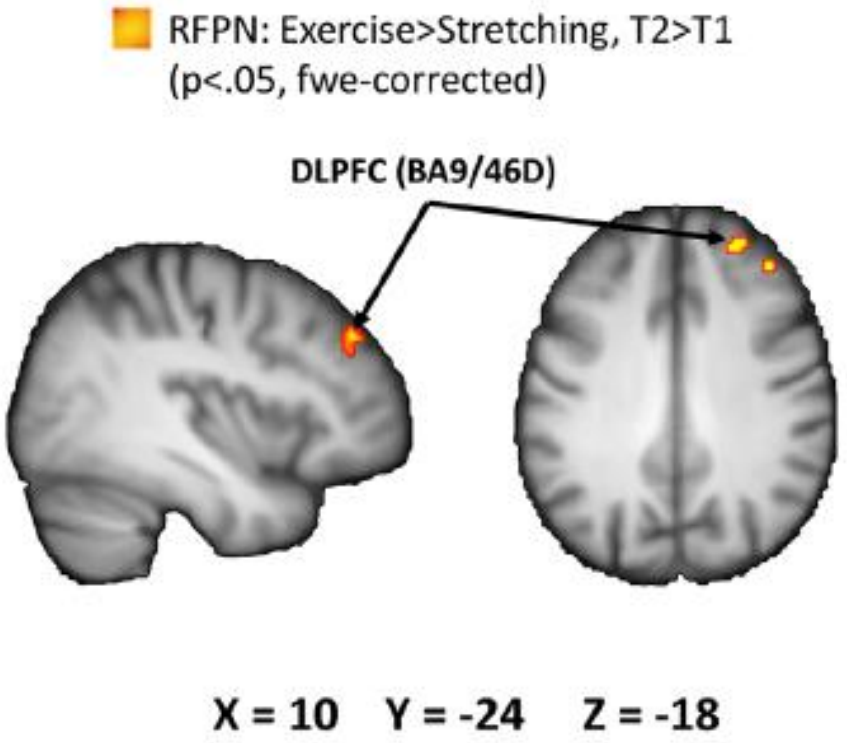


237 early-stage PD patients, 5 (4-6) years of follow-up

Tsukita et al. Neurology 2022;98:e859-e871

Physical Activity





Johansonn et al. Ann Neurol 2022;91:203

Conclusions

- MAOBI are mildly efficacious and well tolerated
- Anticholinergics are effective against tremor and not well tolerated, particularly in the elderly
- Amantadine is mildly efficacious and not well tolerated, particularly in the elderly
- Dopamine agonists are moderately efficacious and not particularly well tolerated
- Levodopa remains the gold standard
- There is no evidence to support delaying the use of levodopa

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