

“Continuous” dopaminergic stimulation minimizes levodopa-induced motor complications:
Maybe so, but not necessarily!

Ergun Uc, MD

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DISCLAIMER

- Joe Quinn to Ergun Uc:
 - I'm writing to invite you to participate as a speaker in the VA Parkinson's consortium conference in Pittsburgh in September. I believe you're already planning to attend, and I will be there as well. Jay Nutt was scheduled to debate Jeff Bronstein on the subject "continuous dopaminergic stimulation minimizes levo-dopa induced motor complications", but Jay cannot make it. Would you be willing to fill in for him? I have attached the tentative agenda. (Con: Jeff Bronstein)
- Ergun to Joe:
 - Couldn't I debate that exercise is good for PD or driving in PD is affected by cognitive/visual rather than motor deficits? Joking aside, it would be hard for me to fill Jay's shoes on this topic, but I will try.
- From Becky Martine:
 - My apologies...there was a typo on the agenda. Jeff will take the side of pro continuous dopaminergic stimulation and Dr. Uc will be con. Please let me know if this poses any problems. Thanks!
- Last words of Ergun to Jeff, Joe, and Jay:
 - This is doubly unfair! First, trying to fill Jay's shoes in an area which is not my active research topic; and now, debating against conventional wisdom.
 - Mercy!



Issues

- Definitions of continuous and pulsatile stimulation
- Natural history of PD
- Problems with study design and analysis and interpretation supporting “CDS”
- Pharmacokinetic/dynamic considerations



“Continuous” vs. “Pulsatile” Stimulation

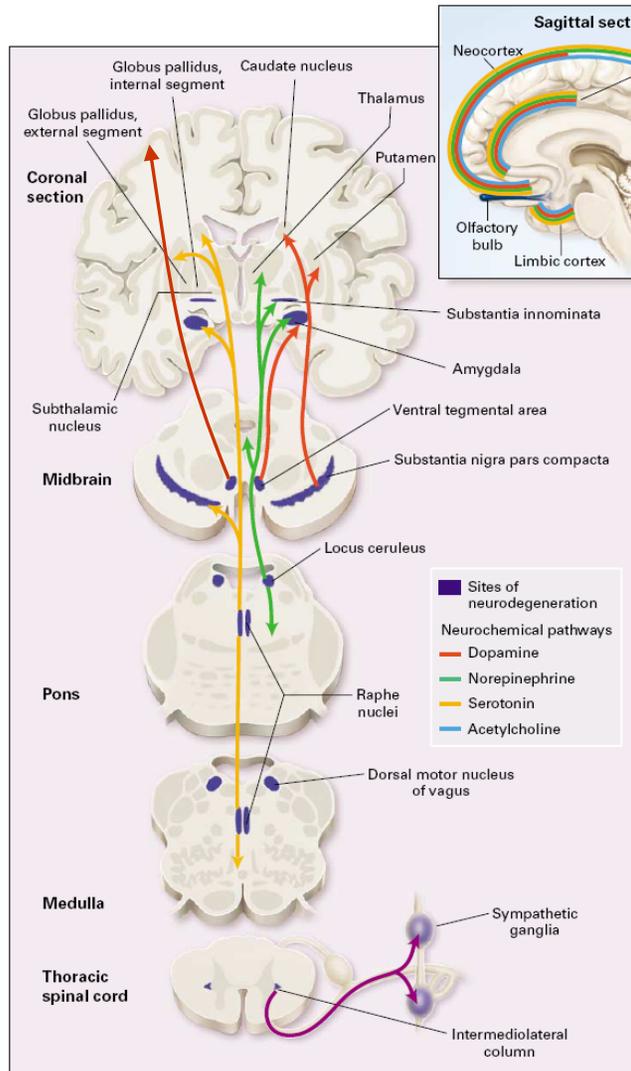
Dopaminergic agent	Half-life (hours)
Apomorphine	0.5
Levodopa/carbidopa	1–1.5
Sustained-release levodopa	3–6
Rotigotine	5–7
Ropinirole	6–8
Pramipexole	8–12
Pergolide	7–16
Bromocriptine	12–15
Cabergoline	65–110
Entacapone/tolcapone	↑ AUC of levodopa 30-70%

What is physiologic dopaminergic stimulation?
Location, receptor type, concentration, situation

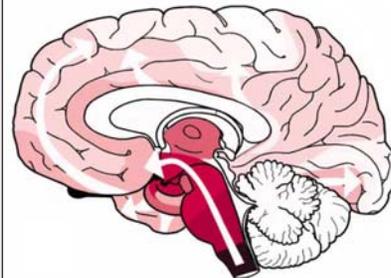
How does it change in PD?



PD is not just a motor condition with nigrostriatal dopaminergic dysfunction!



Lang & Lozano, NEJM 1998



Braak et al.,
Neurobiol
Aging 2003

• Motor

Bradykinesia, rigidity, tremor,
postural instability-gait disorder

• Cognitive

▪ Impairment:
Executive, attention, visuospatial,
memory, language

▪ Dementia

• Psychiatric

▪ Depression, apathy

▪ Hallucinations, psychosis

• Autonomic

▪ Cardiovascular

▪ Gastrointestinal

▪ Genitourinary

• Sleep

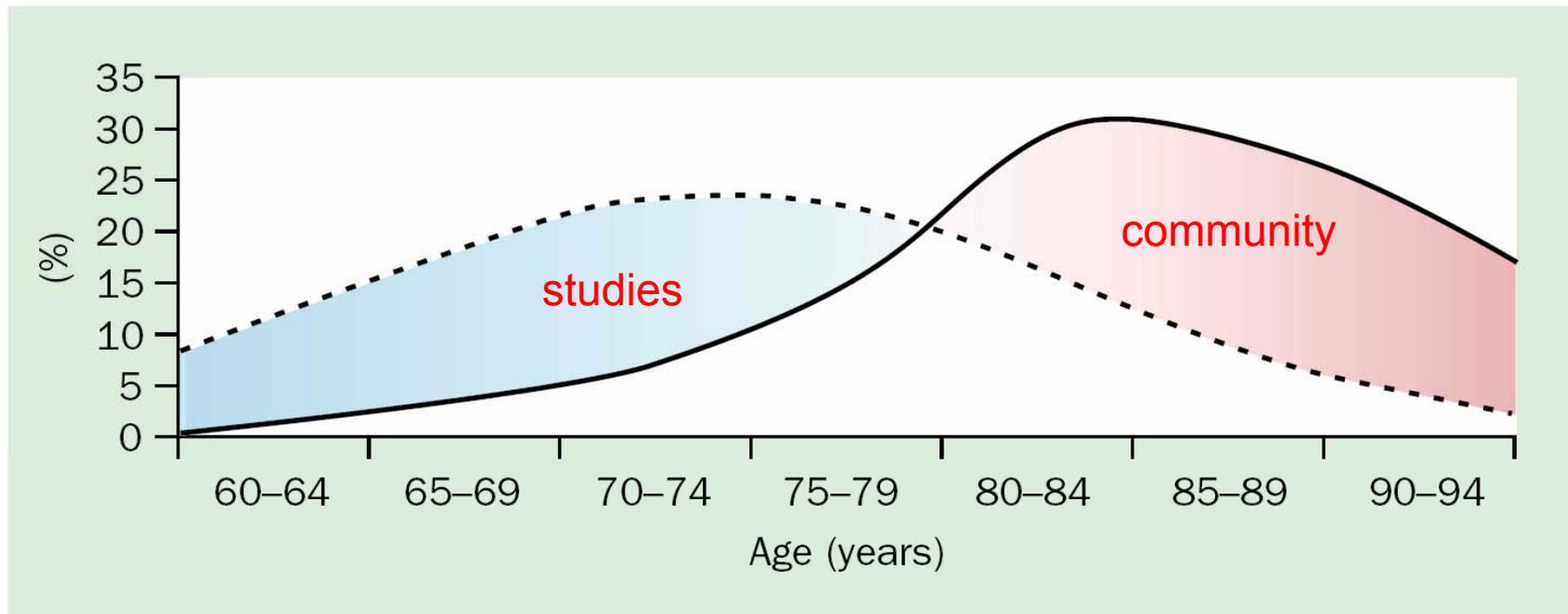


Figure 1. Age distribution of patients with dementia that were included in clinical research of diagnostic methods and therapeutic trials (broken line, $n=6953$) compared with the age distribution of demented patients from the general population of the Netherlands (solid line, $n=180\,961$). The wide age gap results in a gross over-representation of relatively young patients in clinical research (blue area) and a serious under-representation of elderly demented patients from the general population (red area).

The age gap between patients in clinical studies and in the general population: A pitfall for dementia research



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Schoenmaker & Van Gool, Lancet Neurol 2004

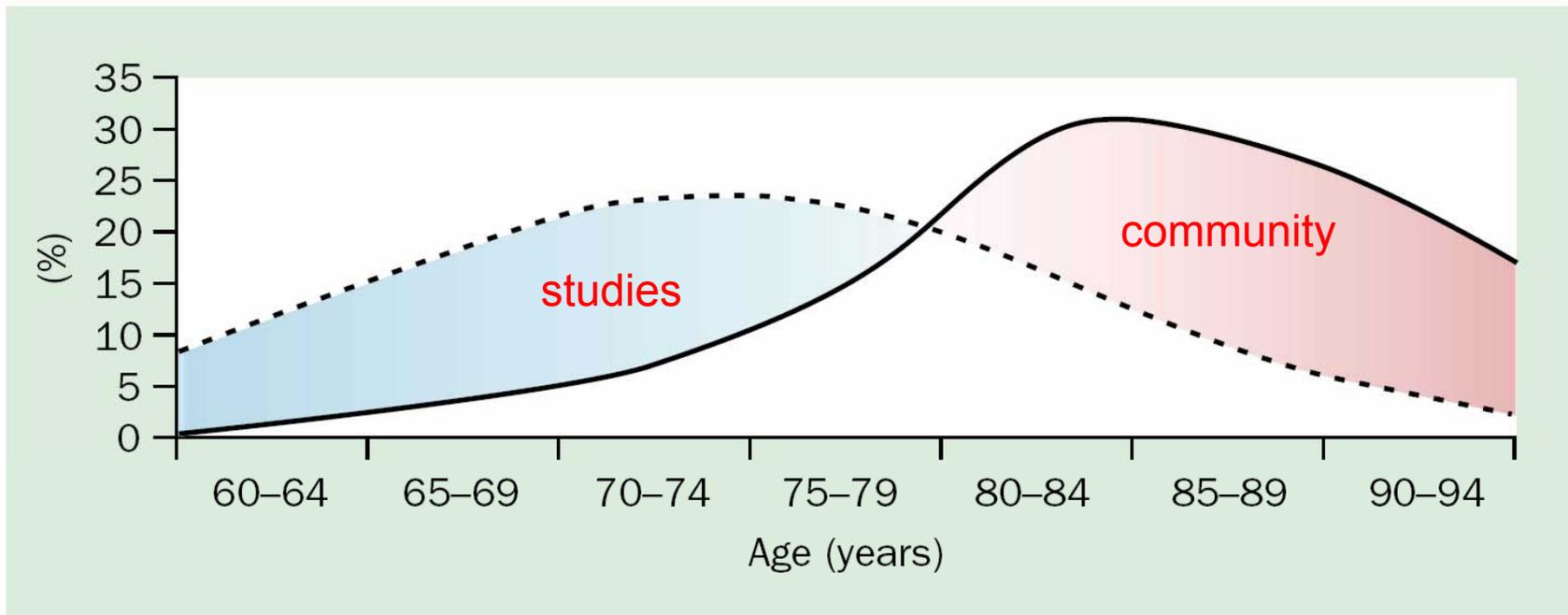


Figure 1. Age distribution of patients with dementia that were included in clinical research of diagnostic methods and therapeutic trials (broken line, n=6953) compared with the age distribution of demented patients from the general population of the Netherlands (solid line, n=180 961).

Age of Onset of PD

De Novo clinical trials Community Incident Cohorts



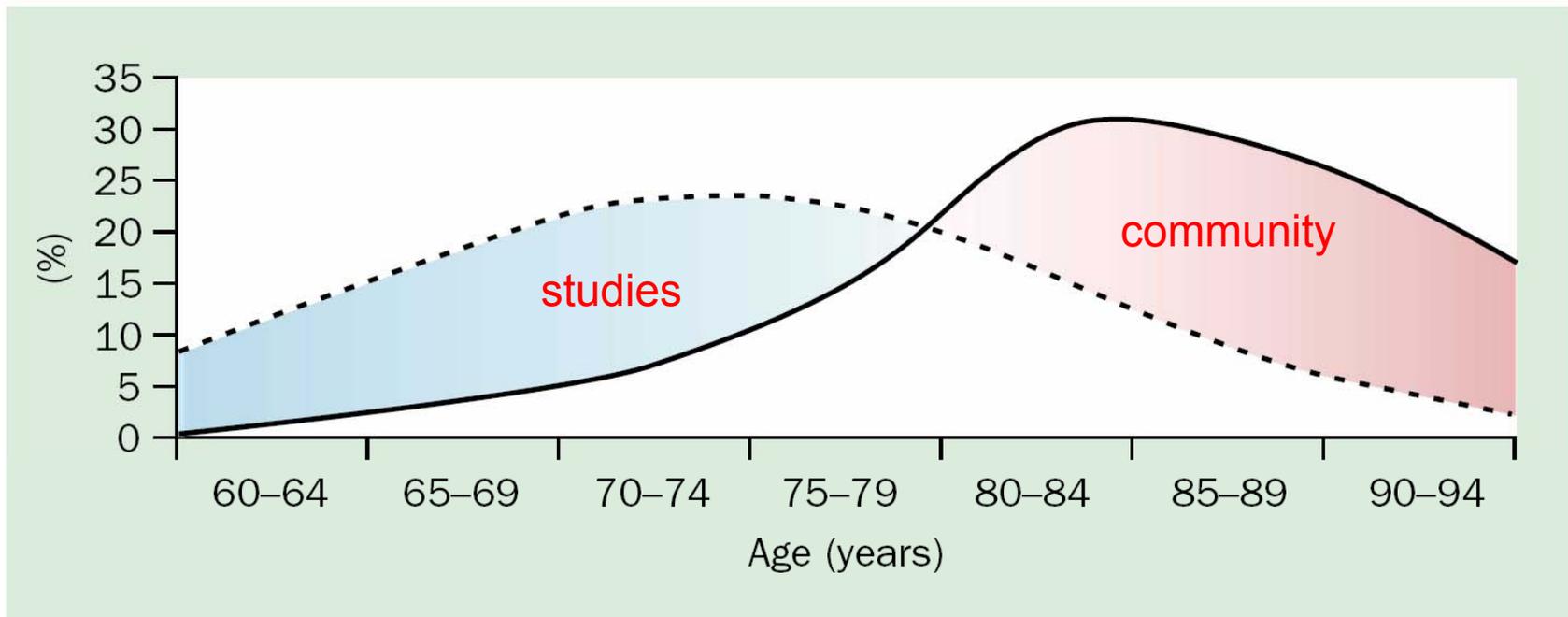


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Age of Onset of PD

De Novo clinical trials
60-63

Community Incident Cohorts
68-73



Patterns of levodopa response in Parkinson's disease: a clinico-pathological study

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¹Queen Square Brain Bank for Neurological Disorders and Institute of Neurology, University College, London, UK,

²Neurosciences Department, Monash Medical Centre and ³Faculty of Medicine (Neuroscience), Monash University (Alfred Hospital Campus), Melbourne, Australia

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Patients with Parkinson's disease who develop disabling levodopa-induced motor fluctuations have a stronger therapeutic response than those who experience a more modest but stable response. A difference in the histopathological lesion between the two groups might be responsible. Case records from 97 patients with pathologically proven Parkinson's disease were reviewed to determine the pattern of levodopa response. Pathological findings for fluctuating and non-fluctuating cases were compared. Patients with motor fluctuations had a younger age of onset and longer disease course ($P < 0.001$), although mean age at death was almost the same. Four milestones of advanced disease (frequent falls, visual hallucinations, cognitive disability and need for residential care) occurred at a similar time from death in each group; this interval was not proportionate to the disease duration. There were no significant differences in the severity or distribution of Lewy body or other pathologies. Irrespective of the pattern of levodopa response, patients reach a common pathological endpoint at a similar age, and the duration and manifestations of end-stage disease are alike. A non-linear or exponential time relationship may govern the late clinical and pathological progression of Parkinson's disease.

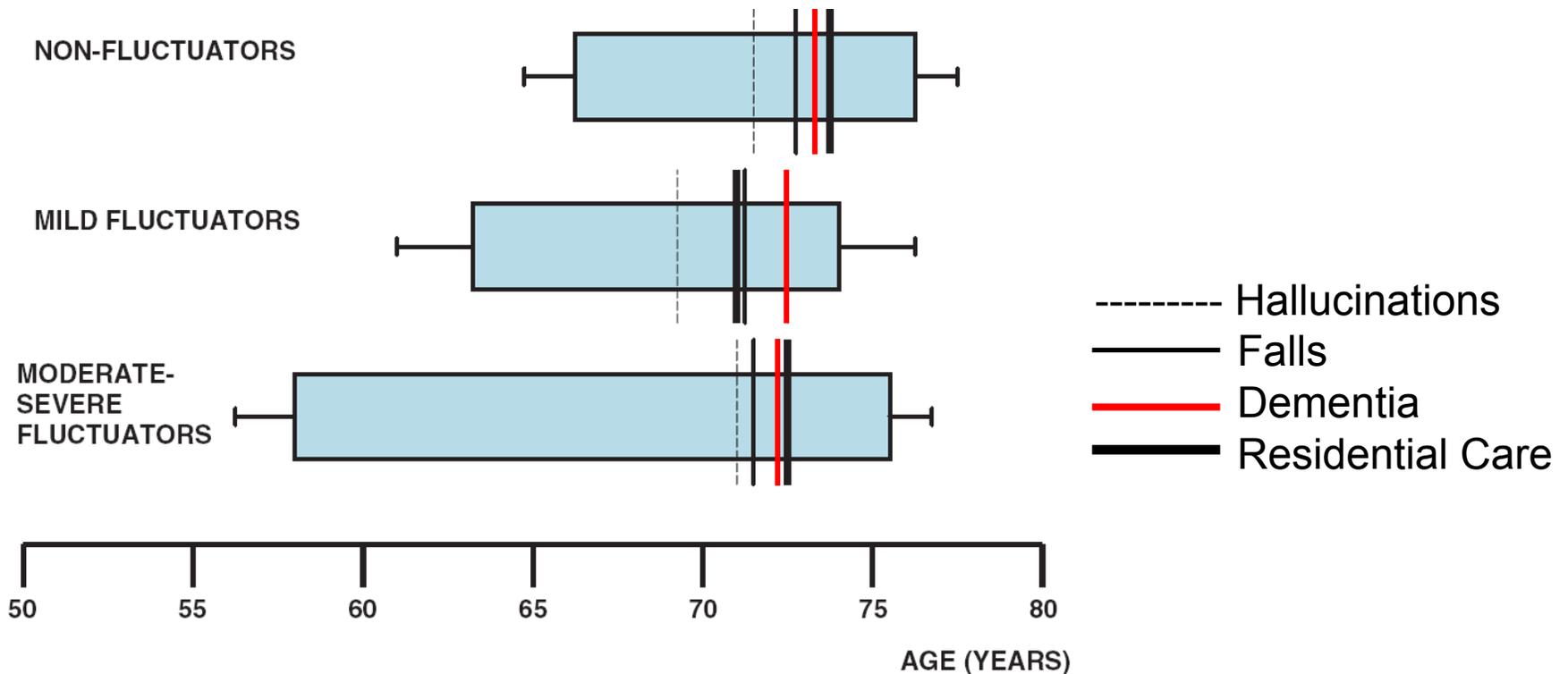


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Milestones and disease course in pathologically proven PD



rectangles represent disease duration; n=97

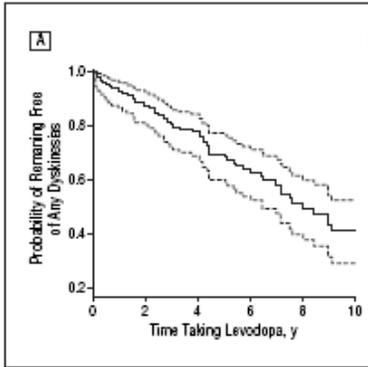


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Levodopa-Associated Dyskinesia Risk Among Parkinson Disease Patients in Olmsted County, Minnesota, 1976-1990

Arch Neurol. 2006;63:205-209

Jay A. Van Gerpen, MD; Neeraj Kumar, MD; James H. Bower, MD; Stephen Weigand; J. Eric Ahlskog, PhD, MD



Kaplan-Meier estimates (95% CI) of the probability that a PD patient on levodopa will be free of dyskinesias of any severity (A)

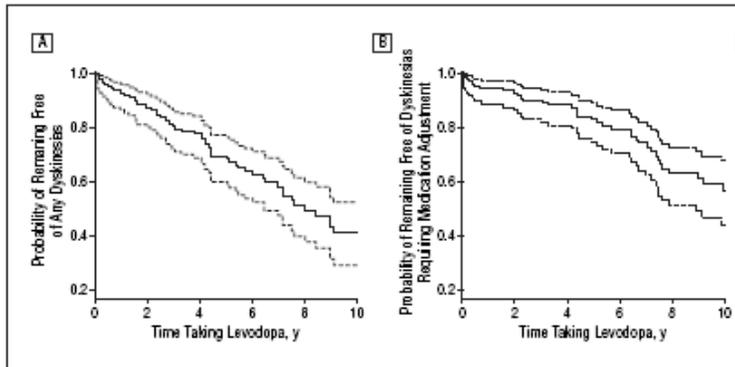


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Kaplan-Meier estimates (95% CI) of the probability that a PD patient on levodopa will be free of dyskinesias of any severity (A), will be free of dyskinesias requiring medication adjustment (B)

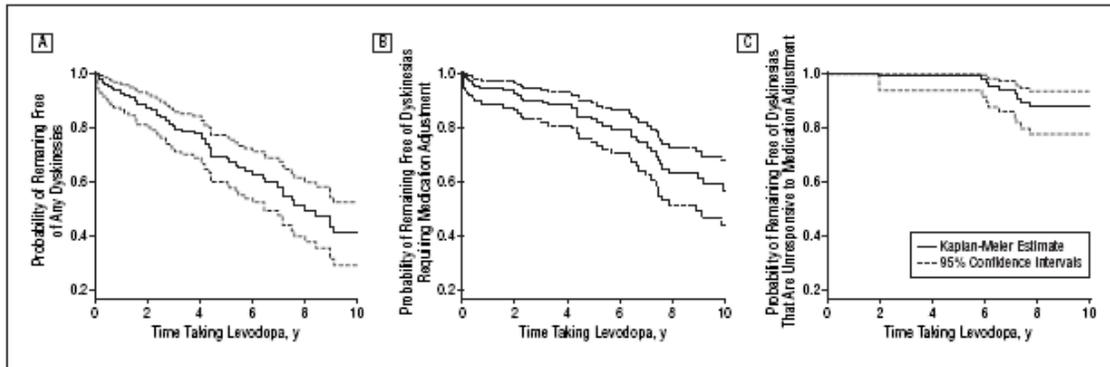


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Kaplan-Meier estimates (95% CI) of the probability that a PD patient on levodopa will be free of dyskinesias of any severity (A), will be free of dyskinesias requiring medication adjustment (B), and will be free of dyskinesias that are unresponsive to medication adjustment (C)

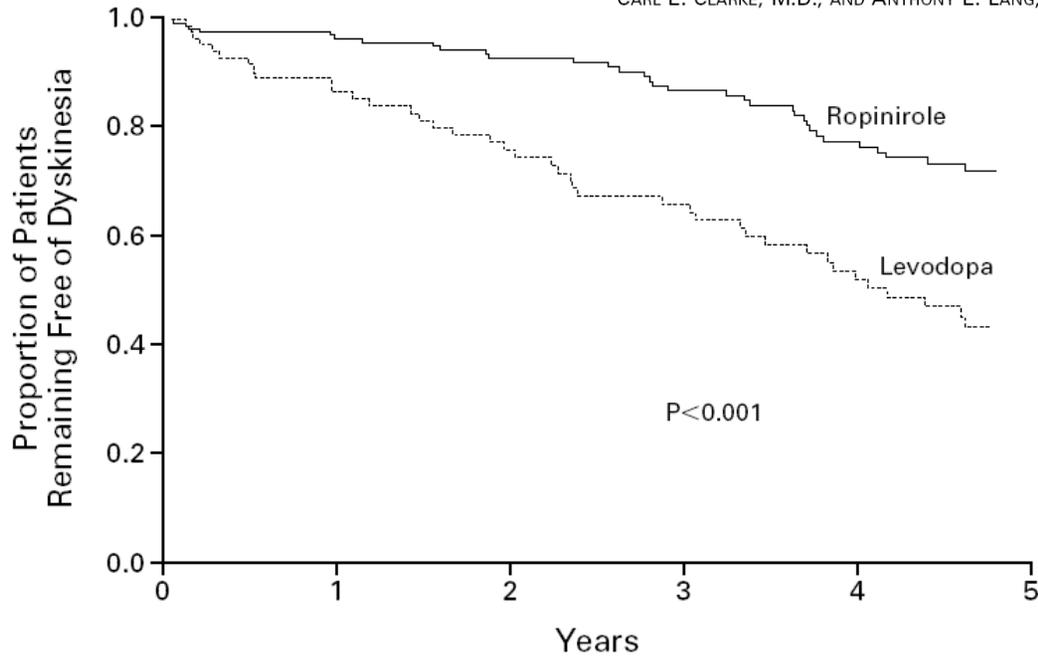
Levodopa-associated dyskinesias can be expected to develop in nearly 60% of patients after 10 years, but these will be severe enough to require medication adjustments in only 43% of patients. At 10 treatment years, nearly 90% of these patients can expect to be spared dyskinesias that could not be controlled by drug adjustments. This population based study suggests dyskinesia risk may not be a major concern for most PD patients.

Table 2. The HRs for Time-to-Event (Dyskinesia) Models*

Time-to-Event Model and Risk Factors	HR (95% CI)	
	Univariate Analysis	Multivariable Analysis†
Dyskinesias of any severity (grade ≥ 1)		
Age at first symptoms, 10-y increase‡	0.72 (0.55-0.94)§	0.74 (0.56-0.97)§
Sex, male vs female	1.23 (0.70-2.15)	0.94 (0.53-1.68)
Log of initial levodopa dose, increase equivalent to IQR	1.76 (1.08-2.85)§	1.68 (1.03-2.74)§
Dyskinesias sufficient to require medication adjustment (grade ≥ 2)		
Age at first symptoms, 10-y increase‡	0.66 (0.47-0.91)§	0.67 (0.48-0.94)§
Sex, male vs female	1.06 (0.55-2.03)	0.76 (0.40-1.49)
Log of initial levodopa dose, increase equivalent to IQR	2.38 (1.30-4.38)¶	2.24 (1.22-4.14)¶
Dyskinesias failing to respond to medication adjustment (grade ≥ 3)		
Age at first symptoms, 10-y increase‡	0.70 (0.38-1.29)	0.73 (0.39-1.40)
Sex, male vs female	1.06 (0.33-3.34)	0.87 (0.27-2.79)
Log of initial levodopa dose, increase equivalent to IQR	2.47 (0.81-7.54)	2.26 (0.74-6.85)

A FIVE-YEAR STUDY OF THE INCIDENCE OF DYSKINESIA IN PATIENTS WITH EARLY PARKINSON'S DISEASE WHO WERE TREATED WITH ROPINIROLE OR LEVODOPA

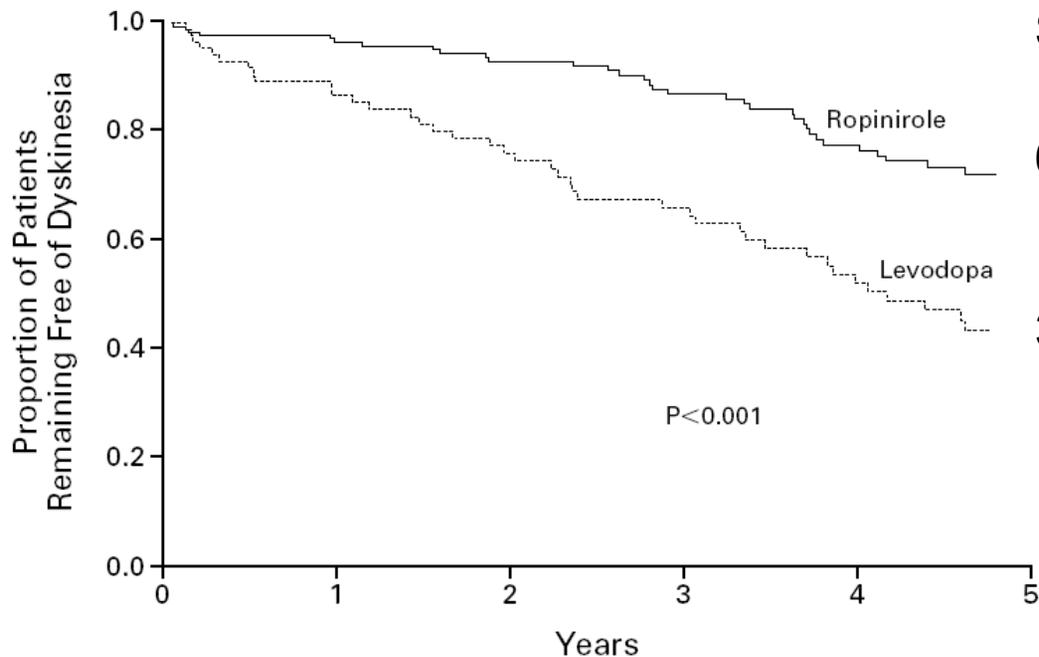
OLIVIER RASCOL, M.D., PH.D., DAVID J. BROOKS, M.D., D.Sc., AMOS D. KORCZYN, M.D., PETER P. DE DEYN, M.D., PH.D., CARL E. CLARKE, M.D., AND ANTHONY E. LANG, M.D., FOR THE 056 STUDY GROUP*



No. AT Risk						
Ropinirole	179	143	125	111	101	85
Levodopa	89	73	67	62	56	45

Figure 2. Proportions of Patients Remaining Free of Dyskinesia in the Ropinirole and Levodopa Groups. The hazard ratio for remaining free of dyskinesia in the ropinirole group as compared with the levodopa group was 2.82 (95 percent confidence interval, 1.78 to 4.44).





Supplemental open label L-dopa

66%

16.5 ± 6.6 mg (plus 427 ± 221 mg)

36% (753 ± 398 mg)

HR for open LD: Rop vs. LD
2.1 (1.4, 4.5), $P < 0.0001$

No. AT RISK

Ropinirole	179	143	125	111	101	85
Levodopa	89	73	67	62	56	45

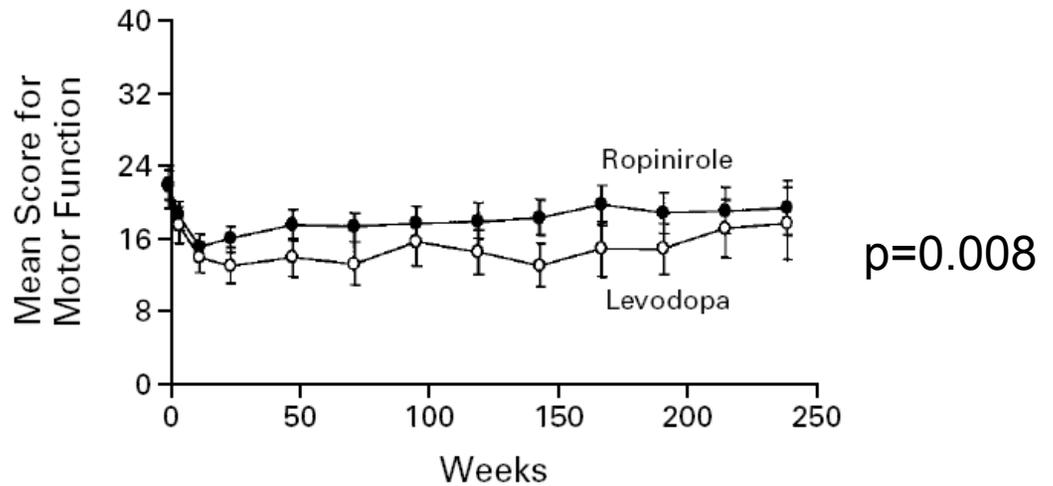
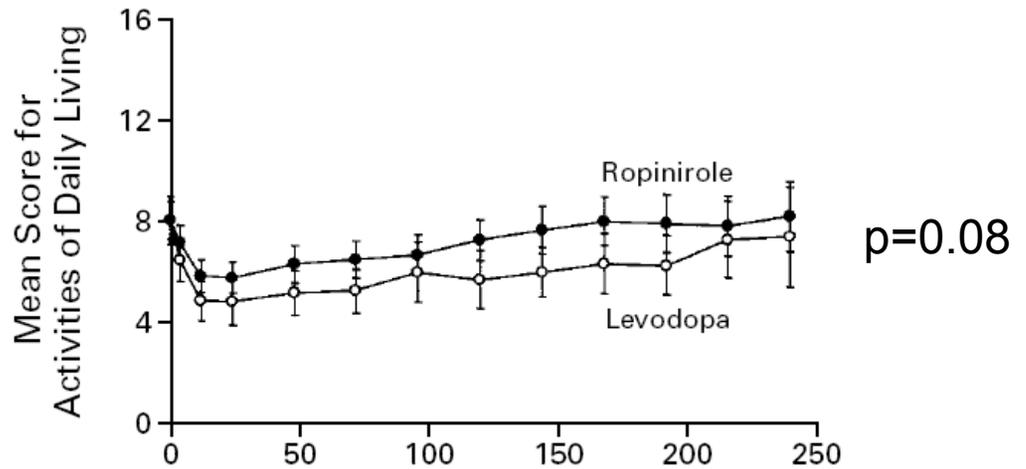
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Rascol et al., NEJM 2000

Better Motor Function and ADL on Levodopa



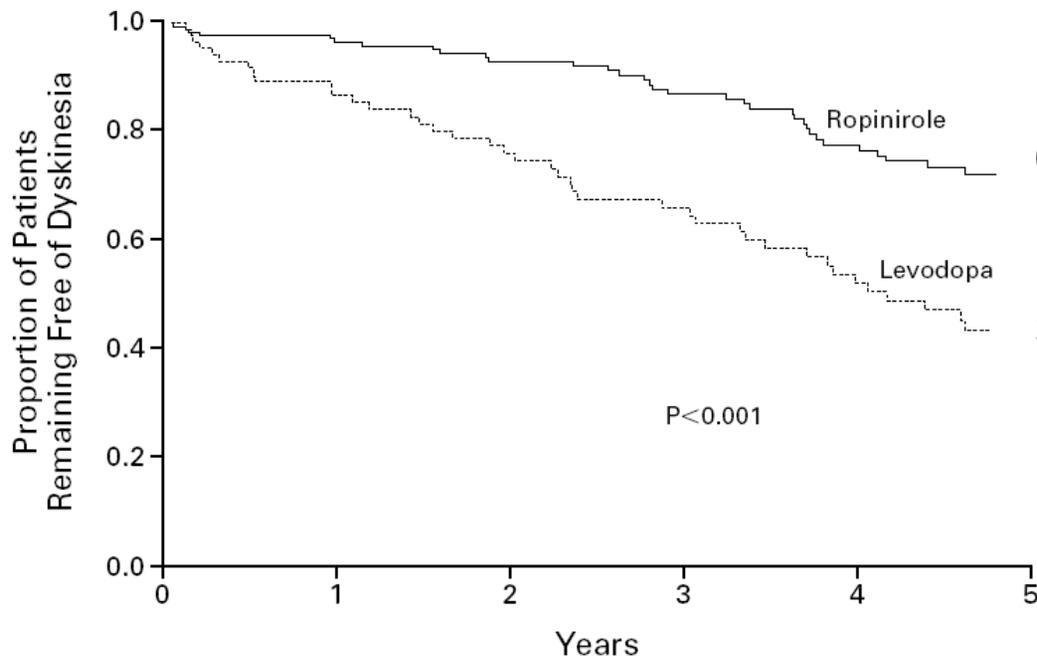
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Ropinirole	179	143	125	111	101	85
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“The **early use of ropinirole did not reduce** the occurrence of **wearing-off** and **freezing** during walking to the same extent as it did the occurrence of dyskinesia. This finding suggests that these complications of motor function may not have the same pathophysiologic mechanisms as dyskinesia.”



TABLE 2. REPORTS OF ADVERSE EVENTS OCCURRING IN 10 PERCENT OR MORE OF EITHER GROUP IN THE INTENTION-TO-TREAT ANALYSIS.

ADVERSE EVENT*	ROPINIROLE (N=179)	LEVODOPA (N=89)
	no. (%)	
Nausea	87 (48.6)	44 (49.4)
Somnolence	49 (27.4)	17 (19.1)
Insomnia	45 (25.1)	21 (23.6)
Aggravated Parkinson's disease	40 (22.3)	18 (20.2)
Dyspepsia	37 (20.7)	15 (16.9)
Dizziness	36 (20.1)	17 (19.1)
Hallucinations	31 (17.3)	5 (5.6)
Vomiting	29 (16.2)	10 (11.2)
Tremor	29 (16.2)	11 (12.4)
Abdominal pain	27 (15.1)	13 (14.6)
Depression	26 (14.5)	20 (22.5)
Headache	25 (14.0)	16 (18.0)
Edema of the legs	25 (14.0)	5 (5.6)
Ataxia	25 (14.0)	8 (9.0)
Anxiety	21 (11.7)	8 (9.0)
Postural hypotension	21 (11.7)	11 (12.4)
Constipation	17 (9.5)	11 (12.4)
Dyskinesia†	16 (8.9)	23 (25.8)
Dystonia	12 (6.7)	11 (12.4)
Increased sweating	11 (6.1)	9 (10.1)

*Patients often had more than one adverse event.

†Dyskinesia, the primary outcome measure, was assessed on the basis of both the Unified Parkinson's Disease Rating Scale and reports of adverse events.



Development of Dyskinesias in a 5-Year Trial of Ropinirole and L-Dopa

Olivier Rascol, MD, PhD,^{1*} David J. Brooks, MD,² Amos D. Korczyn, MD,³ Peter P. De Deyn, MD,⁴
Carl E. Clarke, MD,⁵ Anthony E. Lang, MD,⁶ Mona Abdalla, PhD,⁷ and the 056 Study Group

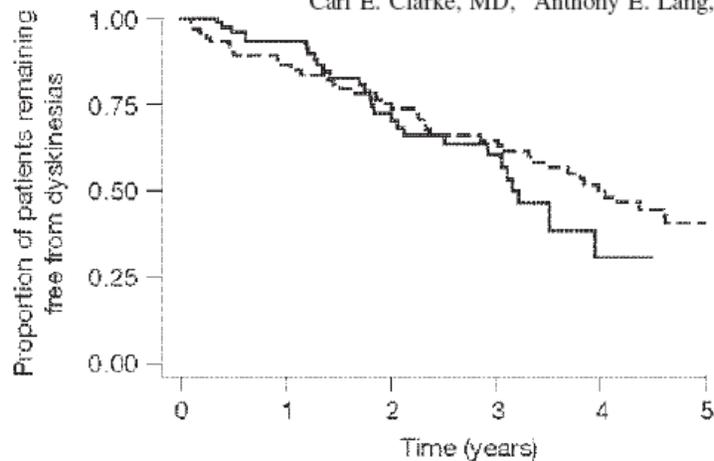
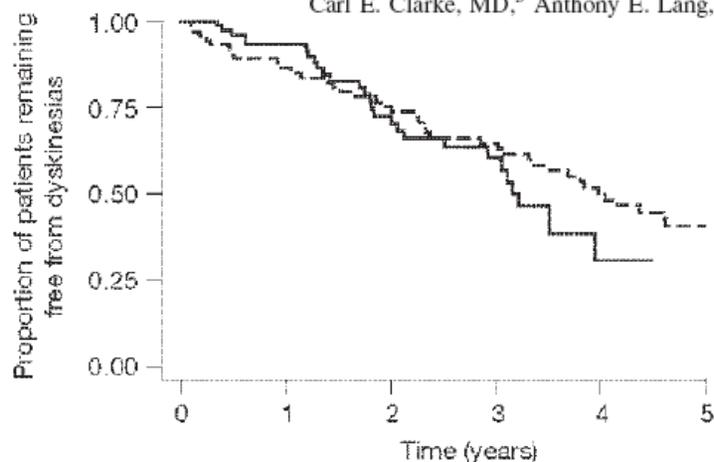


FIG. 3. Survival analysis of patients remaining free from dyskinesias in the group receiving L-dopa (dotted line) at the start of the trial and in those receiving ropinirole supplemented with L-dopa (solid line; HR, L-dopa/ropinirole, 0.80; 95% CI, 0.48–1.33. Time of starting L-dopa therapy is taken as the time of origin in this figure; therefore, in the ropinirole group, the origin is chronologically later than that in the L-dopa group.



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Number at risk:						
	0	1	2	3	4	5
Ropinirole	86	59	34	20	5	1
L-dopa	89	64	51	42	30	5

FIG. 3. Survival analysis of patients remaining free from dyskinesias in the group receiving L-dopa (dotted line) at the start of the trial and in those receiving ropinirole supplemented with L-dopa (solid line; HR, L-dopa/ropinirole, 0.80; 95% CI, 0.48–1.33. Time of starting L-dopa therapy is taken as the time of origin in this figure; therefore, in the ropinirole group, the origin is chronologically later than that in the L-dopa group.

TABLE 1. Significant baseline and follow-up predictors of time to development of dyskinesias using covariate analysis

Variable	Hazard ratio (95% CI)	P value
Baseline predictors		
Initial L-dopa vs. ropinirole therapy	3.03 (1.92–4.76)	< 0.001
Age (yr)	0.97 (0.94–0.99)	0.014
1-category increase in baseline disease stage ^a	1.42 (1.16–1.74)	0.001
UK patients vs. all others	2.03 (1.28–3.22)	0.003
Baseline and follow-up predictors		
L-dopa vs. ropinirole therapy	1.30 (0.70–2.38)	0.404
Age (yr)	0.96 (0.94–0.99)	0.006
1-category increase in baseline disease stage	1.46 (1.19–1.80)	< 0.001
UK patients vs. all others	1.96 (1.24–3.11)	0.004
Current total daily L-dopa dose ^b	1.19 (1.10–1.28)	< 0.001

^aHoehn & Yahr stage.

^bPer 100-mg increase.

CI, confidence interval.



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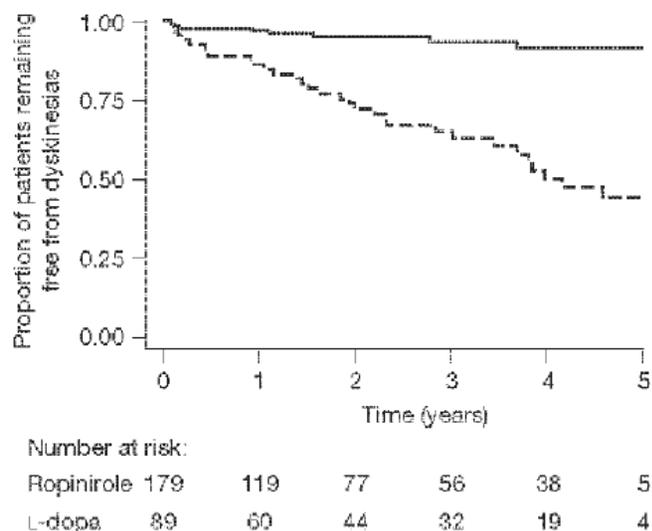


FIG. 2. Survival analysis of patients remaining free from dyskinesias in the groups receiving L-dopa (dotted line) or ropinirole monotherapy (solid line) at the start of the trial, who developed dyskinesias before receiving supplementary L-dopa (HR, L-dopa/ropinirole, 6.67; 95% CI, 3.23–14.29).

TABLE 2. Baseline and follow-up predictors of L-dopa supplementation on covariate analysis

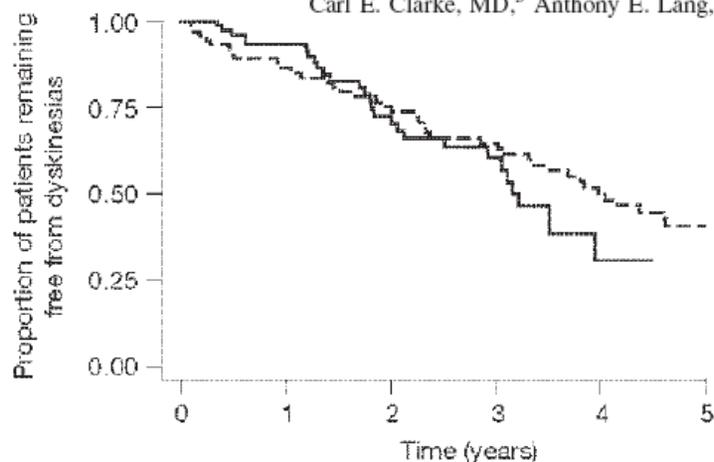
Variable	Hazard ratio (95% CI)	P value
Baseline predictors		
L-dopa vs. ropinirole therapy	0.46 (0.31–0.71)	< 0.001
Baseline ADL score	1.08 (1.04–1.11)	< 0.001
Baseline and follow-up predictors		
L-dopa vs. ropinirole therapy	0.52 (0.35–0.79)	0.002
Latest ADL score	1.15 (1.11–1.19)	< 0.001

CI, confidence interval; ADL, activities of daily living.



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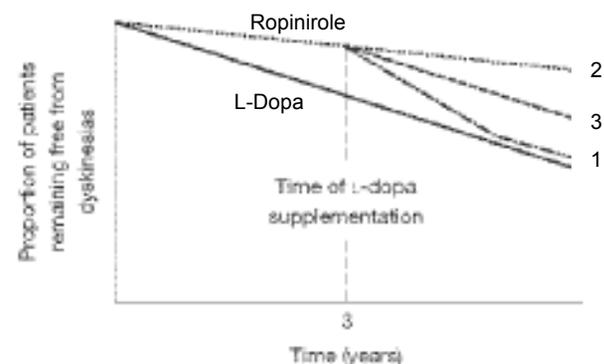


FIG. 4. Schematic representation of the possible outcomes (numbers 1–3 in the figure) in the survival analyses for dyskinesias after L-dopa supplementation (see text for details).

- 1- disease progression sole cause
- 2- neuroprotection by ropinirole
- 3- sparing of levodopa



Ten-Year Follow-Up of Parkinson's Disease Patients Randomized to Initial Therapy with Ropinirole or Levodopa

Robert A. Hauser, MD,^{1*} Olivier Rascol, MD, PhD,² Amos D. Korczyn, MD,³ A. Jon Stoessl, MD,⁴
Ray L. Watts, MD,⁵ Werner Poewe, MD,⁶ Peter P. De Deyn, MD,⁷ and Anthony E. Lang, MD⁸

- Over 10 years, the strategy of initiating treatment with ropinirole provided comparable long-term control of PD signs and symptoms, with a longer time to the development of dyskinesia, a lower incidence of dyskinesia, and a lower incidence of at least moderate wearing off.
- However, a clear functional benefit related to the lower incidence of motor complications in the ropinirole group was not demonstrated, as the incidence of disabling dyskinesia, and changes in Quality Of Life and Clinical Global Impression scores, were not significantly different between groups.



Born Again...

“Finally, from a global clinical perspective, it is obvious that dyskinesias are not the sole difficulty faced by patients when their disease is progressing. Consequently, the present results focusing on dyskinesias should be placed in the context of the entire spectrum of the clinical problems posed by progressing PD, especially when one discusses the overall management of this disease, considering the great efficacy of L-dopa on motor symptoms and its lower propensity to induce hallucinations, somnolence, and leg edema than the agonists.”

Rascol et al., Mov Disord 2006



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Pramipexole vs Levodopa as Initial Treatment for Parkinson Disease

A Randomized Controlled Trial

Parkinson Study Group
JAMA, 2000

Table 2. Treatment Effects on Dopaminergic End Points*

End Points	No. (%)		HR (95% CI)†	P Value
	Pramipexole (n = 151)	Levodopa (n = 150)		
First dopaminergic complications‡	42 (27.8)	76 (50.7)	0.45 (0.30-0.66)	<.001
Wearing off	36 (23.8)	57 (38.0)	0.57 (0.37-0.88)	.01
Dyskinesias	15 (9.9)	46 (30.7)	0.33 (0.18-0.60)	<.001
On-off fluctuations	2 (1.3)	8 (5.3)	0.27 (0.06-1.32)	.11

*All analyses are stratified by enrolling investigator.

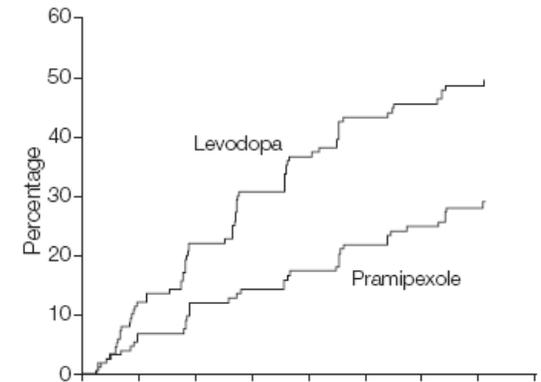
†HR indicates hazard ratio; CI, confidence interval. The HR is the ratio of the risk of reaching the end point per unit of time for patients assigned to initially receive pramipexole treatment to the corresponding risk for patients assigned to initially receive levodopa treatment.

‡Defined as first occurrence of wearing off, dyskinesia, or on-off fluctuations.

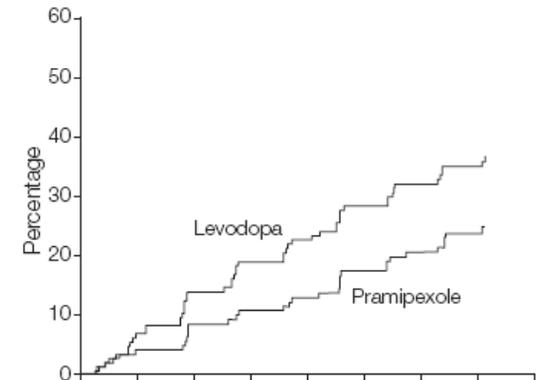


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A Patients Experiencing First Dopaminergic Complication



B Patients Experiencing Wearing Off



C Patients Experiencing Dyskinesias

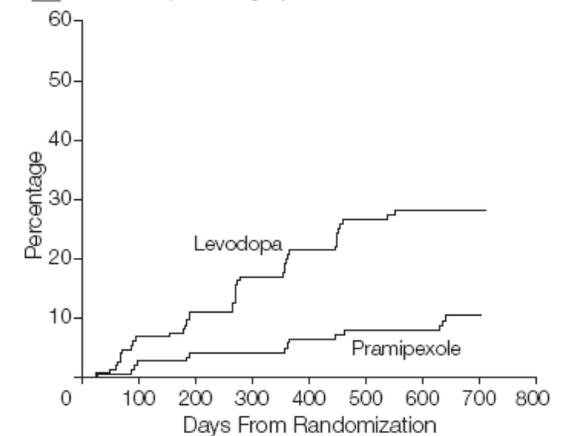
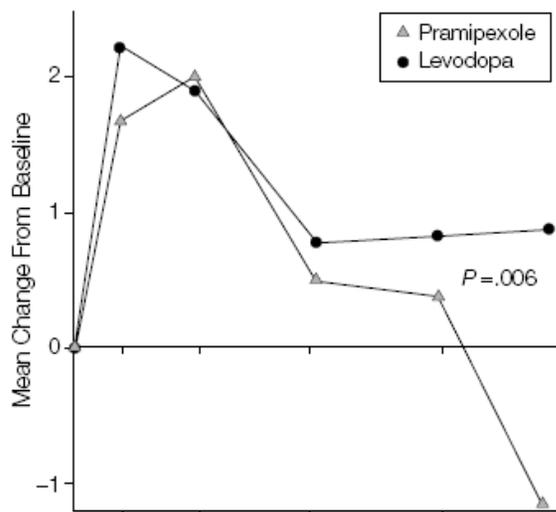


Table 4. Mean Changes From Baseline to Month 23.5 in Unified Parkinson's Disease Rating Scale (UPDRS) Scores*

Variable	Pramipexole (n = 151)	Levodopa (n = 150)	Difference in Treatments (95% CI)†	P Value
Total UPDRS	4.5 (12.7)	9.2 (10.8)	-5.0 (-7.6 to -2.4)	<.001
Motor	3.4 (8.6)	7.3 (8.6)	-3.9 (-5.7 to -2.1)	<.001
ADL	1.1 (4.5)	2.2 (3.2)	-1.4 (-2.2 to -0.5)	.001
Mental	0.0 (1.6)	-0.2 (1.2)	0.1 (-0.2 to 0.3)	.72

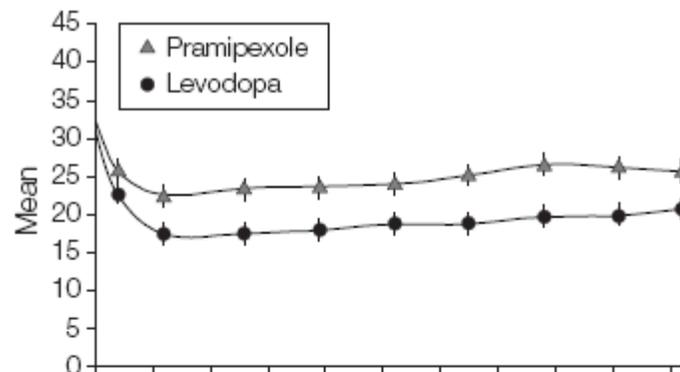
*Values are expressed as mean (SD). Positive values indicate improvement. ADL indicates activities of daily living.
 †Difference in treatment is the difference in mean change between the groups (pramipexole minus levodopa) and is adjusted for investigator effects and the baseline value of the outcome variable in an analysis of covariance model.

A Parkinson's Disease Quality of Life Scores

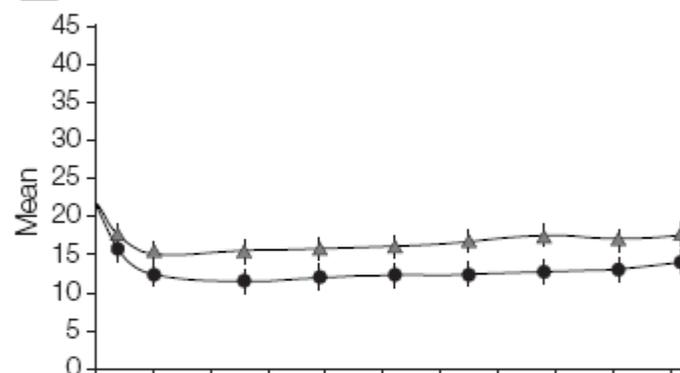


Pramipexole use was associated with a greater likelihood of somnolence, hallucinations, and edema.

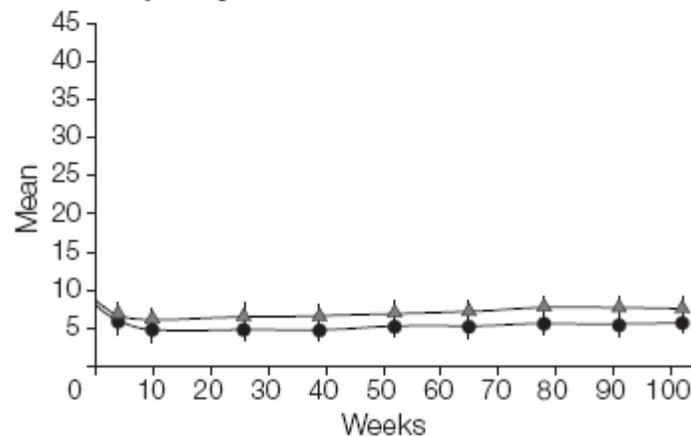
A Unified Parkinson's Disease Rating Scale Total



B Unified Parkinson's Disease Rating Scale Motor



C Unified Parkinson's Disease Rating Scale Activities of Daily Living



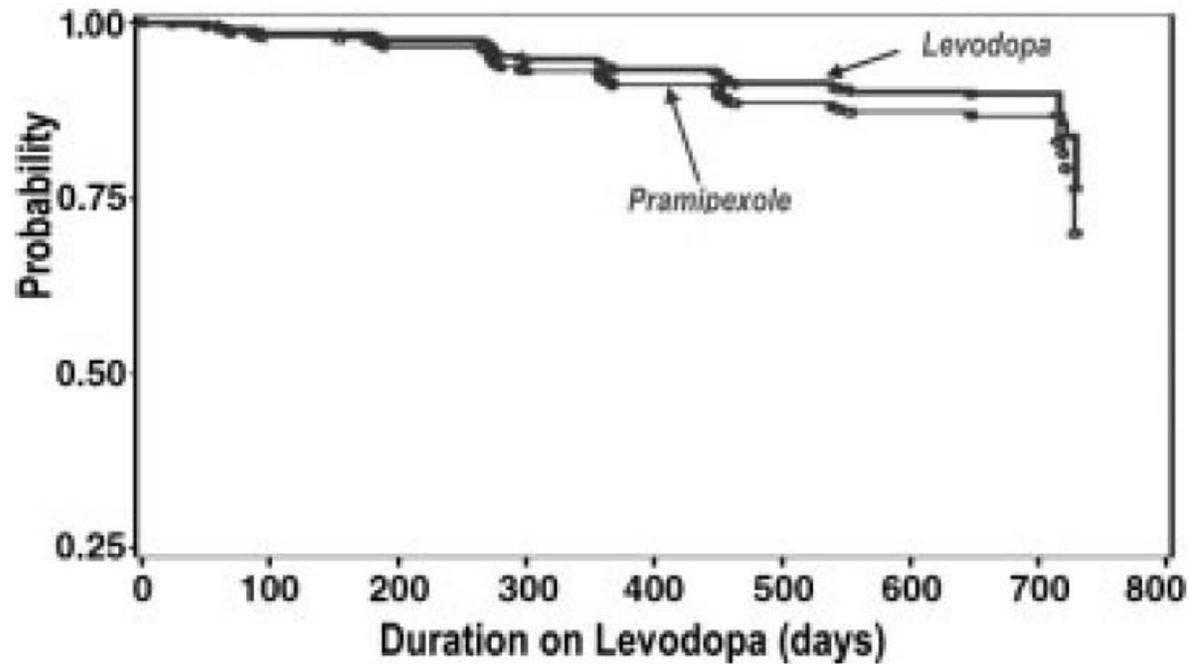


FIG. 1. Probability of not having dyskinesias onset throughout time on levodopa (adjusted for center, levodopa dose, and duration of Parkinson's disease diagnosis).

Incidence of dyskinesias after initiation of levodopa among subjects with PD initially treated with pramipexole was not significantly different (neither better nor worse) from that of those who only received levodopa, after adjusting for years since diagnosis and the daily levodopa dosage. Although initial treatment with pramipexole (vs. levodopa) significantly delays the onset of dyskinesias, this appears to be primarily through a levodopa-delaying effect rather than a protective effect.



Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease

- 3 year outcomes: BMJ 1993
 - All better than baseline
 - Levodopa arms more efficacious and with less adverse effects than 3, but with more motor fluctuations and dyskinesia
- 10 year outcomes: Neurology 2001
 - Levodopa more efficacious and with less adverse effects than brom
 - No group difference for moderate-severe dyskinesia
- 14 year outcomes: Neurology 2008
 - Initial Rx with bromocriptine did not reduce mortality or motor disability. The initially reduced frequency in motor complications was not sustained.
 - No evidence of a long-term benefit or clinically relevant disease-modifying effect with initial dopamine agonist treatment



COMT Inhibitors in De Novo PD

- STRIDE-PD (**ST**alevo **R**eduction in **D**yskinesia **E**valuation) ongoing
- No study results published/presented yet
- In fluctuators, tolcapone or entacapone decreased “off” time and increased dyskinesia, which could be managed by decreasing levodopa.



Continuous Dopaminergic Stimulation: Is It the Answer to the Motor Complications of Levodopa?

John G. Nutt, MD

Movement Disorders
Vol. 22, No. 1, 2007, pp. 1–9

*Northwest PADRECC, Portland VAMC, and Parkinson Center of Oregon,
Oregon Health & Science University, Portland, Oregon, USA*

- Conventional wisdom: CDS is desirable because it is physiological and will prevent or reverse motor complications and particularly dyskinesia.
- CDS hypothesis based on several unproven assumptions:
 - CDS does not mimic the function of the dopaminergic system in normal brain.

Tonic Dopaminergic Tone?



PRO: 1) Dopaminergic neurons fire tonically during motor tasks in monkeys (DeLong et al, 1983).

CON: 1) Increased dopamine turnover and extracellular dopamine in rats during exercise (Freed 1985, Hatton 1994, Meeusen 1997).

2) Decreased raclopride binding in putamen contralateral to moving limb in humans (Ouchi 2002) or while playing a video game (Goerendt).

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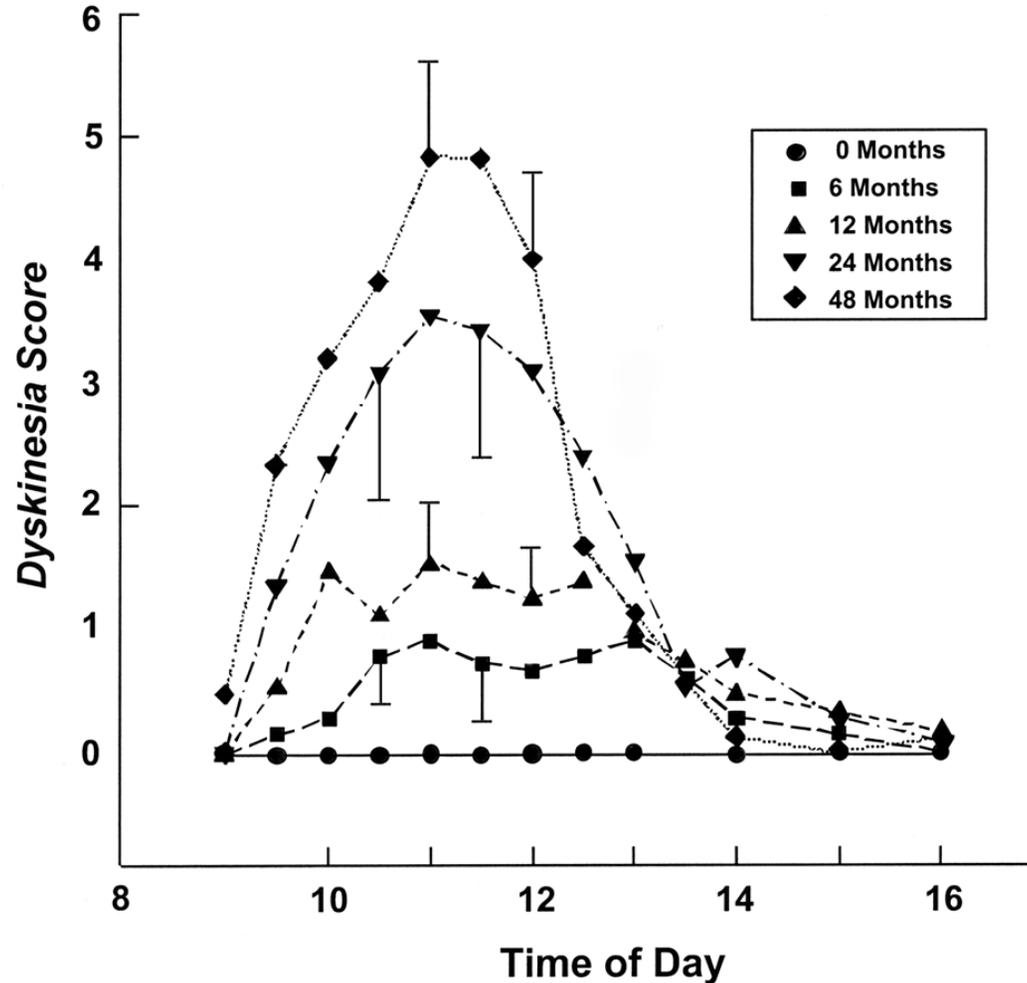
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CDS hypothesis based on several unproven assumptions:

- CDS does not mimic the function of the dopaminergic system in normal brain.
- Although dyskinesia may represent sensitization, motor fluctuations (wearing-off) are more compatible with tolerance than sensitization.
 - Sensitization to L-dopa is not uniformly bad or undesirable. Large intermittent, levodopa doses better for building long duration response
- Motor effect and dyskinesia not dissociable.
 - Sensitization probably increases the severity and reduces latency, but doesn't change threshold (increased levodopa dose does not cause these).

Development of Dyskinesia Over First 4 Years of L-DOPA



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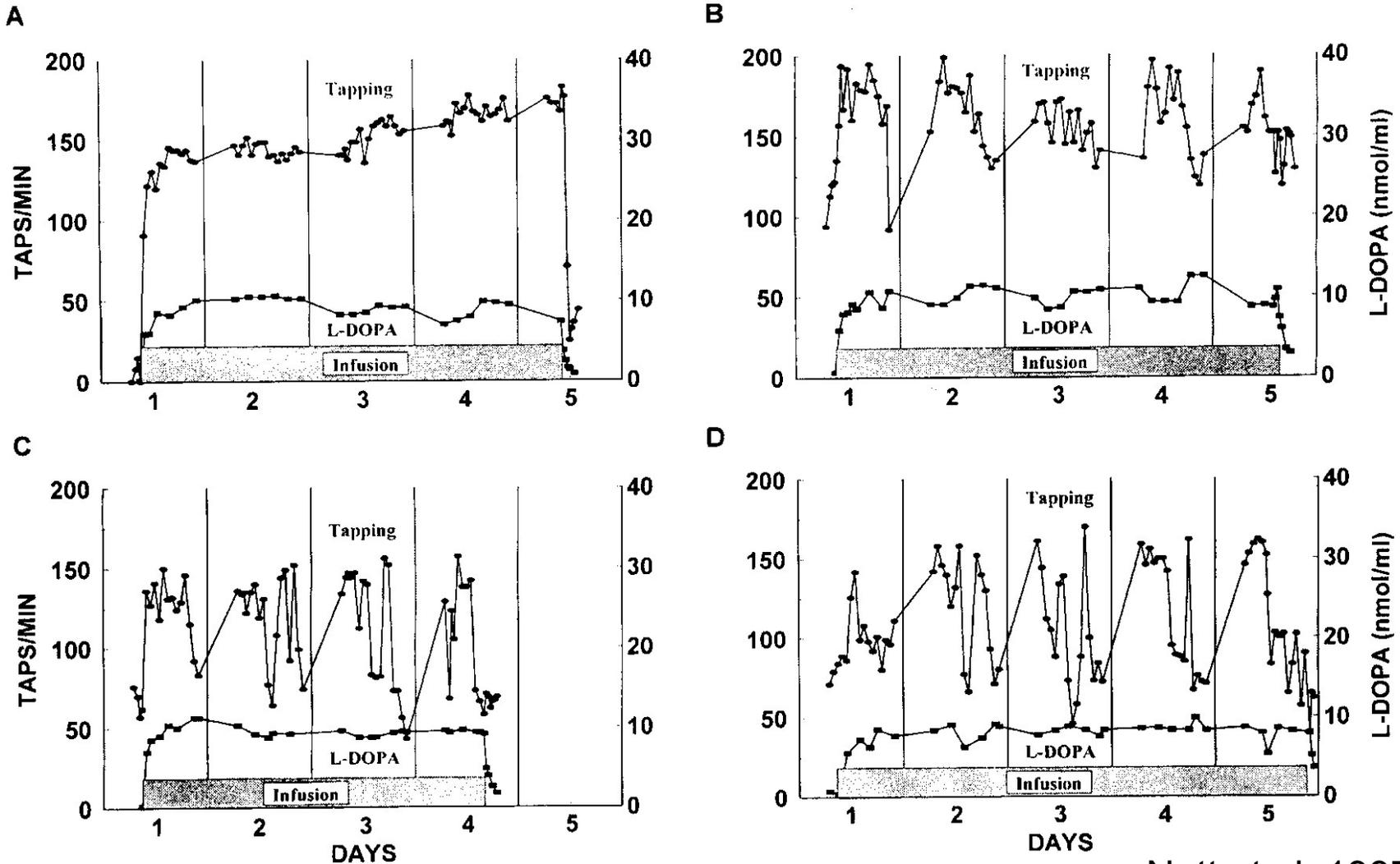
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Motor Fluctuations During Continuous IV L-DOPA



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 - The benefits of CDS on *off* time are likely due to do pharmacokinetic effects, and probably do not require pharmacodynamic effects (reversal of supersensitivity).
 - There are no robust randomized clinical trials that test the effects of CDS on dyskinesia or motor fluctuations.

CLOSING STATEMENT

There is not a continuous dopaminergic stimulation and a pulsatile dopaminergic stimulation - there's the physiologic dopaminergic stimulation. And, we are not there yet.



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CLOSING STATEMENT

There is not a continuous dopaminergic stimulation and a pulsatile dopaminergic stimulation - there's the physiologic dopaminergic stimulation. And, we are not there yet.

We may not agree on “CDS”, but surely we can agree on providing the best care for our patients. The reality of motor fluctuations may be different for older folks than for those young patients plagued by severe dyskinesia, but don't tell me we can't treat old disabled patients with levodopa while we try different alternatives on young patients at risk for severe fluctuations.



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CDS is an eloquent concept which can do great things for PD patients in the years ahead. But eloquence is no substitute for a record — when we treat PD patients with tough problems.



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VA PD Consortium, we cannot turn back. Not with so much research to be done, and so many veterans with PD to care for. At this moment, in this debate, we must pledge once more to march into the future. Let us keep that promise - that scientific promise - to judge the merits of “CDS” in well designed, robust, randomized clinical trials with relevant outcome measures.



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I am Ergun Uc and I approve this message.



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