



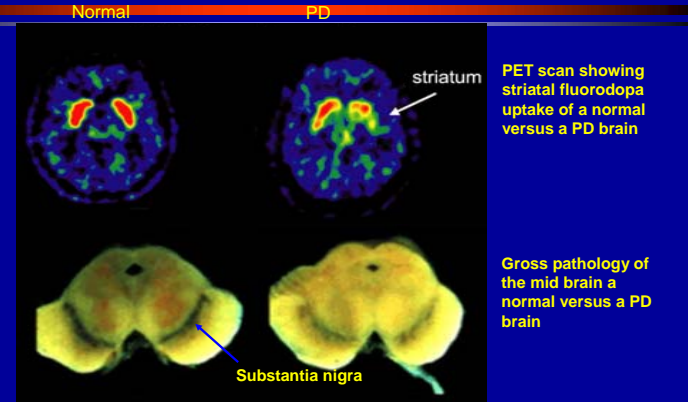
Clinical trials with catechol-O-methyltransferase (COMT) inhibitors, entacapone and tolcapone

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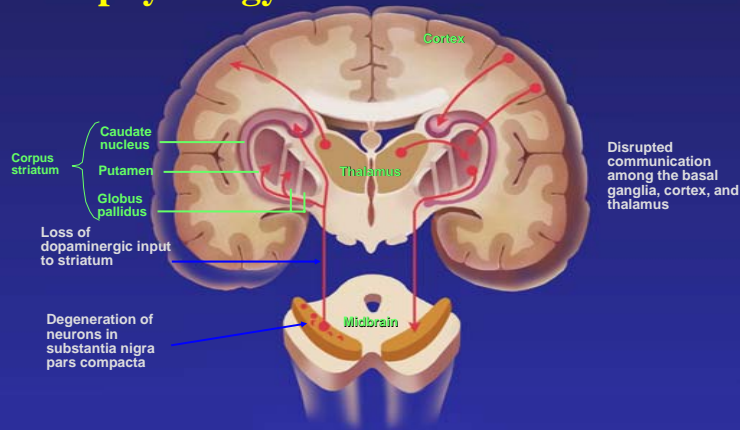
HDR 2008



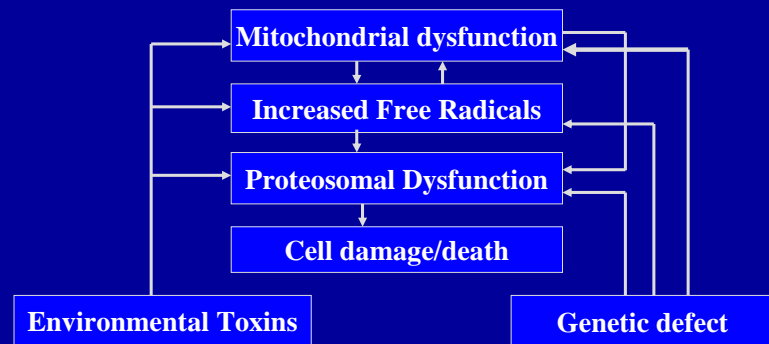
Parkinson's disease: Pathology



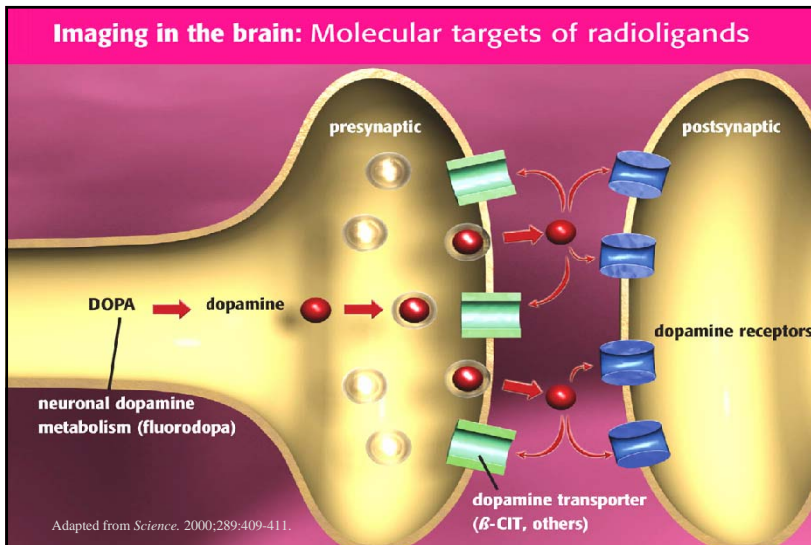
Pathophysiology of PD



The etiological and pathogenetic network of PD



Schapira Lancet 2006



Levodopa - precursor of dopamine

- * Birkmayer W & Hornykiewicz O. The effect of L-3,4-dihydroxyphenylalanine on akinesia in Parkinsonism. *Wiener Klinische Wochenschrift* 1961.
- * Cotzias GC et al. Aromatic amino acids and modification of parkinsonism. *N Engl J Med* 1967

Levodopa => dopamine

- * Levodopa is rapidly metabolised in gi- tract
=> only about 1% of oral levodopa will enter the brain
- * DCI (carbidopa/benserazide) will decrease peripheral decarboxylation => 5- 10% of levodopa will reach the brain
- * COMT inhibitor will decrease metabolism into 3 MD, e.g. with L/C/E
=> $T_{1/2}$ of levodopa will increase up to 85%
=> 13.5% of oral levodopa can enter the brain

Levodopa in PD

- The most effective drug for treatment of PD
- Short-term side effects are easily manageable
- Preferable in older patients (70-75 years) and among those with cognitive impairment
- Many long-term complications
 - wearing-off, dyskinesia
 - abnormal pulsatile stimulation of DA-receptors

Antiparkinsonian treatment in Spanish cohort of patients Grandas & Kulisevsky 2003

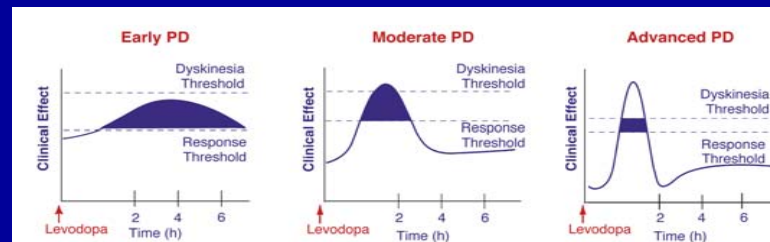
| Treatment | n | % | Dose* (mg/day) |
|--------------------|-------|------|----------------|
| L Dopa | 1,630 | 90,4 | |
| L dpa/carbidopa SD | 914 | 50,6 | 490,0 ± 2 63,0 |
| L dpa/carbidopa CR | 732 | 40,6 | 443,0 ± 201,0 |
| L dpa/benserazide | 262 | 14,6 | 660,0 ± 283,0 |

Levodopa: Short-term challenges

- Poor bioavailability and short plasma half life
- Erratic gastric retention and/or intestinal absorption-delays oral levodopa uptake
- Competition with neutral amino acids (proteins) for transport across gastrointestinal tract and blood-brain barrier

Nutt 1998
Olanow et al 2001

Long-term challenges: Changes in levodopa response

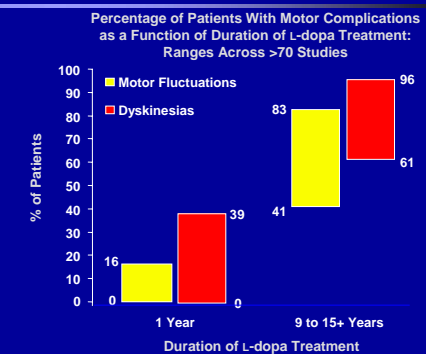


Obeso et al. 2000

Role of L-Dopa on the Emergence of Motor Complications

Motor complications are introduced

- Motor fluctuations across >70 studies
 - 0% to 16% of patients after 1 year of treatment
 - 41% to 83% of patients after 9 to 15+ years of treatment
- Dyskinesias across >70 studies
 - 0% to 39% of patients after 1 year of treatment
 - 61% to 96% of patients after 9 to 15+ years of treatment



Ahlskog & Muentzer. *Mov Disord.* 2001;16:448-458.

Risk Factors for L-Dopa–Associated Motor Complications

➤ Disease

- Younger age of onset of Parkinson’s disease (for motor fluctuations)
- Longer duration of Parkinson’s disease (for motor fluctuations)

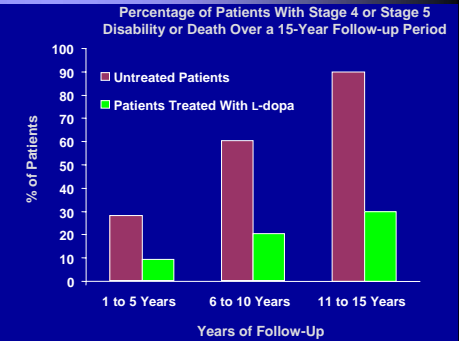
➤ Drug

- Longer duration of treatment with L-dopa (for dyskinesias and motor fluctuations)
- Higher doses of L-dopa (for dyskinesias)

Schrag & Quinn. *Brain*. 2000;123:2297-2305.

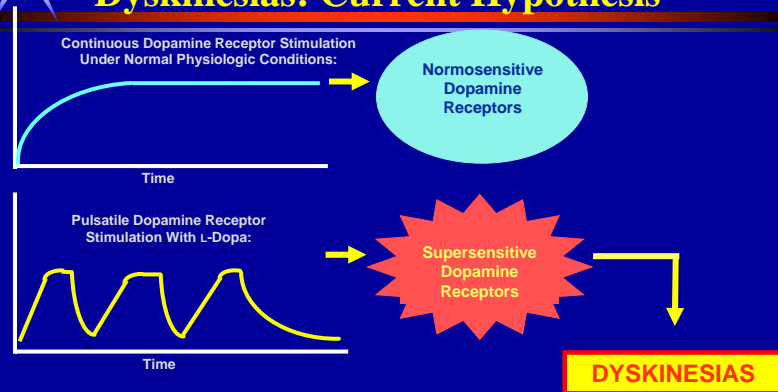
Role of L-Dopa on the Clinical Progression of PD

- Rate of clinical progression is slowed, sometimes dramatically
- Life expectancy is substantially increased



Poewe & Wenning. *Neurology*. 1996;47(6 suppl 3):S146-S152.

Etiology of L-Dopa–Associated Dyskinesias: Current Hypothesis

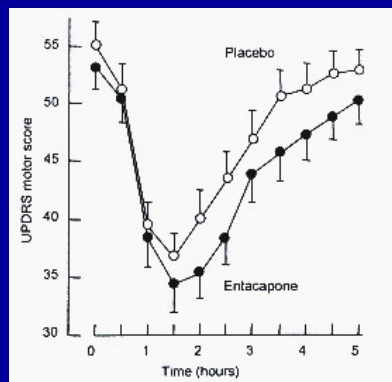
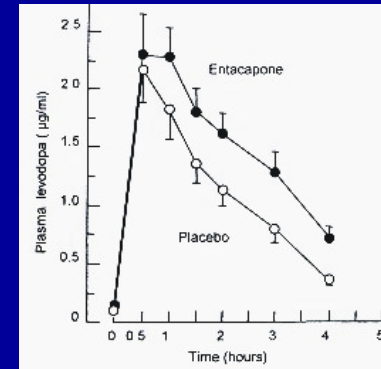
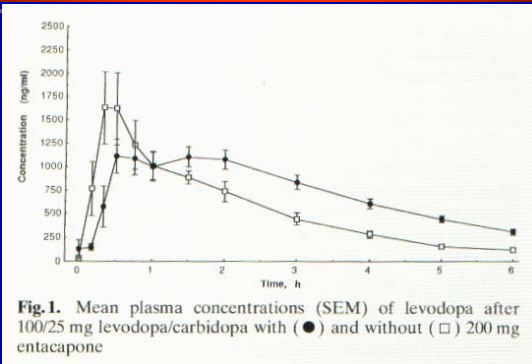


Olanow et al. *Trends Neurosci*. 2000;23(suppl):S117-S126.

COMT-inhibitors

- Prolong plasma L-dopa levels and half lives
- Entacapone
 - Peripherally acting
 - Similar half-life as L-dopa
 - Entacapone/L-dopa/carbidopa combination
- Tolcapone
 - Enters the brain
 - Administered three times daily

Plasma concentrations of levodopa after entacapone (Myllylä et al. 1993)



Randomised, double-blind, clinical studies of entacapone in patients with wearing-off

| Study | Country | Duration | Patients (n) | On-time | Off-time |
|----------|--|----------|---|--|--|
| NOMECOMT | Sweden Denmark Finland Norway | 6 months | 171 (Entacapone: 85 Placebo: 86) | Entacapone: +1,4 h Placebo: +0,2 h (p<0,001) | Entacapone: -1,3 h Placebo: -0,1 h (p<0,001) |
| SEESAW | US Canada | 6 months | 205 (Entacapone: 103 Placebo: 102) | Entacapone: +6,7 % Placebo: +2,0 % (p<0,05) | Entacapone: -1,2 h Placebo: -0,3 h (p<0,01) |
| CELOMEN | Germany Austria | 6 months | 301 (Entacapone: 197 Placebo: 104) Subgroup of non-fluctuating patients (n=41) | Entacapone: +1,7 h Placebo: +0,5 h (p<0,05) | Entacapone: -1,5 h Placebo: -0,6 h (p<0,05) |
| UK-Irish | United Kingdom Ireland | 6 months | 300 (Entacapone: 203 Placebo: 97) Subgroup of non-fluctuating patients (n=128) | Entacapone: +1,3 h Placebo: +0,1 h (p<0,01) | Entacapone: -1,1 h Placebo: -0,3 h (p<0,05) |

Daily "on-time" with levodopa/DDCI plus entacapone (NOMECOMT, Rinne et al. 1998)

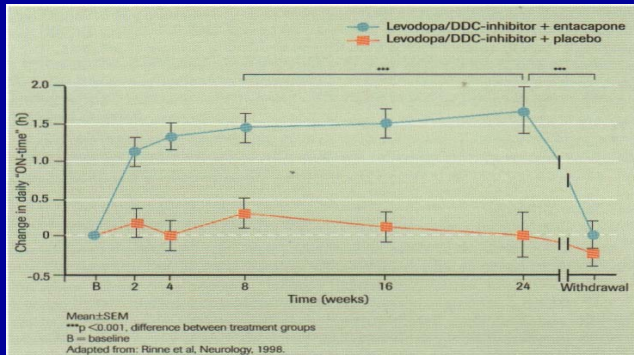


Figure 11: Improvements in the daily "on-time" with levodopa/DDC-inhibitor plus entacapone treatment in the NOMECOMT study.

Most frequent adverse events (> 5 %) (Myllylä et al. 2001, Larsen et al. 2003)

| Adverse event | Entacapone (%) | Placebo (%) | P |
|-------------------------|----------------|-------------|--------|
| Dyskinesia | 28,9 | 11,1 | <0,001 |
| Parkinsonism Aggravated | 13,8 | 11,1 | NS |
| Nausea | 13,3 | 11,1 | NS |
| Abdominal pain | 9,6 | 5,6 | NS |
| Diarrhoea | 9,2 | 1,9 | <0,05 |
| Fatigue | 7,8 | 5,6 | NS |
| Pain | 7,8 | 5,6 | NS |
| Urine Discoloration | 6,9 | 0 | <0,01 |
| Mouth Dryness | 6,0 | 0 | <0,01 |
| Insomnia | 5,0 | 6,5 | NS |
| Back pain | 5,0 | 4,6 | NS |
| Postural hypotension | 2,8 | 5,6 | NS |

Efficacy of combining levodopa with entacapone on QoL and ADL in patients experiencing wearing-off fluctuations

(Reichmann H, Boas J, MacMahon D, Myllylä V et al. Acta Neurol Scand 2005;111:21-28)

Levodopa combined with entacapone demonstrated good efficacy in terms of ADL, global function, motor performance and was well tolerated. However, this short-term study did not generate significant improvements in QoL.

Patient satisfaction with switching to L/C/E: an open-label evaluation in PD patients experiencing wearing-off

(Myllylä V et al. Acta Neurol Scand 2006;114:181-186)

L/C/E was simple to dose, more convenient to use, easier to handle, easier to remember and easier to swallow compared with their previous medication.

The study shows that L/C/E is an effective, preferred and well-tolerated means of delivering levodopa/carbidopa/entacapone in one easy-to-use tablet.



Dyskinesia avoidance with levodopa and entacapone

Data of experimental MPTP marmosets support the notion that pulsatile stimulation contributes to the development of dyskinesia and suggests that more frequent dosing of L-dopa plus entacapone may decrease motor complications (Smith et al. 2005).

FIRST-STEP study with early PD patients suggest a better therapeutic result with L/C/E combination.



Tolcapone trials

| Study | Patients |
|--|------------|
| Rajput et al Neurology 1997 | 202 |
| Myllylä et al Eur J Neurol 1997 | 154 |
| Baas et al J Neurol Neurosurg Psych 1997 | 177 |
| Adler et al Arch Neurol 1998 | 215 |
| <u>Waters et al Neurology 1997 (stable PD)</u> | <u>298</u> |



Tolcapone efficacy results and change in levodopa dosage (Myllylä et al. 1997)

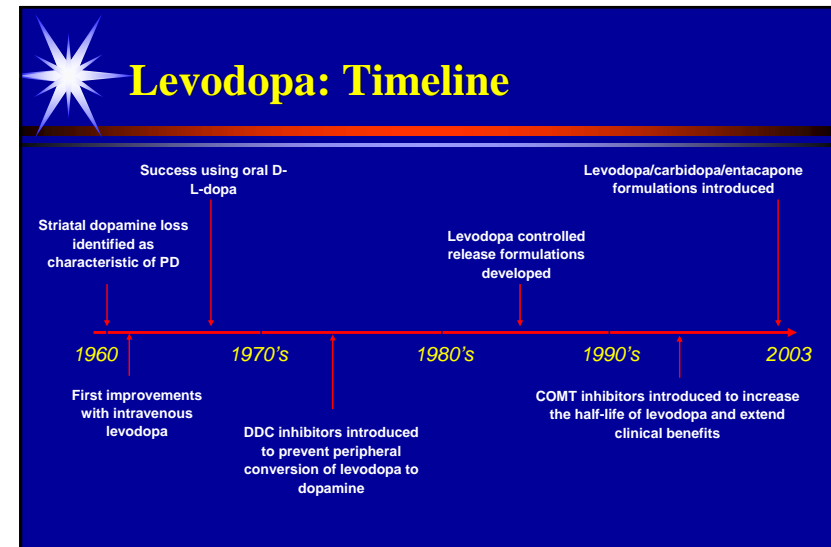
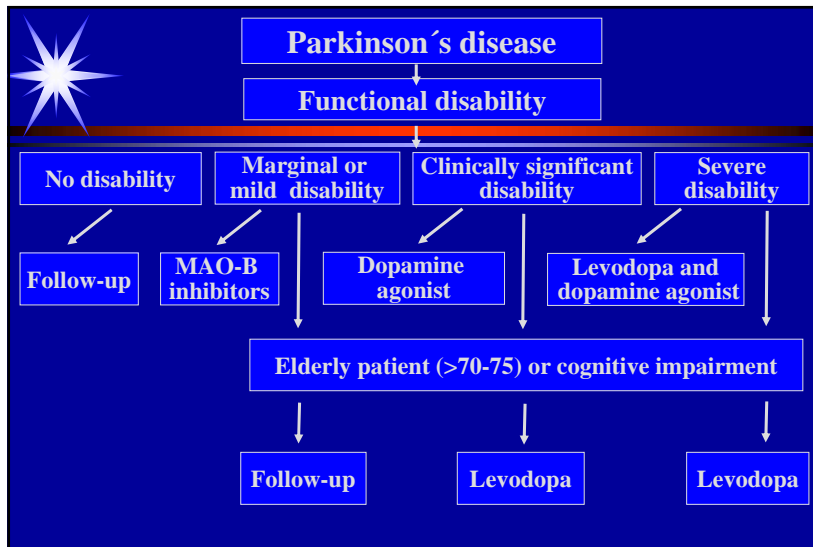
| | Placebo n=37 | Tolcapone | | |
|-----------------------------|-----------------|----------------------|----------------------|----------------------|
| | | 50 mg t.i.d. n=34 | 200mg t.i.d. n=31 | 400mg t.i.d. n=31 |
| *On*-time (% waking day) | | | | |
| Baseline | 44,3 (3,0) | 37,6 (3,4) | 37,9 (3,5) | 38,3 (3,6) |
| Week 6 | 40,7 (3,9) | 47,8 (4,4) | 50,8 (4,5) | 47,8 (4,6) |
| Change | -2,1 (3,2) | 10,3 (3,5)* | 13,0 (3,6)** | 8,9 (3,7)* |
| *Off*-time (% waking day) | | | | |
| Baseline | 24,5 (3,0) | 29,5 (3,4) | 26,7 (3,4) | 24,7 (3,5) |
| Week 6 | 25,3 (3,4) | 23,6 (3,8) | 16,4 (3,9) | 18,9 (4,0) |
| Change | -0,7 (2,7) | -5,9 (3,0) | -11,1 (3,1)* | -7,2 (3,2) |
| Total daily L-dopa dose(mg) | | | | |
| Baseline | 761,0 (41,8) | 762,6 (46,0) | 693,9 (46,0) | 722,5 (46,8) |
| Week 6 | 762,7 (44,0) | 705,9 (48,4) | 616,1 (48,4) | 710,0 (49,2) |
| Change | 2,4 (18,0) | -56,0 (19,8) | -79,1 (19,9)** | -13,3 (20,2) |

Data are means (sem). *p<0,05, **p<0,01 vs placebo (unadjusted).



Tolcapone safety

- * Preclinical testing: no hepatotoxicity
- * Clinical trials: More than 3 UNL of liver enzymes
 - 1% when tolcapone 100 mg given TID
 - 3% when given 200 mg TID
- * Fatal hepatitis in 3 out of 60 000 patients
- * Frequent monitoring of liver tests is required and written consent is recommended



Conclusions

- Levodopa revolutionized PD treatment
 - Can significantly improve rigidity and bradykinesia in PD, particularly in early stages of PD
 - Is associated with good response in the short-term but in many problems in long term
- COMT inhibitors provide an important tool for improving the long-term benefit of PD treatment

