Michael J Fox Foundation and the International Society for CNS Clinical Trials and Methodology Satellite Meeting:

Neuroprotective Clinical Trials in Parkinson's Disease

The Mystique of Neuroprotection for Parkinson's Disease

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Neuroprotection' or 'Disease Modification'

A therapy that slows, prevents or reverses disease pathogenesis (neuronal loss or dysfunction)

- Valuable mechanistic concepts for identifying targets and discovering agents that might favorably modify pathogenesis and relevant clinical outcomes.
- Controlled clinical trials are powerful research tools to detect 'clinically meaningful' effects, if indeed they exist.
- Clinical trials are relatively weak in clarifying pathogenetic mechanisms (although biomarkers may help).

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The Clinical Research Mystique of Neuroprotection

- Relevant clinical outcomes, not clinical trial designs, are key for developing substantive Rxs that slow or stop PD.
- No single study or design can prove that a treatment is ‘neuroprotective’.
- The ‘mystique of neuroprotection’ exceeds the evidence.

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Relevant PD Clinical Outcomes

- Symptomatic Benefits
- Disability (accrued)
- Functional Capacity
- Independence
- Activities of Daily Living
- Quality of Life
- UPDRS (S/E ADL)
- Clinical Global Impression (CGI)
- Mortality
- Onset illness in ‘Pre-Manifest PD’
- ‘Neuroprevention’

Validity, Reliability, Responsiveness, Reproducibility, Predictive Value

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Basis for Disability Sufficient to Require ('need for') Dopaminergic Therapy

- Employability
- Domestic Tasks
- Activities of Daily Living
- Station and Gait

Not just 'time to levodopa or dopaminergic therapy'

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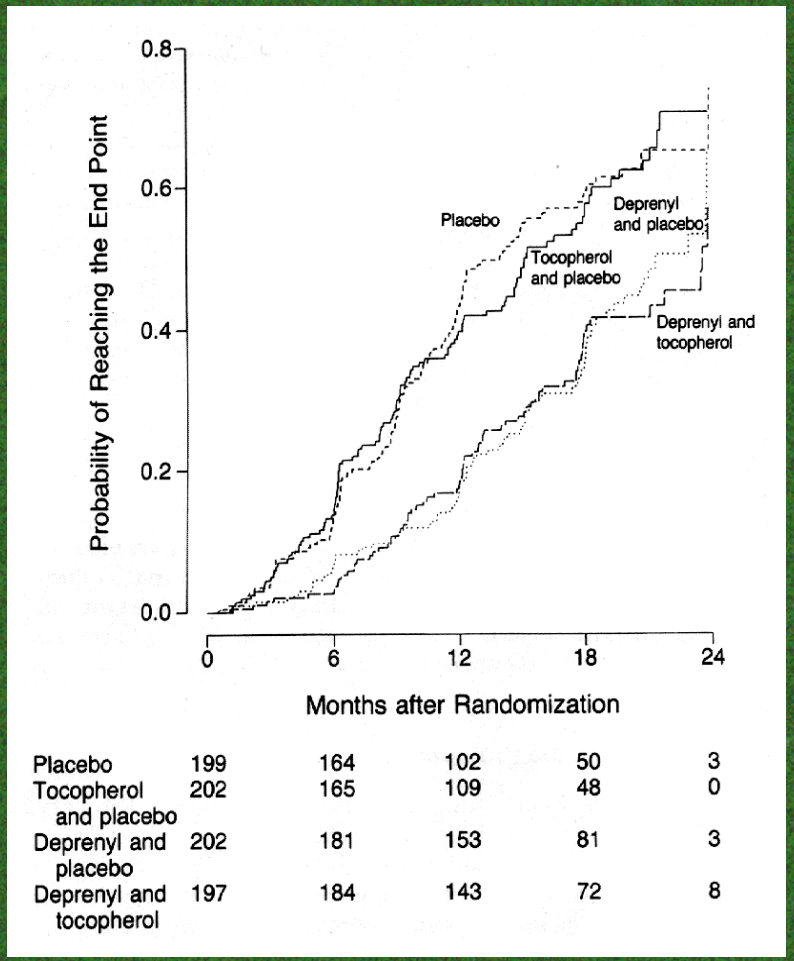
DATATOP



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

"Although the primary effect of treatment was unequivocal, the mechanism (symptomatic, protective, or both) of the effect is unclear."

"The primary effects of treatment are not fully explained by the apparently variable and the clinically trivial short-term effects of deprenyl on symptoms"

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	DATATOP Trial (US, Canada)	Syndey Multicentre PD Trial (Australia)	Community-Based Observational Study (Norway)
Starting sample size	800 (selegiline-tocopherol, 2x2 factorial)	149 (bromocriptine, levodopa)	245
Patient Age (duration of illness) at entry in years	61 (1)	62 (2)	73 (9)
Duration of observation in years	7.5 clinical followup 13 for vital status	15-18 (10 minimal)	8
Deceased	17% after 7.5 yrs 37% after 13 yrs	67%	50%
Postural instability	30%	80% (falls) 25% (fractures)	90%
Demented	None over 14 $\pm$ 6 months	50%	75% (OR=3.3)
Depression		50% ($\pm$ hallucinations)	5.1% (moderate- severe) 45.5% (mild)
Treatment-related fluctuators	50%	95%	
Urinary incontinence		40%	
UPDRS decline (units/yr)	10 prior to levodopa 3 on levodopa		3 on dopaminergic therapy

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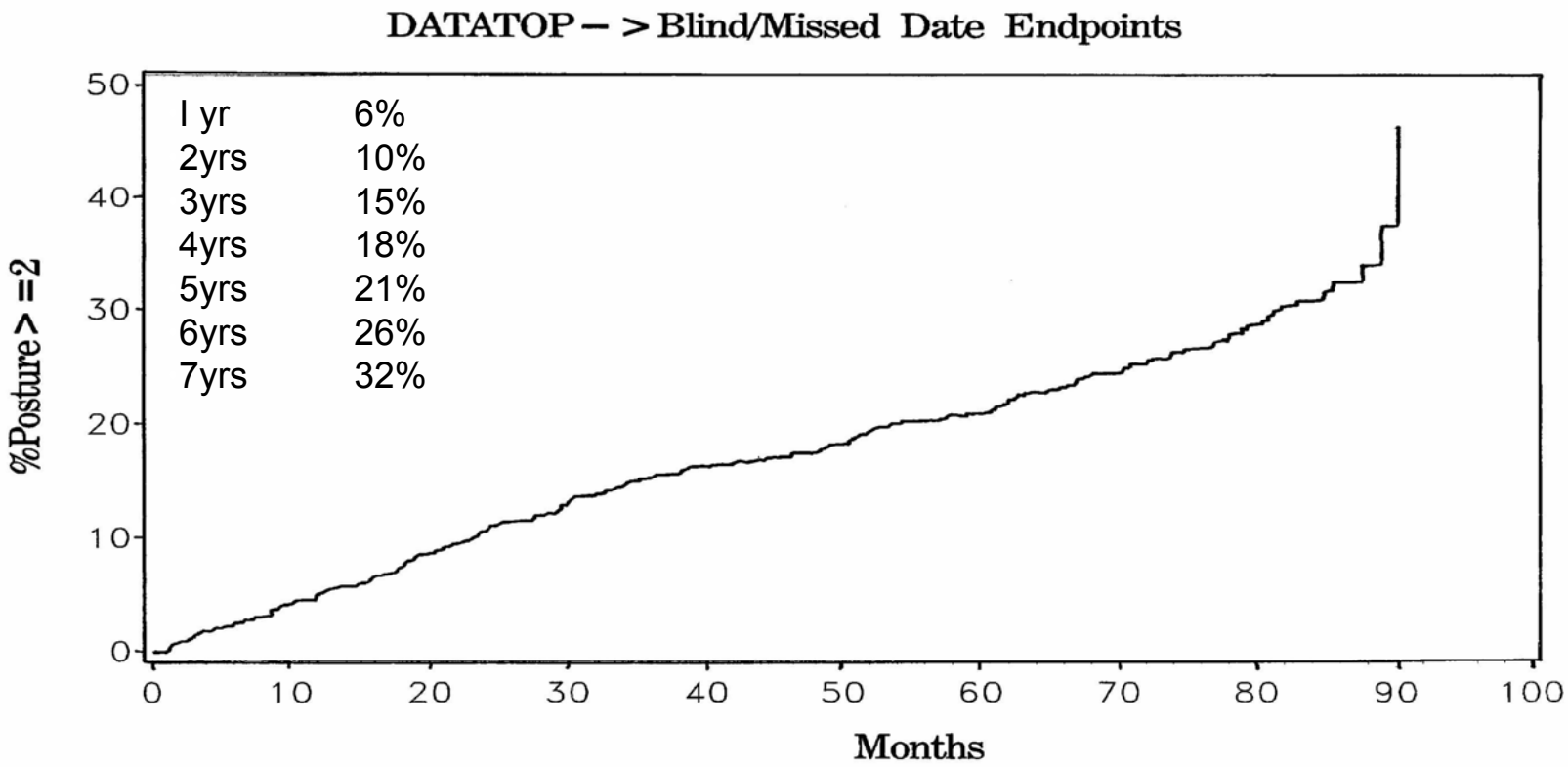
Cumulative Incidence of Postural Instability in the DATATOP (N=800) Cohort



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What's in a Name (Label) ?

- If a Rx reduced postural instability by 50% over ≥ 3 yrs of observation, what would it matter if such an effect was thought to be 'neuroprotective' (disease-modifying) or not?
- The putative mechanism of the effect is not as important as the clinical relevance of the outcome and the 'company it keeps.'

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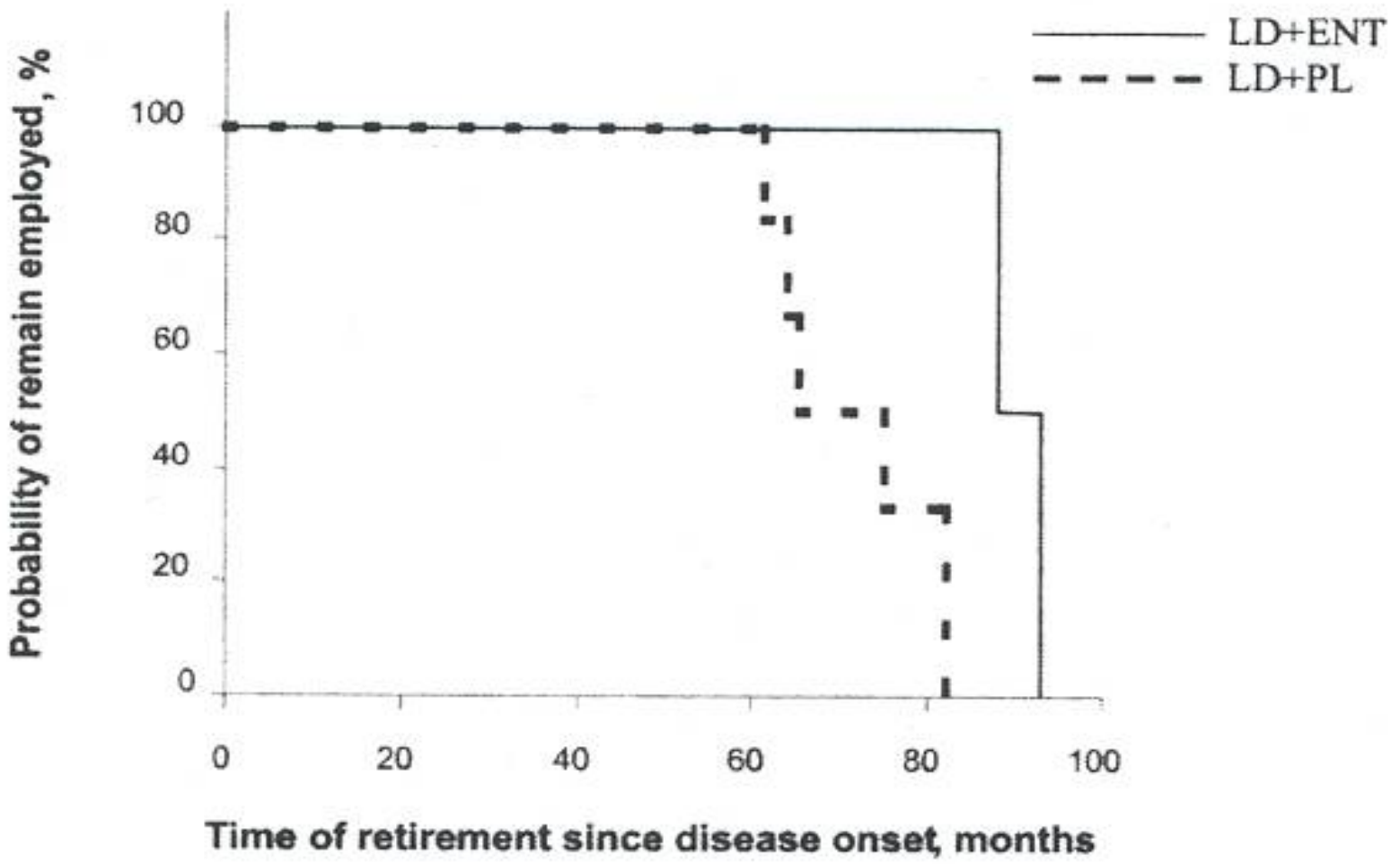

FIG. 1. Kaplan–Meier survival analysis of retirement if treated with LD + PL or LD + ENT.

Korchounov A & Bogomazov G, Employment, Medical Absenteeism, and Disability Perception in PD: A pilot double-blind, randomized, placebo-controlled study of entacapone adjunctive therapy. *Movement Disorders* 2006; 21:2220-2224.

Minimal Clinically Important Change in UPDRS

CGI by investigator	Motor UPDRS change from baseline -6 months Mean absolute change (upper, lower 95% CI)	Clinical Trial
unchanged	-2.2 (-4.3, 0.0)	ropinerole #1
unchanged	-1.3 (-3.7, 1.1)	ropinerole #2
minimal improvement	-5.0 (-6.6, -3.4)	ropinerole #1
minimal improvement	-5.3 (-6.8, -3.7)	ropinerole #2
minimal improvement	-1.5 (3.0, -0.1)	rasagiline (TEMPO)

Schrag A, Sampaio C, Counsell N, Poewe W. *Movement Disorders* 2006;21:1200-1207

Rascol P. *Movement Disorders* 2006;21:1059-1061

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Prospects for Success Depend On

- Scientific discovery pipeline of rational disease-modifying interventions that appear safe for long-term treatment
- Development and conduct of multi-site observational studies and clinical trials that examine clinically relevant outcomes for Parkinson's disease, including sub-populations defined by phenotype and genotype, and potentially useful biomarkers.

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Biomarkers

- Objective measure of biological function, pathogenic process, or pharmacologic response (co-varies with and predicts clinical outcome)
- State, Trait, Treatment
- Pre-clinical (pre-manifest) vs clinical (manifest)
- Distinguish from clinical endpoints (eg, smell testing) and surrogate endpoints (that might substitute for clinical endpoints)
- Need for validation in clinical trials

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Hazard ratios (HR)† for reaching the PD disability endpoint in PRECEPT according to baseline serum urate

Schwarzschild MA, Schwid SR, Marek K, Oakes D, Watts A, Lang EA, Shoulson I, Ascherio A & the PSG PRECEPT Investigators, Soc Neuroscience 2006 Annual Meeting (abstract #510.2; http://www.sfn.org/am2006)

Serum urate quintile	Median serum urate (mg/dL)	All (n=804)		Men (n=517)			Women (n=287)		
		HR (95% CI)	p value	n	HR (95% CI)	p value	n	HR (95% CI)	p value
1	3.8	1.00 (Ref)	-	45	1.00 (Ref)	-	132	1.00 (Ref)	-
2	4.8	0.80 (0.60-1.07)	0.12	87	0.61 (0.40-0.94)	0.03	70	0.93 (0.63-1.37)	0.70
3	5.5	0.85 (0.63-1.15)	0.29	110	0.66 (0.44-1.00)	0.05	37	1.00 (0.61-1.64)	0.99
4	6.3	0.65 (0.47-0.88)	0.006	143	0.51 (0.34-0.76)	0.001	26	0.76 (0.41-1.39)	0.37
5	7.5	0.51 (0.37-0.72)	<0.0001	132	0.39 (0.26-0.60)	<0.0001	22	0.77 (0.39-1.50)	0.44
p, for trend			0.0002			<0.0001			0.33
p, for gender-urate interaction			0.15						

†Adjusted for age and gender

- 492 of 804 subjects reached endpoint over an average of 21 months.
- Associations not appreciably affected by also controlling for smoking, BMI, CEP-1347 and other potential confounders.

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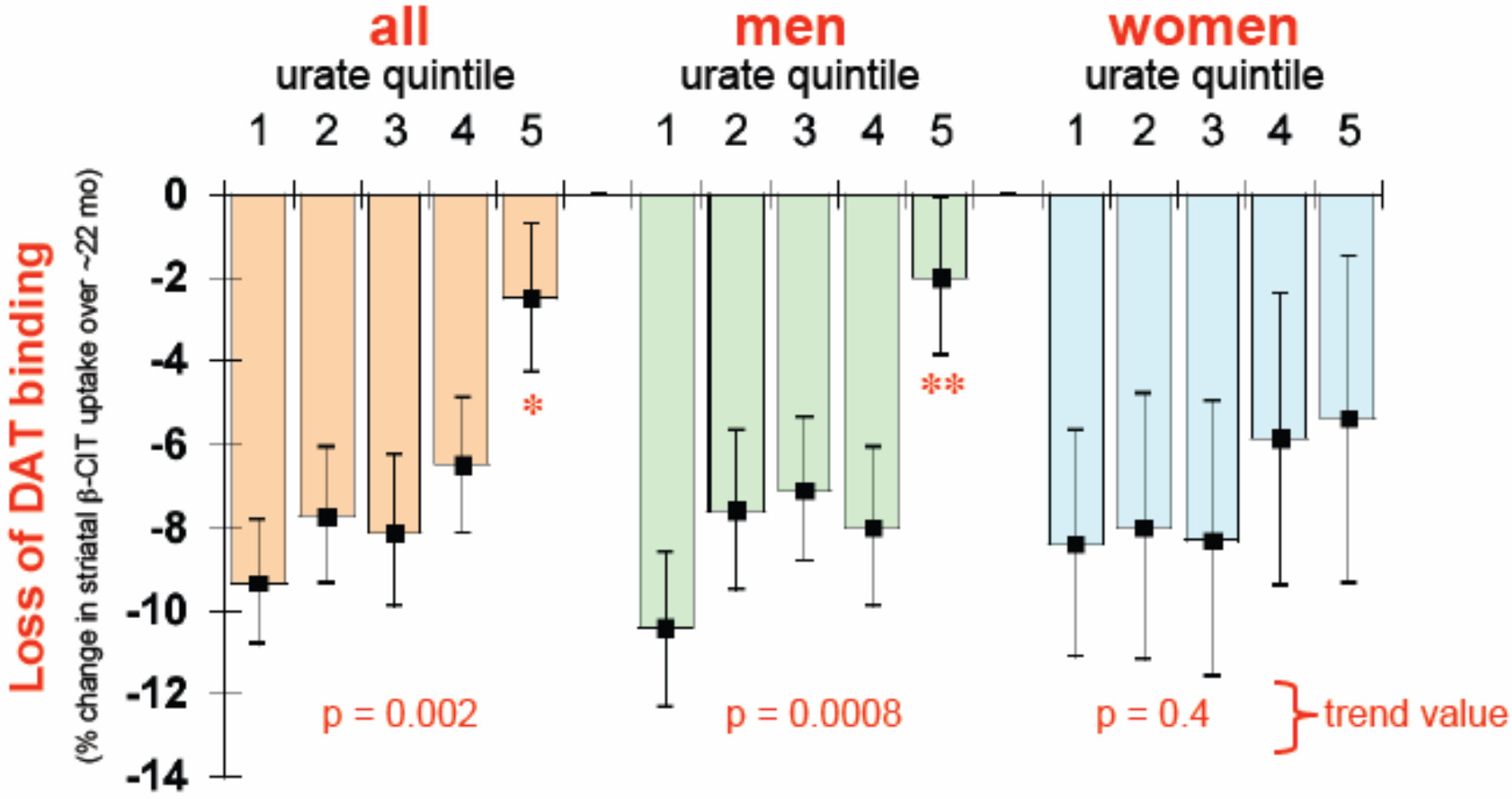
Higher serum urate at baseline indicates a slower rate of losing DA transporter binding sites in PD

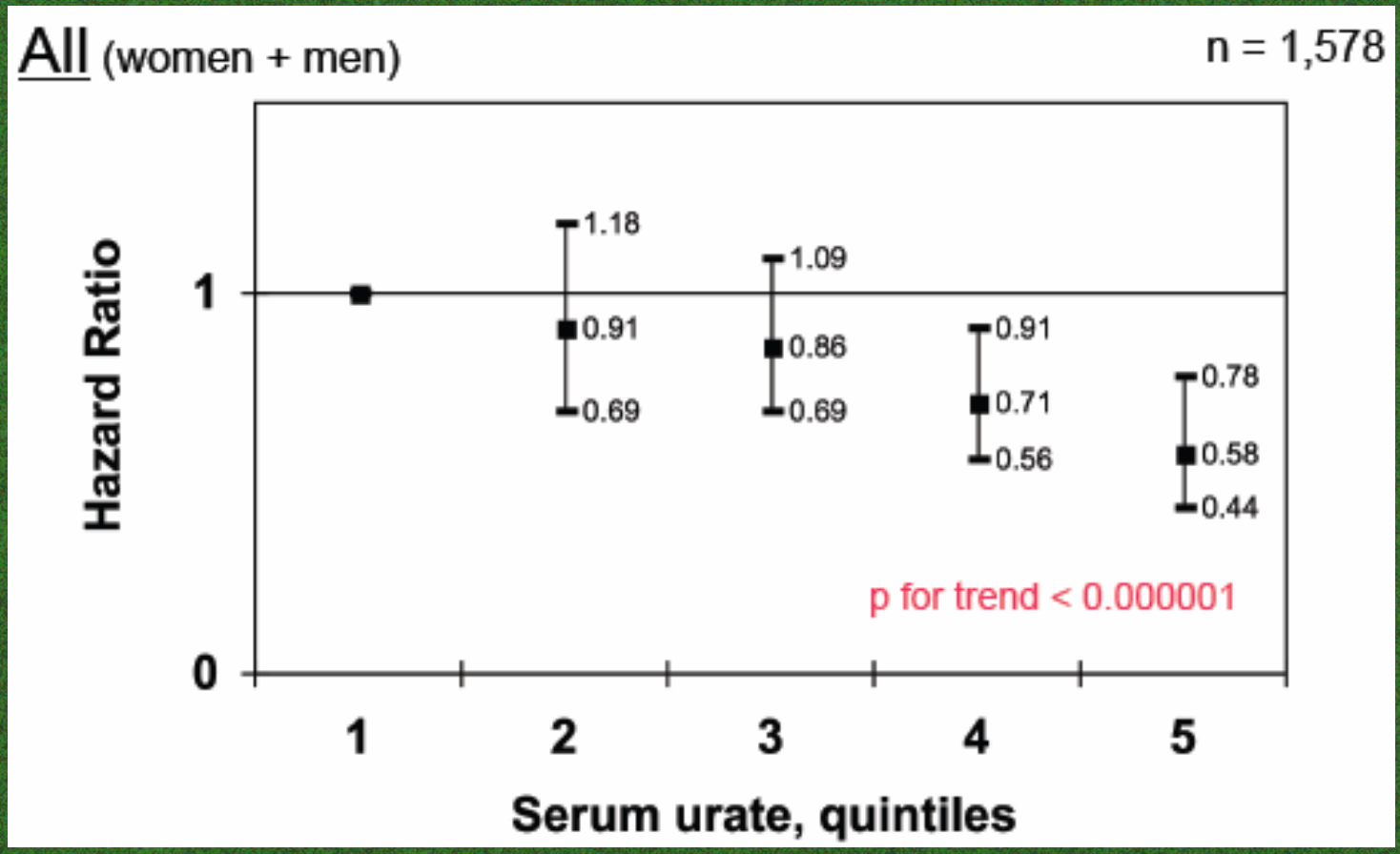
Schwarzschild MA, Schwid SR, Marek K, Oakes D, Watts A, Lang EA, Shoulson I, Ascherio A & the PSG PRECEPT Investigators, Soc Neuroscience 2006 Annual Meeting (abstract #510.2; http://www.sfn.org/am2006)



Age-adjusted % change in striatal [123]β-CIT uptake by overall and gender-specific quintiles of baseline serum urate; n=399.

Hazard ratios of reaching primary endpoint of disability requiring levodopa therapy according to serum urate at DATATOP baseline

Ascherio A, LeWitt PA, Watts A, Kieburtz K, Rudolph A, Schwid SR, Matson WR, Beal MF, Lang AE, Oakes D, Fahn S, Shoulson I & Schwarzschild MA on behalf of the PSG DATATOP investigators. (2006) CSF as well as serum urate are predictors of Parkinson¹s disease progression. Movement Disorders Society International Congress on Parkinson¹s Disease and Movement Disorders. Kyoto [Abstract #LB-2.] *Movement Disorders* (in press).



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Higher CSF urate and slower PD progression in DATATOP

Ascherio A, LeWitt PA, Watts A, Kieburtz K, Rudolph A, Schwid SR, Matson WR, Beal MF, Lang AE, Oakes D, Fahn S, Shoulson I & Schwarzschild MA on behalf of the PSG DATATOP investigators. (2006) CSF as well as serum urate are predictors of Parkinson¹s disease progression. Movement Disorders Society International Congress on Parkinson¹s Disease and Movement Disorders. Kyoto [Abstract #LB-2.] *Movement Disorders* (in press).

CSF urate quintile	ALL (n=290)			Men (n=196)			Women (n=94)		
	Median CSF urate mg/dL	HR (95% CI)	p value	Median CSF urate mg/dL	HR (95% CI)	p value	Median CSF urate mg/dL	HR (95% CI)	p value
1	0.47	1.00 (Ref)	-	0.60	1.00 (Ref)	-	0.38	1.00 (Ref)	-
2	0.67	0.76 (0.50 – 1.15)	0.20	0.79	0.89 (0.54 – 1.48)	0.66	0.50	0.64 (0.29 – 1.44)	0.28
3	0.86	0.80 (0.52 – 1.25)	0.49	0.92	0.82(0.50 – 1.35)	0.44	0.66	0.47 (0.20 – 1.09)	0.08
4	1.04	0.66 (0.43 – 1.03)	0.15	1.09	0.74 (0.45 – 1.23)	0.25	0.78	0.67 (0.30 – 1.50)	0.33
5	1.39	0.52 (0.33 – 0.81)	0.004	1.44	0.53 (0.32 – 0.90)	0.02	1.18	0.43 (0.19 – 0.98)	0.04
CSF urate, 1SD		0.80 (0.69 – 0.93)	0.004		0.78 (0.66 - 0.93)	0.007		0.85 (0.62 - 1.16)	0.29

†Adjusted for age, gender, and treatment group (deprenyl or placebo)

1 standard deviation (SD = 0.37 mg/dL)

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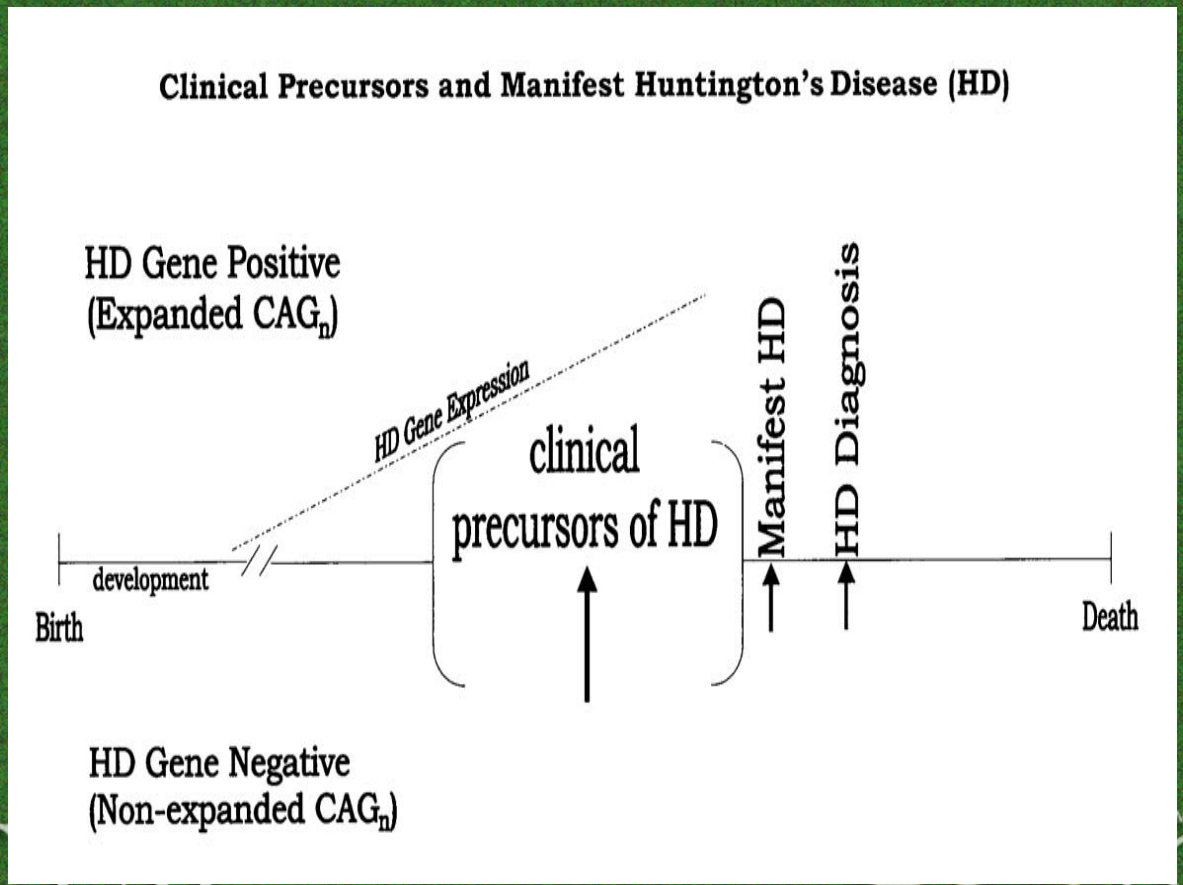
'Neuro Prevention'

Experimental interventions that postpone or prevent the onset of illness in individuals who are at high risk to develop the (neurodegenerative) disease.



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  - H. Lundbeck A/S
- PRECEPT/DATATOP study patients and families

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