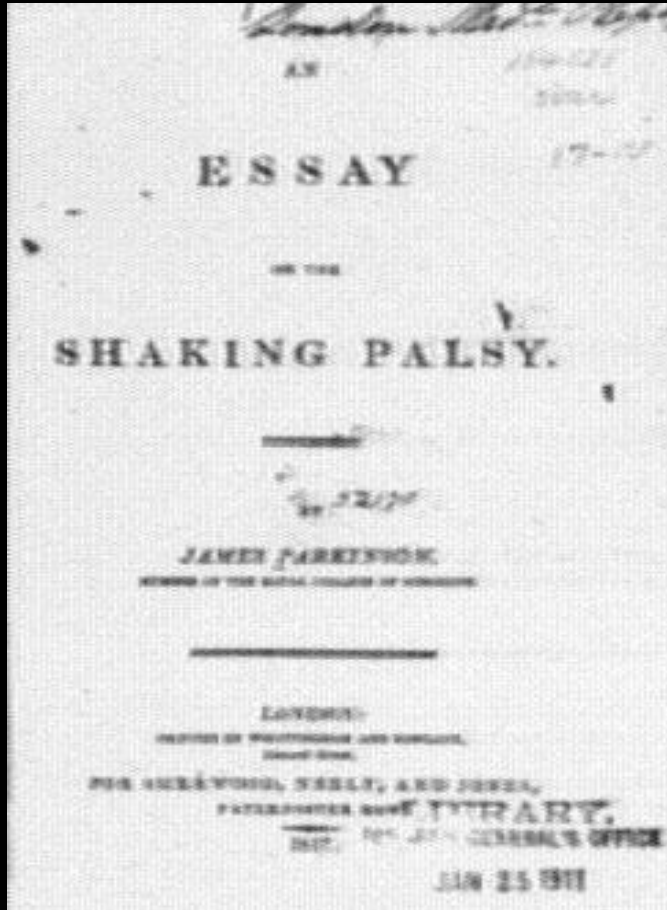




Novità terapeutiche nel morbo di Parkinson

Giuseppe Bellelli

The history of PD treatment



- 1817, James Parkinson provided the first detailed description in his monography "An essay on the Shaking Palsy"
- 1960, Ehringer discovered dopamine deficiency in corpus striatum and SN
- 1961, Hornykiewicz & Birkmayer and the antiparkinsonian effect of L-Dopa
- 1967, Cotzias et al. efficacy of oral L-dopa for the treatment of chronic Parkinsonism

New pharmacologic horizons in the treatment of Parkinson disease

- Parkinsons' disease (PD) is a progressive neurodegenerative condition characterized by resting tremor, bradykinesia, rigidity and postural instability as result of loss of dopaminergic neurons in the substantia nigra pars compact (**SN pc; area A-9**)
- As the disease progresses, neuron degeneration continues, involving other systems, including mesocortical dopaminergic cells (**area A-10**), noradrenergic (**locus coeruleus**), serotonergic (**dorsal raphe nuclei**), cholinergic (**nucleus basalis of Meynert**), histaminergic, and peptidergic systems

New pharmacologic horizons in the treatment of Parkinson disease

- According to the staging proposed by Braak et al, at first pathology is confined to the medulla (dorsal motor nucleus of the vagus and intermediate reticular region of the medulla).
- SN degeneration represents an intermediate stage
- Later there is involvement of the forebrain and ultimately of the neocortex.
- *Widespread multisystem nature of the neurodegenerative process of PD and explains the appearance of new motor (gait disturbances, disequilibrium, falls, camptocormia, swallowing, and speech difficulties) and non motor (autonomic dysfunction, sleep disorders, pain, depression, dementia) symptoms that are only partially responsive to or nonresponsive to dopaminergic treatment*

Sommario

- Motor symptoms
 - Neuroprotective agents
 - Symptomatic therapy
 - DBS
 - Rehabilitation
- Non motor symptoms
 - Depression
 - Cognitive deficits

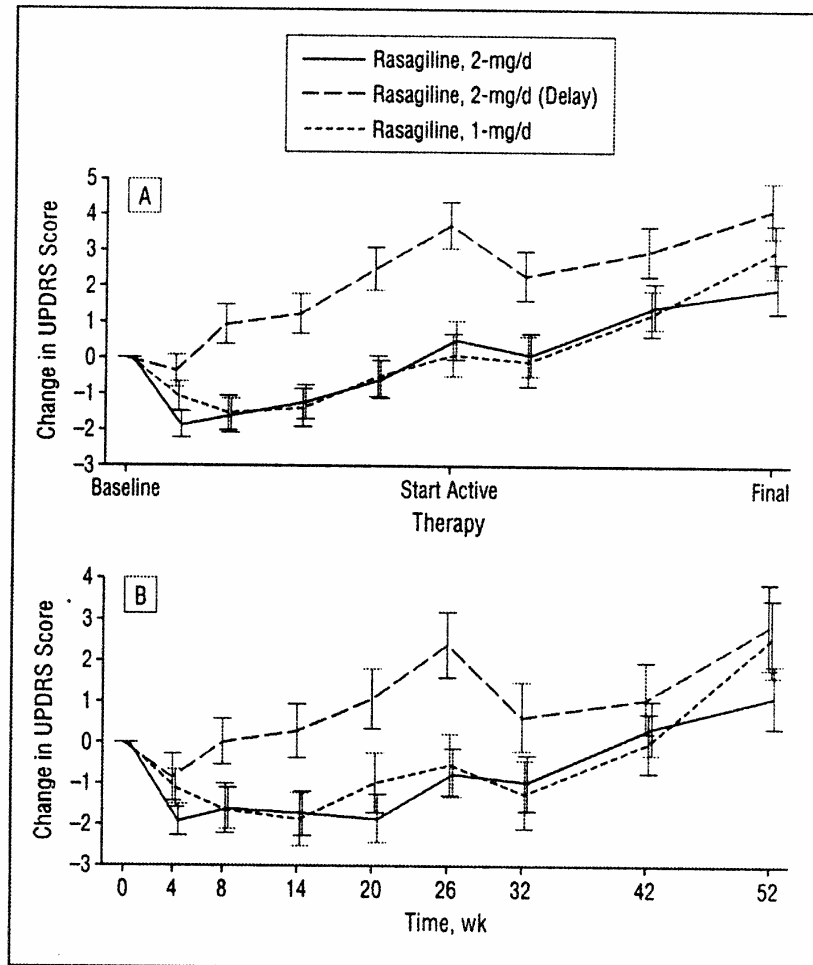
Potential neuroprotective drugs (CINAPS)

- Caffeine Adenosine antagonist
- Coenzyme Q 10 Antioxidant/mitochondrial enhancer
- Creatine Mitochondrial enhancer
- Estrogen Undetermined /multiple
- GPI 1485 Trophic factor
- GM-1 ganglioside Trophic factor
- Mynocycline Anti-inflammatory/anti-apoptotic
- Nicotine Unknown
- Pramipexole Antioxidant/vesicular trafficking
- Ropinirole Antioxidant
- Rasagiline Antioxidant/anti-apoptotic
- Selegiline Antioxidant/anti-apoptotic

PD Neuroprotection: Vitamin E and Selegiline

- DATATOP trial (1993)
 - Randomized, double-blind, prospective
 - 800 patients randomized to a dose of 2,000 IU of vitamin E/day or placebo
 - Followed for 14 ± 6 months
 - Primary endpoint: onset of disability requiring use of levodopa
 - No difference between **tocopherol** and placebo groups in the average time to required levodopa (hazard ratio 0.91, 95% CI .74 to 1.12)
 - **Selegiline** was able to delay the requirement for levodopa by 9 months compared to placebo (symptomatic effect?)

PD Neuroprotection: Rasagiline



- Irreversible and selective MAO-B inhibitor with a 5-10 greater potency than selegiline
- “Delayed-started” trial to assess the neuroprotective effect of rasagiline
- 371 subjects treated with rasagiline 2 and 1 mg/day for 12 months showed better UPDRS score than subjects whose treatment was delayed for 6 months ($P=.001$ and $P=.005$, respectively)
- Inconclusive results

Effects of Coenzyme Q₁₀ in Early Parkinson Disease

- **Conclusions:** Coenzyme Q₁₀ was safe and well tolerated at dosages up to 1200 mg/d. less disability developed in subjects assigned to Coenzyme Q₁₀ than in those assigned to placebo, and the benefit was greatest in those receiving the highest dosage. Coenzyme Q₁₀ appears to slow the progressive deterioration of function in PD but these results needs to be confirmed in a larger study

Slowing Parkinson's disease progression

Recent dopamine agonist trials

J. Eric Ahlskog, PhD, MD

Abstract—In recent clinical trials, chronic treatment of patients with PD with pramipexole or ropinirole was associated with a slower decline of imaged striatal dopaminergic signal, compared to levodopa monotherapy. Although this could reflect slowed progression of PD, equally plausible is a pharmacologic effect on proteins that interact with the imaging radioligands. To date, there is no compelling evidence favoring dopamine agonists over levodopa; either is an appropriate choice for initial treatment of PD.

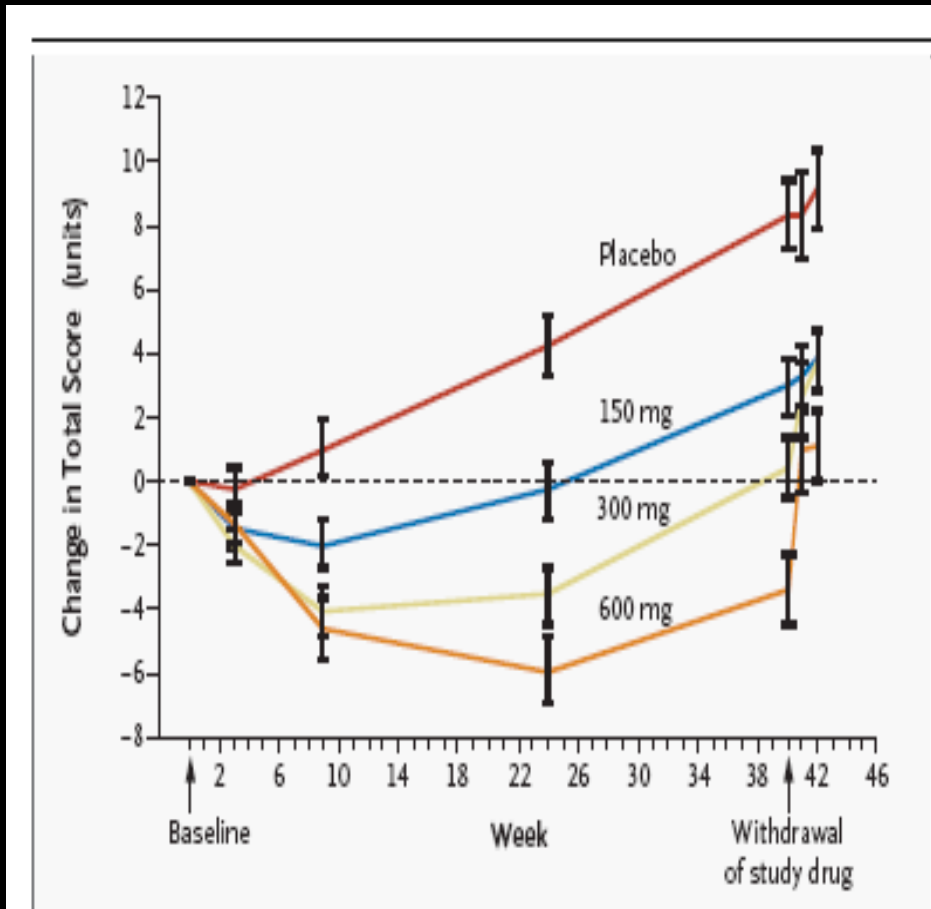
NEUROLOGY 2003;60:381–389

Recommendations for Neuroprotection

- There is insufficient evidence for neuroprotection (Level U):
 - Amantadine
 - Ropinirole
 - Pramipexole
 - NMDA receptor antagonist
 - Riluzole

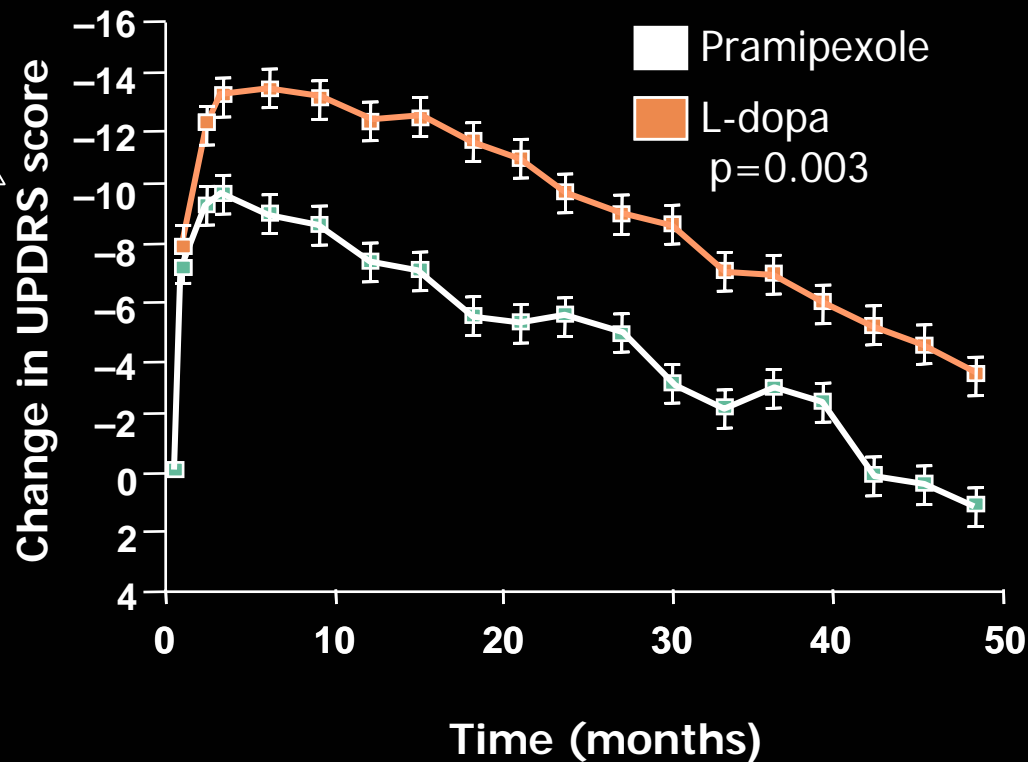
Symptomatic treatment of motor symptoms of PD

The efficacy of L-dopa is unsurpassed



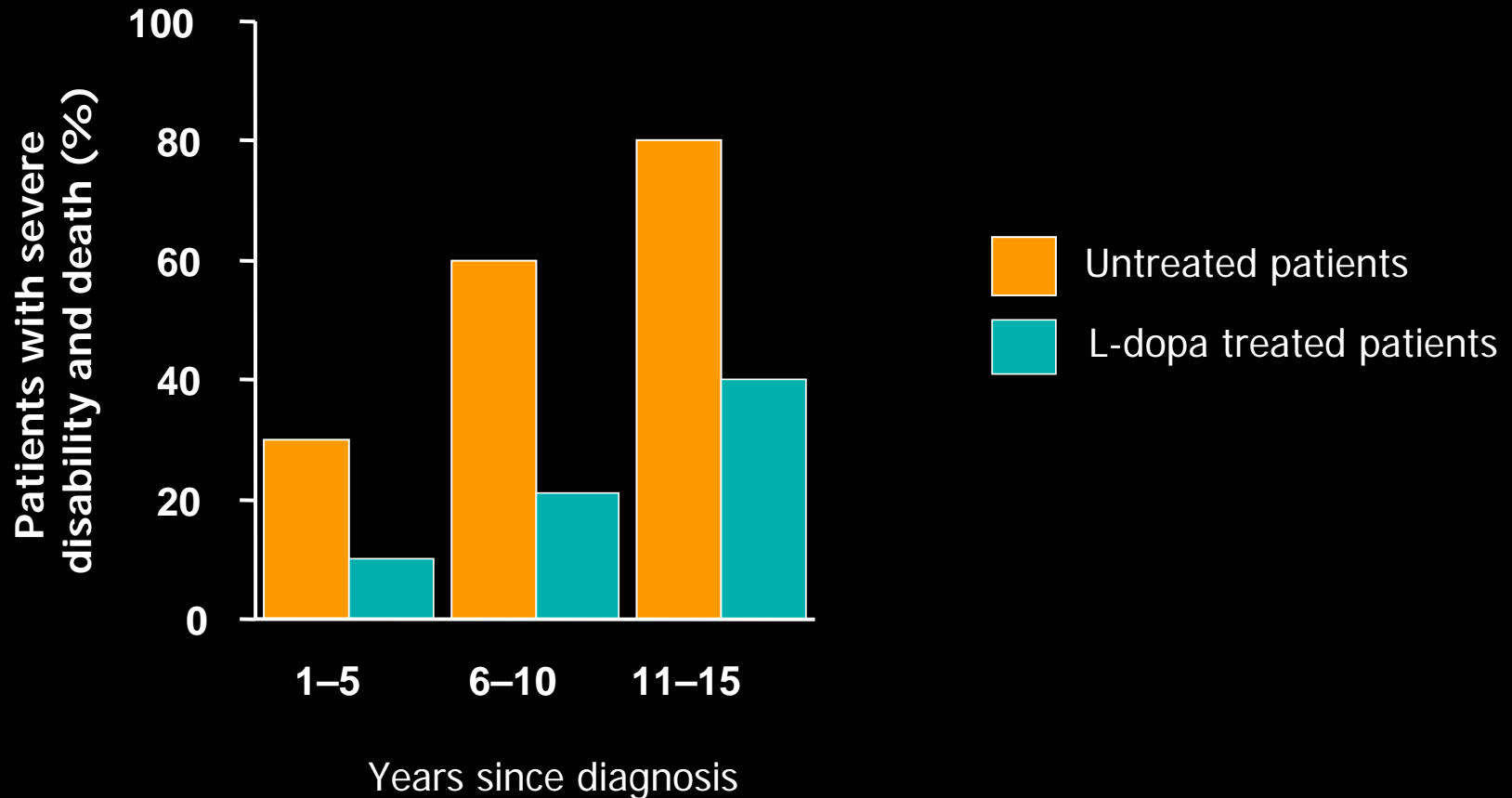
- Double-blinded, RCT
- 361 PD patients to placebo or L-dopa (150mg/day, 300 mg/day, or 600 mg/day)
- Primary outcome: masked assessment of change in UPDRS from baseline after 40 weeks of treatment and 2-week washout
- Patients randomized to all L-Dopa doses: significantly better UPDRS scores than patients on placebo
- Highest doses greatest benefit

L-Dopa è più efficace dal punto di vista sintomatologico rispetto ai dopamino-agonisti (CALM-PD study)



- Improvement with levodopa:
 - **5.9 points vs pramipexole** ($p=0.003$) on total UPDRS at 4 years
 - **4.48 points vs ropinirole** ($p=0.008$) on UPDRS motor subscale at 5 years
 - **2.9 points vs cabergoline** ($p<0.001$) on UPDRS motor subscale at 5 years

Il trattamento con L-dopa ha significativamente ridotto la mortalità associata al PD dal 1960 ad oggi



*Hoehn and Yahr, 1967;
Hoehn, 1983*

I problemi connessi all'uso di L-Dopa

- L-Dopa è tossica?
- L-Dopa accelera la perdita dei neuroni dopaminergici?
- L-Dopa favorisce la comparsa di fluttuazioni motorie e discinesie?
- Problemi associati con il rilascio pulsatile di L-Dopa

Levodopa

Is toxicity a myth?

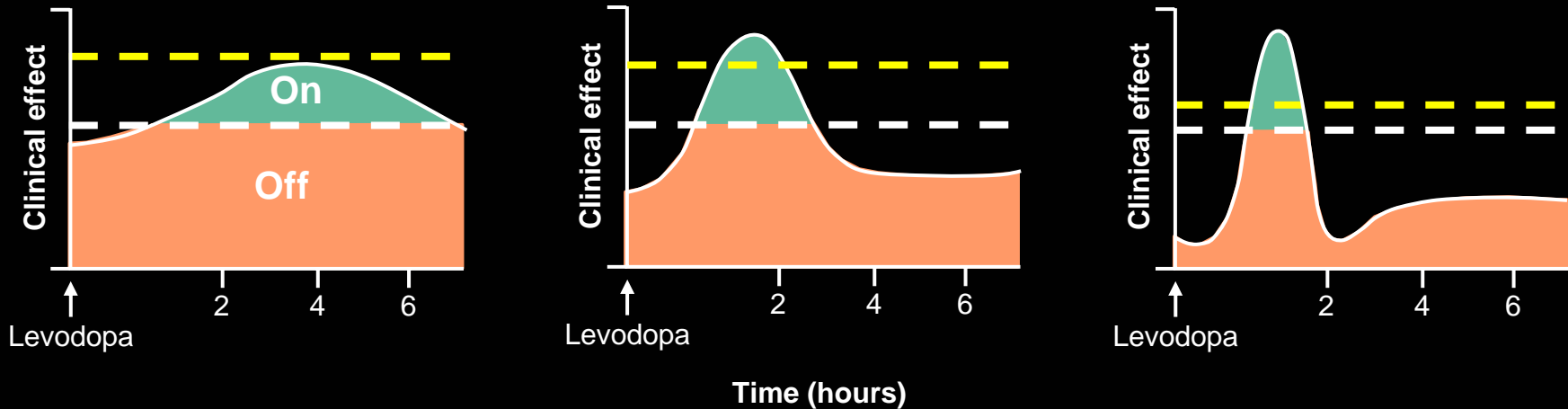
Y. Agid, MD, PhD

Article abstract—Whether a drug such as levodopa, which is prescribed for long periods, may be toxic is a legitimate and even indispensable question. The problem is no different from that posed by other drugs—such as calcium antagonists, antihypertensives, or hormones—normally prescribed for chronic diseases. What, however, is meant in this context by “toxic” (from the Greek *toxicon*, meaning poison)? Irrevocable damage such as cell loss should not be confused with reversible side effects resulting from cell dysfunction. Clinically or experimentally, levodopa has not been shown to accelerate neurodegeneration or cause permanent impairment of cell function in a manner that would result in irreversible side effects. These data have been reasonably well established in vivo in animals and humans, although preliminary studies suggesting that levodopa is a trophic factor remain unconfirmed. Like oxygen or calcium, levodopa can be toxic in vitro when it is present in high concentrations or in the absence of glial cells. However, glial cells are much more numerous than neurons in vivo, so these conditions cannot simply be extrapolated to three-dimensional brain structures in which protective interactions with the cellular environment abound. Because levodopa remains the most effective treatment available for Parkinson’s disease, questions regarding timing or manner of administration of the drug should arise not because levodopa is toxic to nerve cells, but because it causes reversible side effects. When the elementary rules of substitutive therapy to provide maximum comfort while limiting side effects are followed, we need not fear that levodopa is dangerous unless the contrary is proven.

Dyskinesias are related to L-dopa use?

- Chronic L-dopa is not toxic for remaining dopamine neurons, but instead promotes their recovery, in rats with moderate nigrostriatal lesions
 - Murer, et. al. Ann Neurol 1998; 43: 561-573.
- ELLDOPA study

La risposta a L-Dopa varia con il progredire della patologia



Early disease

- Smooth, long duration of clinical benefit
- Low incidence of dyskinesias

Mid-stage disease

- Diminished duration of clinical benefit
- Increased incidence of dyskinesias

Advanced disease

- Clinical response mirrors levodopa plasma pharmacokinetic profile
- 'On' time is associated with dyskinesias

--- Dyskinesia threshold
- - - Response threshold

Meccanismi che determinano l'insorgenza di complicanze motorie

La degenerazione progressiva dei neuroni dopaminergici determina una riduzione delle capacità di "storage" dopaminergico nello striato

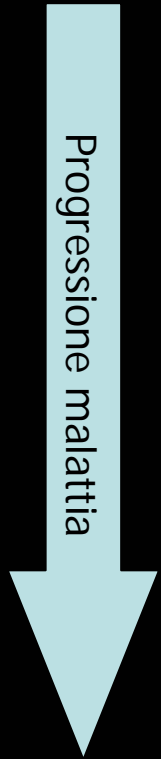


Fluttuazione dei livelli plasmatici di L-Dopa (perdita della capacità di buffer)



Stimolazione pulsatile dei recettori dopaminergici dello striato

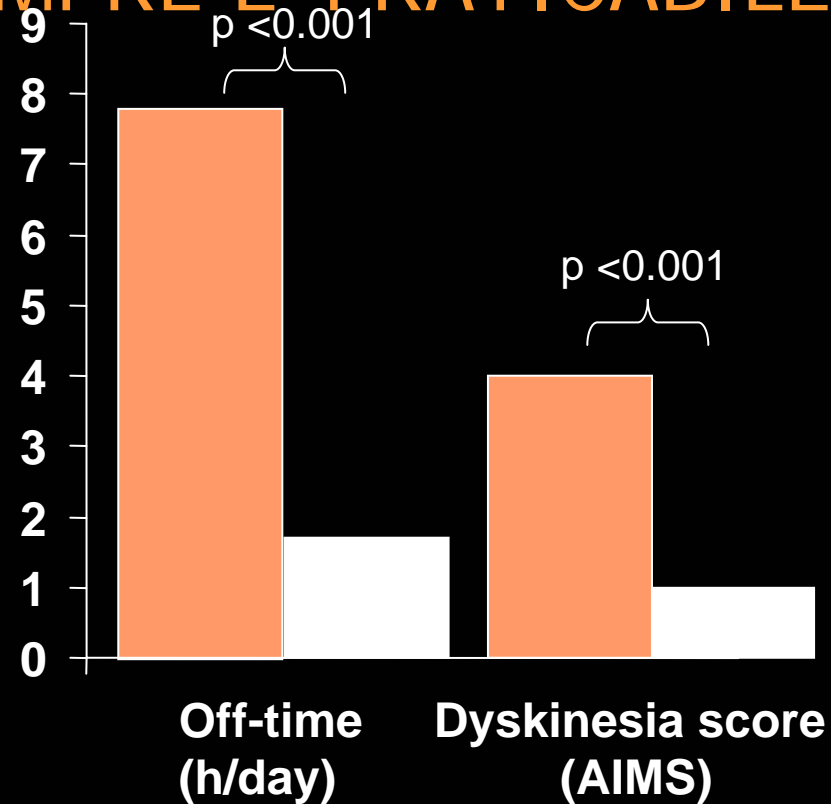
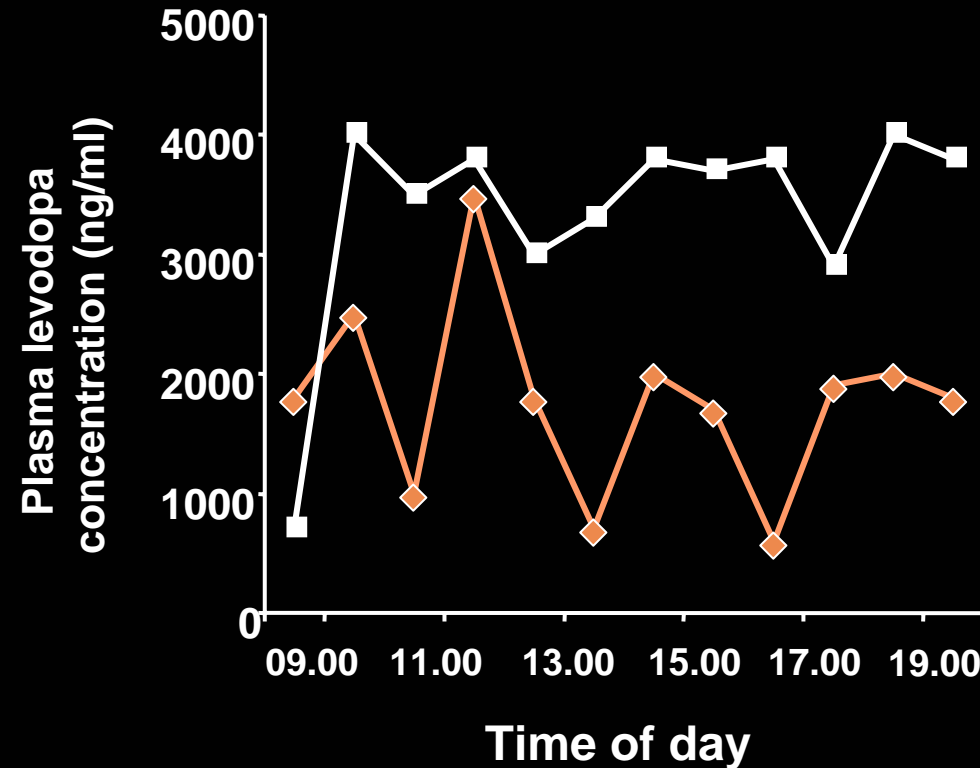
Progressione malattia



Continuous delivery of levodopa by infusion reverses motor complications

- ◆ Oral levodopa
- After 6 months levodopa infusion

MA L'INFUSIONE NON SEMPRE E' PRATICABILE



Complicanze motorie nel PD

- Fluttuazioni motorie
 - End of dose (wearing off)
 - Fluttuazioni motorie imprevedibili (fenomeni on-off)
 - Doses failure
 - Episodi di freezing
- Discinesie
 - Discinesie di picco dose
 - Discinesie difasiche D-I-D
 - Distonie

La L-Dopa fobia



“Levodopa phobia”: A new iatrogenic cause of disability in Parkinson disease

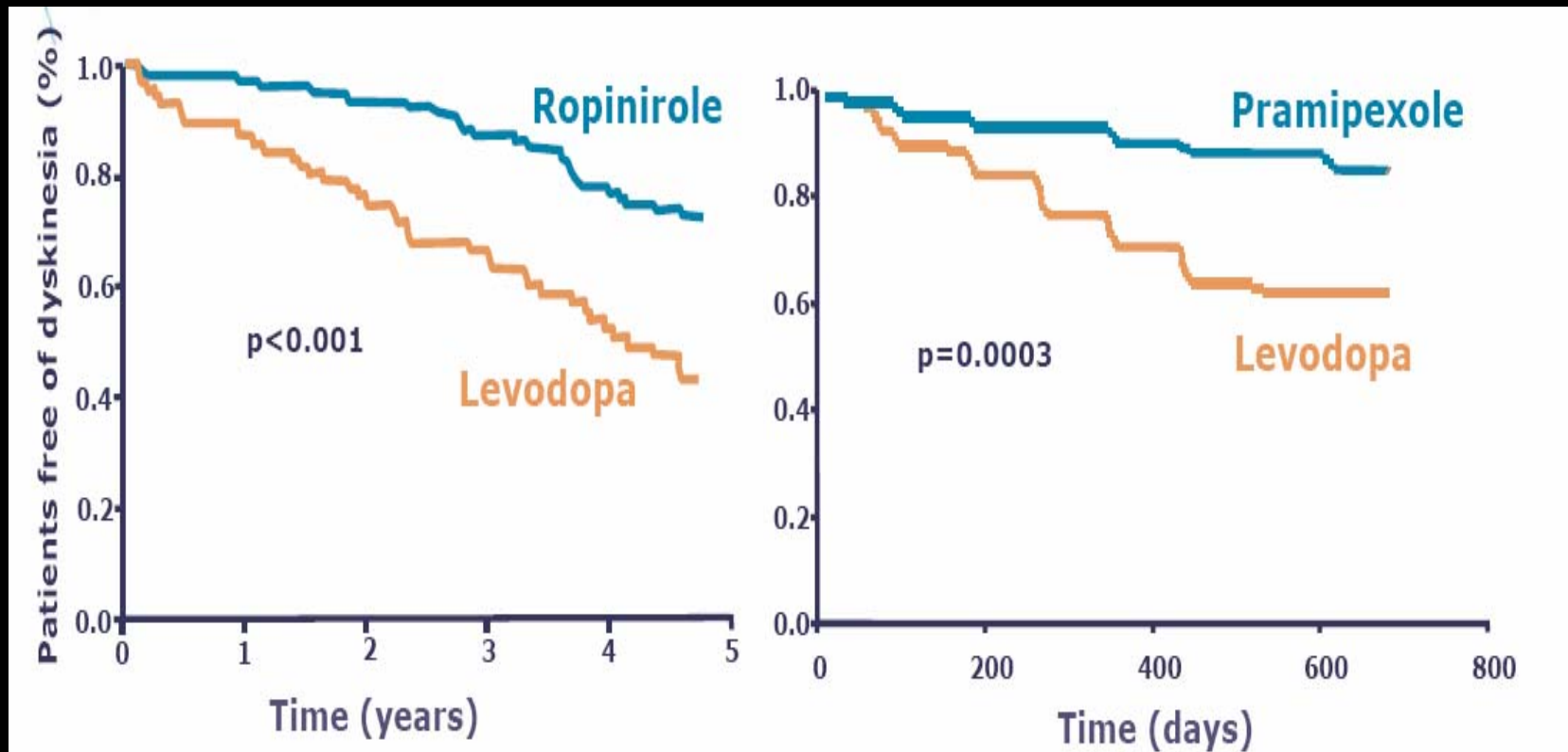
Roger Kurlan, MD

Two recent research directions have raised question about the role of levodopa in treating Parkinson disease (PD). First is evidence that levodopa is toxic in nigral neuronal cell cultures.¹ Second are clinical trials showing that compared to beginning therapy with a dopamine agonist, initial treatment with levodopa is associated with earlier appearance of dyskinesias and wearing-off fluctuations.^{2,3} There has been much publicity about these potential negative aspects of levodopa. I report two patients with PD who

became disabled because their treating neurologists were fearful of prescribing levodopa because of the widespread publicity.

Case reports. Case 1. A 72-year-old man had been diagnosed with PD 3 years earlier. He was initially treated with ropinirole and required steadily increasing dosages up to 24 mg/day. Due to ongoing bradykinesia and gait difficulties, amantadine 300 mg/day and deprenyl 10 mg/day were added. Visual hallucinations and episodes of confusion developed but resolved after discontinuation of amantadine and deprenyl. The patient was functionally disabled by unsteady gait with freezing, overall slowness, and impaired dexterity for daily activities such as dressing and eating and was referred to the University of Rochester PD Program by the treating neurologist “since there are no other medication op-

Insorgenza di discinesie nel PD



Le discinesie insorgono approssimativamente nel 50-75% dei pazienti con PD dopo 5-10 anni di trattamento con L-Dopa

Clinical Questions

1. Quali farmaci riducono i fenomeni off e che efficacia hanno?
2. Quali farmaci riducono le discinesie?
3. Il DBS riduce il time off, le discinesie, l'uso dei farmaci e migliora la funzione motoria?

4 options + 1

- Dopamine agonists
- MAO B inhibitors
- COMT inhibitors
- Sustained release Carbidopa/Levodopa

- Amantadine

Evidence: Dopamine Agonists

Author	Drug	Class	N	Study Duration	Decrease Off time Active	Decrease Off time Placebo
Olanow	Pergolide	I	189/187	24 week	32% (1.8 h)*	4% (0.2 h)
Lieberman	Pramipexole	I	181/179	32 week	31%*	7%
Guttman	Pramipexole	II	79/83	40 week	15% (2.5 h)*	3%
Rascol	Ropinirole	II	23/23	12 week	23%*	4%
Lieberman	Ropinirole	II	95/54	26 week	11.7%*	5%
Dewey	Apomorphine	II	20/9	4 week	34% (2 h)*	0%
Guttman	Bromocriptine	II	84/83	40 week	8%	3%
Steiger	Cabergoline	III	19/10	24 week	40% (2 h)*	18% (0.7 h)
Ahlskog	Cabergoline	III	17/10	24 week	59% (3.3 h)*	NS

Evidence: MAO B Inhibitors

Author	Drug	Class	N	Study Duration	Decrease Off time Active	Decrease Off time Placebo
PSG	Rasagiline (0.5 mg)	I	164/159	26 week	23% (1.4 h)*	15% (0.9 h)
PSG	Rasagiline (1.0 mg)	I	149/159	26 week	29% (1.8 h)*	15% (0.9)
Rascol	Rasagiline (1.0 mg)	I	231/229	18 week	21% (1.2 h)*	7% (0.4 h)
Waters	Orally Disintegrat Selegiline	II	94/46	12 week	32% (2.2 h)*	9% (0.6 h)
Golbe	Selegiline	III	50/46	6 week	NR	NR

Evidence: COMT Inhibitors

Author	Drug	Class	N	Study Duration	Decrease Off time Active	Decrease Off time Placebo
PSG	Entacapone	I	103/102	24 week	NR	NR
Rascol	Entacapone	I	227/229	18 week	21% (1.2 h)*	7% (0.4 h)
Poewe	Entacapone	II	197/104	24 week	25.8% (1.6 h)*	13.4% (0.9 h)
Rinne	Entacapone	II	85/86	24 week	23.6% (1.3 h)*	1.9% (0.1 h)
Fenelon	Entacapone	II	99/63	12 week	0.9 h	0.4 h
Rajput	Tolcapone (100 mg tid)	II	69/66	12 week	32% (2.3 h)	20% (1.4 h)
Rajput	Tolcapone (200 mg tid)	II	67/66	12 week	48% (3.2 h)*	20% (1.4 h)
Baas	Tolcapone (100 mg tid)	II	60/58	12 week	31.5%*	11%
Baas	Tolcapone (200 mg tid)	II	59/58	12 week	26.20%	11%

Evidence: Sustained Release Carbidopa/Levodopa

Author	Drug	Class	N	Study Duration	Decrease Off time
Jankovic	Carbidopa/levodopa CR/IR	III	20	16 week	NS
Hutton	Carbidopa/levodopa CR/IR	III	21	24 week	NS
Ahlskog	Carbidopa/levodopa CR/IR	III	28	16 week	NS
Lieberman	Carbidopa/levodopa CR/IR	III	24	16 week	NS

ORIGINAL ARTICLE

Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease

Renzo Zanettini, M.D., Angelo Antonini, M.D., Gemma Gatto, M.D.,
Rosa Gentile, M.D., Silvana Tesei, M.D., and Gianni Pezzoli, M.D.

BMJ

Pathological gambling in Parkinson's disease

Sui H Wong and Malcolm J Steiger

BMJ 2007;334:810-811

doi:10.1136/bmj.39176.363958.80

Recommendations for Patients with PD and Motor Fluctuations

- Entacapone and rasagiline should be offered to reduce off time in PD patients (Level A)*
- Pergolide, pramipexole, ropinirole, and tolcapone should be considered to reduce off time (Level B)*
 - Tolcapone (hepatotoxicity) and pergolide (valvular fibrosis) should be used with caution and require monitoring
- Apomorphine, cabergoline, and selegiline may be considered to reduce off time (Level C)*
- Sustained release carbidopa/levodopa and bromocriptine may be disregarded to reduce off time (Level C)*

*Strength indicates level of supporting evidence, not hierarchy of efficacy

Relative Efficacy of Medications in Reducing Off Time

- Rasagiline similar to entacapone
- Bromocriptine similar to pramipexole
- Tolcapone similar to pergolide
- Cabergoline similar to bromocriptine
- Tolcapone similar to entacapone
- Ropinirole possibly superior to bromocriptine

- Many of these studies not powered to demonstrate superiority of one drug over another
- Other than comparisons of ropinirole and bromocriptine, there is insufficient evidence to conclude which one agent is superior to another in reducing off time

Recommendations for Medications that Reduce Dyskinesia

- Amantadine may be considered for PD patients with motor fluctuations to reduce dyskinesia (Level C)
- Insufficient evidence to support or refute the efficacy of clozapine in reducing dyskinesia (Level U)

Randomized, Double-blind, Placebo-Controlled Trial on Symptomatic Effects of Coenzyme Q₁₀ in Parkinson Disease

Alexander Storch, MD; Wolfgang H. Jost, MD; Peter Vieregge, MD; Jörg Spiegel, MD; Wolfgang Greulich, MD; Joachim Durner, MD; Thomas Müller, MD; Andreas Kupsch, MD; Henning Henningsen, MD; Wolfgang H. Oertel, MD; Gerd Fuchs, MD; Wilfried Kuhn, MD; Petra Niklowitz, MD; Rainer Koch, PhD; Birgit Herting, MD; Heinz Reichmann, MD; for the German Coenzyme Q₁₀ Study Group

- Conclusions: Nanoparticulate CoQ₁₀ at a dosage of 300 mg/d is safe and well tolerated and leads to plasma levels similar to 1200 mg/d of standard formulations. **Add-on CoQ₁₀ does not display symptomatic effects in midstage Parkinson disease**



Advanced Parkinson disease treated with rotigotine transdermal system

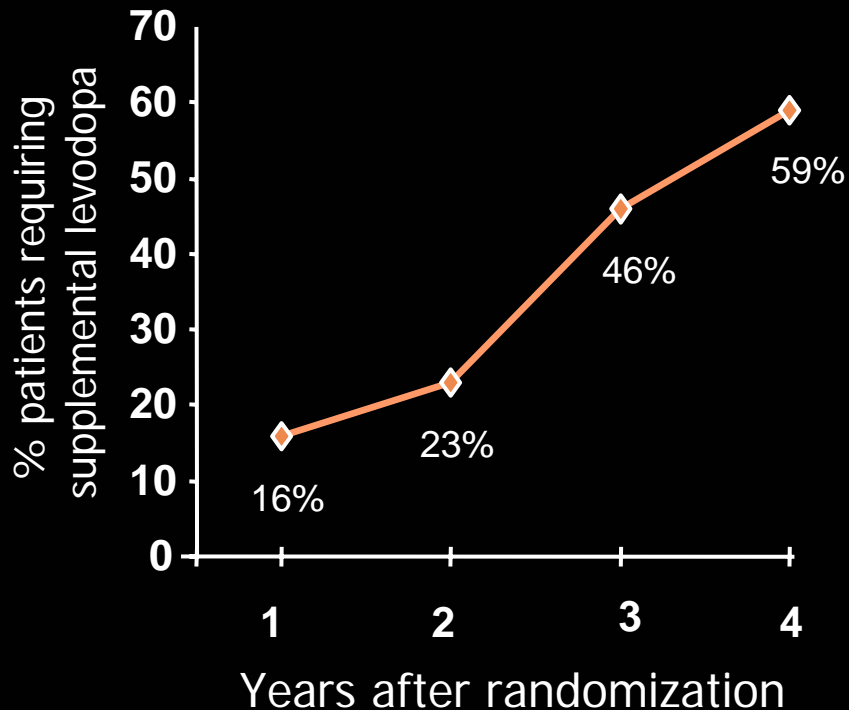
PREFER Study

Peter A. LeWitt, MD; Kelly E. Lyons, PhD; and Rajesh Pahwa, MD; on behalf of the SP 650 Study Group*

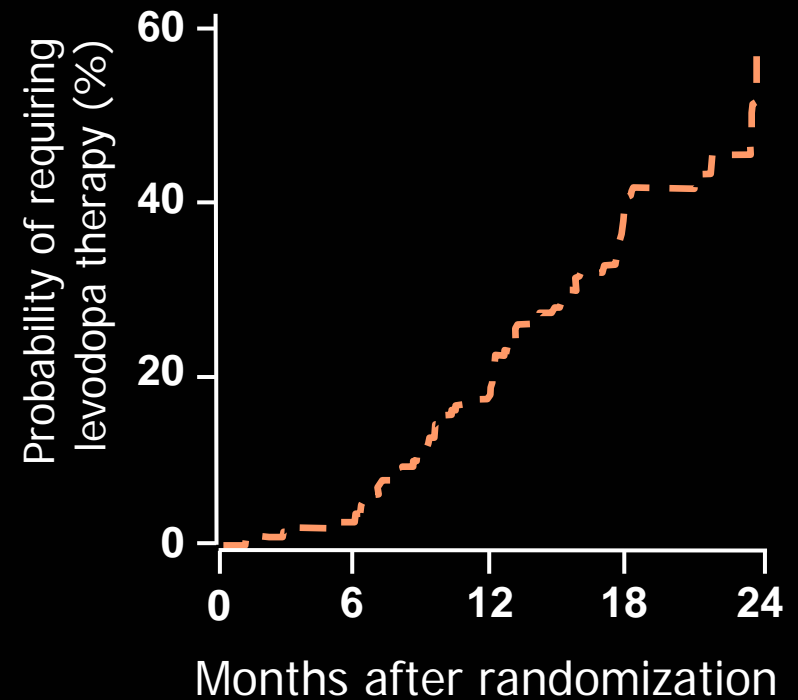
- **Conclusions:** Transdermal rotigotine significantly improved "off " time in subjects with Parkinson disease not optimally controlled with levodopa and was safe and well tolerated, with typical dopaminergic side effects and occasional application site reactions

Il problema: molti pazienti richiedono levodopa per il controllo dei sintomi

Need for L-dopa in patients initiated with dopamine agonist (pramipexole)

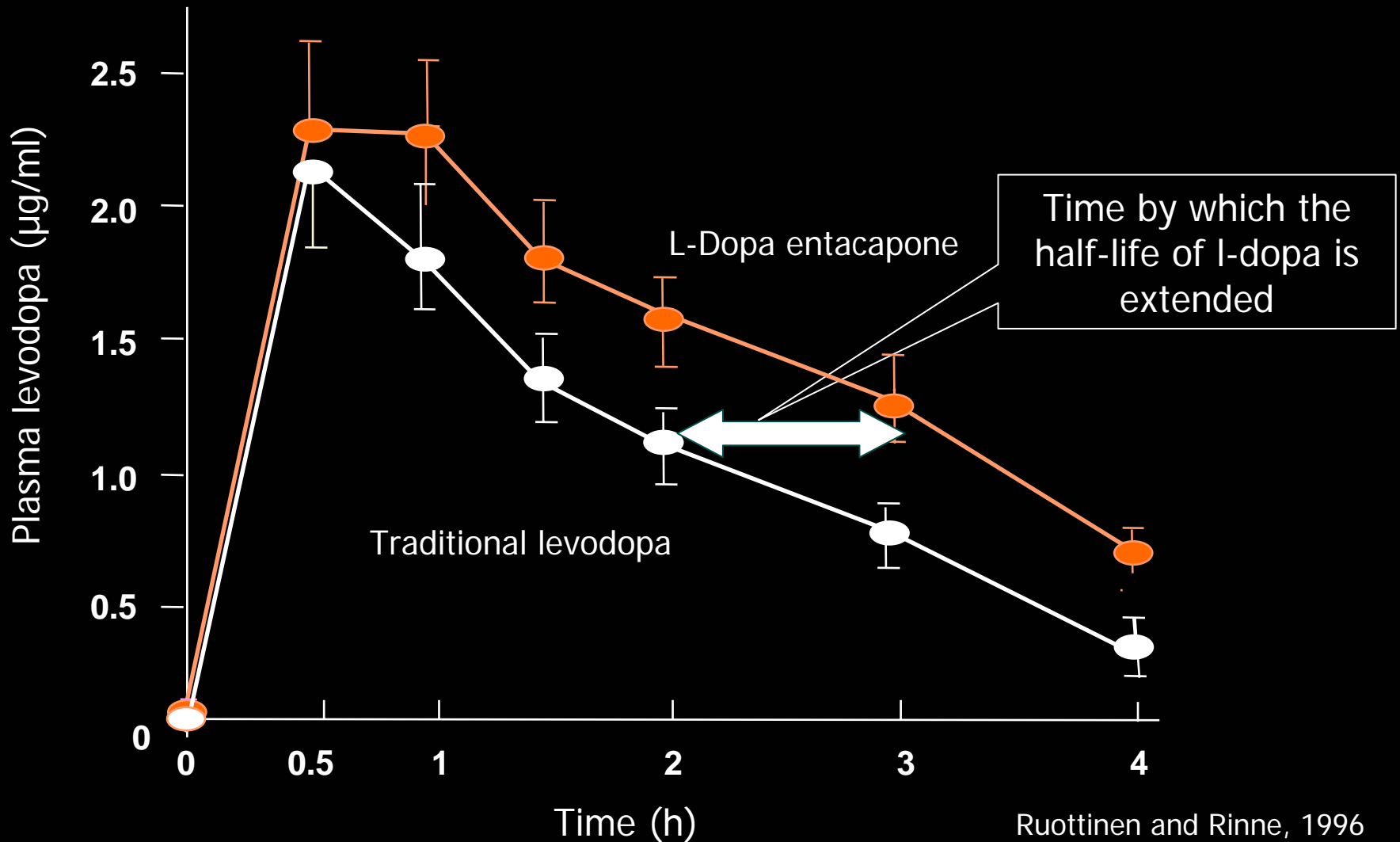


Need for L-dopa in patients initiated with monoamine oxidase inhibitor (selegiline)

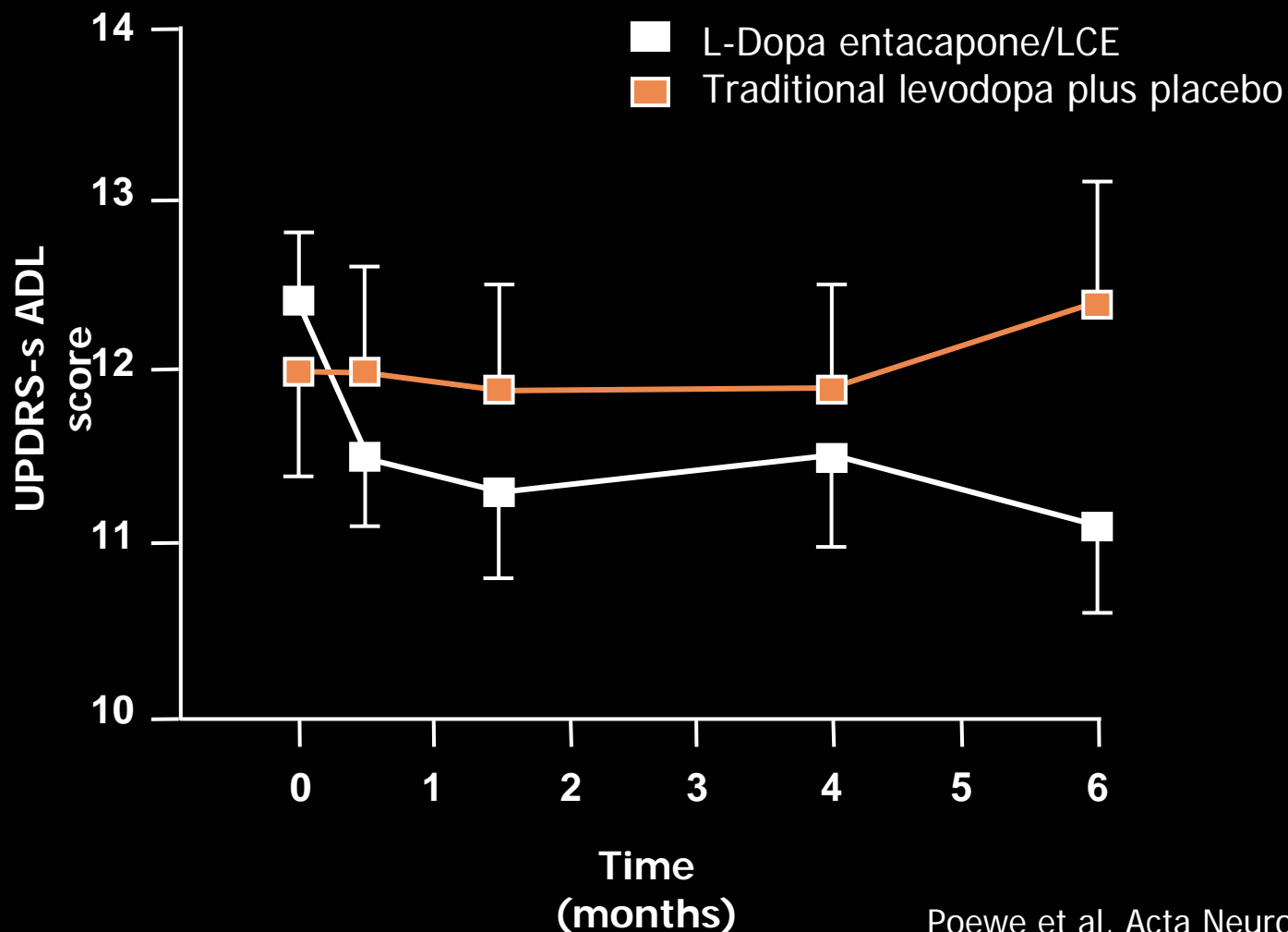


I preparati combinati

L-Dopa + entacapone enhances the pharmacokinetics of levodopa



L-Dopa & entacapone: impatto sulle ADL



Deep Brain Stimulation

Panel 2: Proposed criteria for deep brain stimulation^{141,147}

Inclusion criteria

1. Clinically definite Parkinson's disease
2. Hoehn and Yahr stage 2–4 (moderate to severe bilateral disease, but still ambulatory when on)
3. L-dopa responsive with clearly defined off and on periods
4. Persistent disabling motor fluctuations despite best drug treatment with some combination of
 - At least 3 h of off period daily
 - Unpredictable off periods
 - Disabling dyskinesia
5. Intact cognition as measured by neuropsychological testing and no active psychiatric disturbances
6. Strong social support system and commitment from patient and family members to keep follow-up appointments

Exclusion criteria

1. Parkinson-plus syndromes
2. Atypical parkinsonism—eg, vascular parkinsonism
3. Drug-induced parkinsonism
4. Medical contraindications to surgery or stimulation (serious comorbid medical disorders, chronic anticoagulation with warfarin, cardiac pacemakers, etc)
5. Dementia or psychiatric issues (untreated depression, psychosis, etc)
6. Intracranial abnormalities that would contraindicate surgery—eg, stroke, tumour, vascular abnormality affecting the target area
7. Severe brain atrophy on imaging (makes target localisation difficult)
8. Serious doubt about patient's commitment to return for follow-up visits (several no-shows in the past, poor compliance record, etc)

CME **Surgical and hardware complications
of subthalamic stimulation**

A series of 160 procedures

Kelly E. Lyons, PhD; Steven B. Wilkinson, MD; John Overman, BS, BEE; and Rajesh Pahwa, MD

Abstract—Objective: To assess the surgical and hardware complications in a series of 81 consecutive patients undergoing subthalamic (STN) deep brain stimulation (DBS) for Parkinson disease (PD). **Methods:** The authors prospectively documented surgical and hardware complications occurring at the time of surgery and at subsequent neurologic and surgical evaluations for an average of 17 months, ranging from 1 to 54 months. **Results:** No patient had a serious surgical complication resulting in death or permanent neurologic deficit. One patient had an intracranial hemorrhage but with no permanent deficit. In follow-up, 2.5% had infections requiring system removal, 3.7% had infections requiring implantable pulse generator (IPG) removal, 12.5% had misplaced leads, and 26.2% had hardware complications including lead migration, lead fracture, extension erosion, extension fracture, and IPG malfunction. **Conclusion:** Serious complications leading to permanent neurologic deficit are rare after STN DBS for advanced PD. However, long-term follow-up demonstrated that hardware complications are relatively common, having occurred in approximately 26% of these patients.

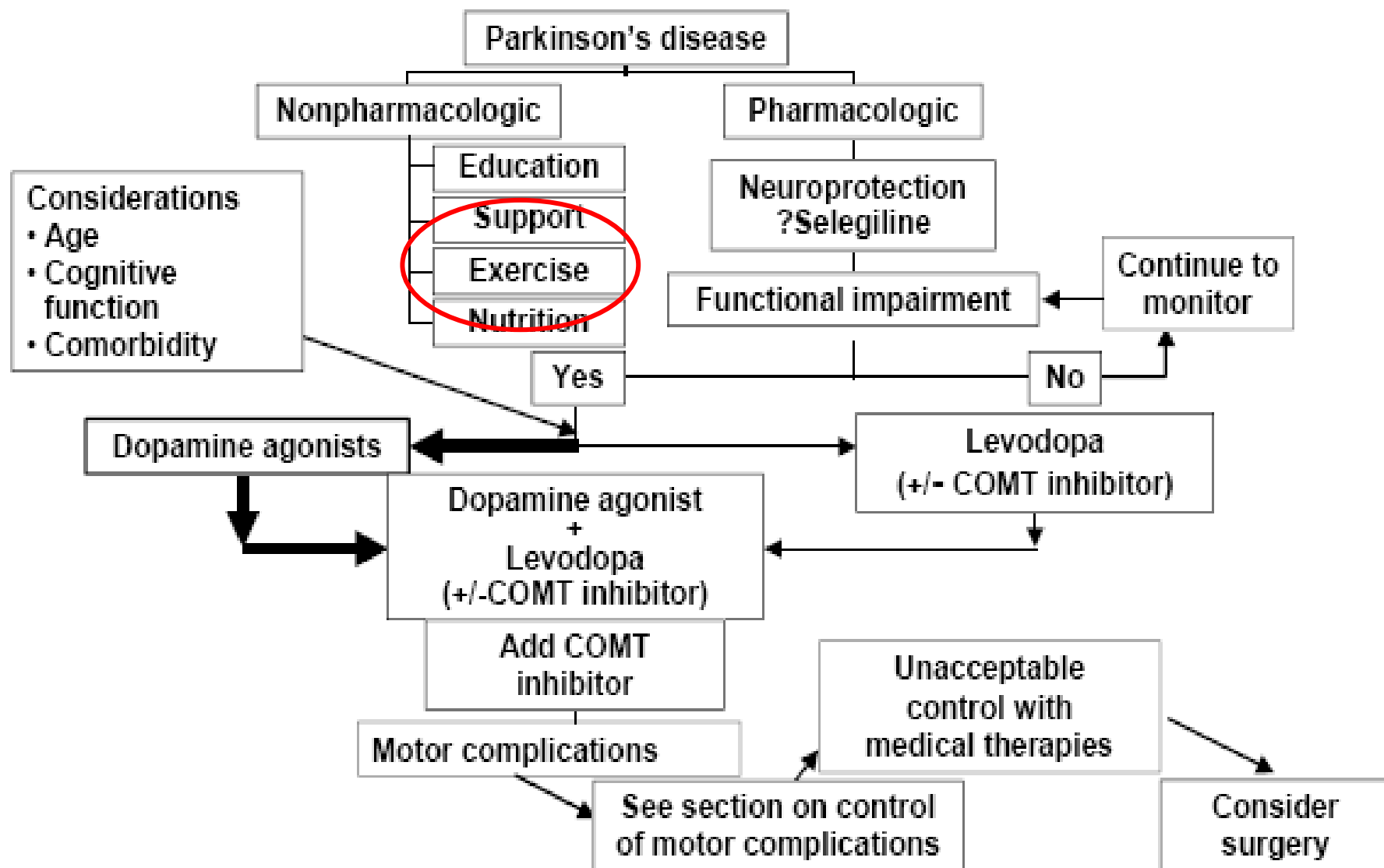
Evidence DBS

- DBS of the STN may be considered as a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (Level C). Patients need to be counseled regarding the risks and the benefits of this procedure.
- There is insufficient evidence to make any recommendations about the effectiveness of DBS of the GPi or VIM nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients (Level U).

Exercise treatment & rehabilitation

Management of Parkinson's Disease

RCFMSL10



Exercise Therapy in PD

Author	Cohort size	Outcome variable	Treatment	Duration
Wade et al 2003	144	PDQ-39, SC-36, peg test, walking	multidisciplinary rehab vs. placebo	1 x per week x 6 weeks, FU 48 weeks
Marchese et al 2000	20	UPDRS	cued vs. non-cued exercises	3 x per week x 6 weeks, FU 12 weeks
Miyai et al 2000	10	UPDRS, ambulation	BWSTT vs. physiotherapy	3 x per week x 4 weeks, FU 8 weeks

Exercise Therapy in PD

Author	Cohort size	Outcome variable	Treatment	Duration
Miyai et al 2002	24	UPDRS, ambulation	BWSTT vs. physiotherapy	3 x per week x 4 weeks, FU 6 months
Hirsch et al 2003	18	balance, falls, strength	Balance/resista nce vs. balance	3 x per week x 10 weeks, FU 14 weeks
Pachetti et al 2000	32	UPDRS, PDQualif	Music therapy vs. physical therapy	1 x per week x 3 months, FU 5 months
Comella et al 1994	18	UPDRS, depression	General exercise vs. placebo	3 x per week x 1 month, FU 12 months

Recommendation for Exercise Therapy in PD

- Exercise therapy may be considered to improve function (Level C)
 - Results in improvement in UPDRS
 - Decrease in falls
- No specific exercise program shown to be superior to another
- Benefit not sustained after exercise is discontinued

Possibili ragioni della ridotta provata efficacia della riabilitazione nel PD

- Eterogeneità della popolazione (durata e gravità malattia)
- Misure di outcomes variabili
 - Intervento adattativo
 - Intervento sulla plasticità neuronale
 - Qualità della vita
- Collaborazione del paziente /interventi educativi (non sempre valutati)

Non motor symptoms

I sintomi non motori sono spesso il primo segno di wearing off

- In addition to the motor-related symptoms of PD, non-motor complications can also be a significant burden for patients.
- Many of these symptoms are associated with PD itself; however, recent evidence suggests that non-motor symptoms such as anxiety, tingling, coldness of limbs and unclear thinking may frequently occur before motor symptoms emerge, highlighting the importance of their recognition in clinical practice.

Background

- Prospective survey n=99 (Shulman et al., 2001)
 - 88% had at least one of
 - Anxiety, depression, sensory disturbance, fatigue, pain, or sleep disturbance
 - 11% had 5 or more
- Low physician recognition of nonmotor features in PD
- Many PD symptoms overlap with features of depression and dementia
- Validated criteria for depression, psychosis and dementia in PD do not exist

Evidence: pharmacological treatment of depression in PD

- Amitriptyline may be considered for depression associated with PD (Level C)
 - Not necessarily the first choice for treatment
- Citalopram and sertraline (no benefit underpowered)
- Insufficient evidence to make recommendations for other pharmacologic depression treatments in PD (Level U)

Recommendations for Psychosis Treatment

- For patients with PD and psychosis
 - Clozapine should be considered (Level B)
 - Associated with agranulocytosis that may be fatal
 - Absolute neutrophil count must be monitored
 - Monitoring requirements may vary by country
 - Quetiapine may be considered (Level C)
 - Olanzapine should not be routinely considered (Level B)
 - Worsens motor function

Conclusioni

- IL PD è una sindrome più che una malattia e deve dunque essere trattata farmacologicamente di conseguenza
- Non vi sono attualmente preparati che svolgano una provata azione neuronoprotettiva
- La L-Dopa è il più potente agente antiparkinsoniano ancora in uso ma è gravato da alcuni problemi
- I farmaci dopaminoagonisti, I-MAO e COMT sono efficaci per le complicanze del PD (fluttuazioni)
- DBS efficacia limitata ed in casi selezionati
- Riabilitazione?