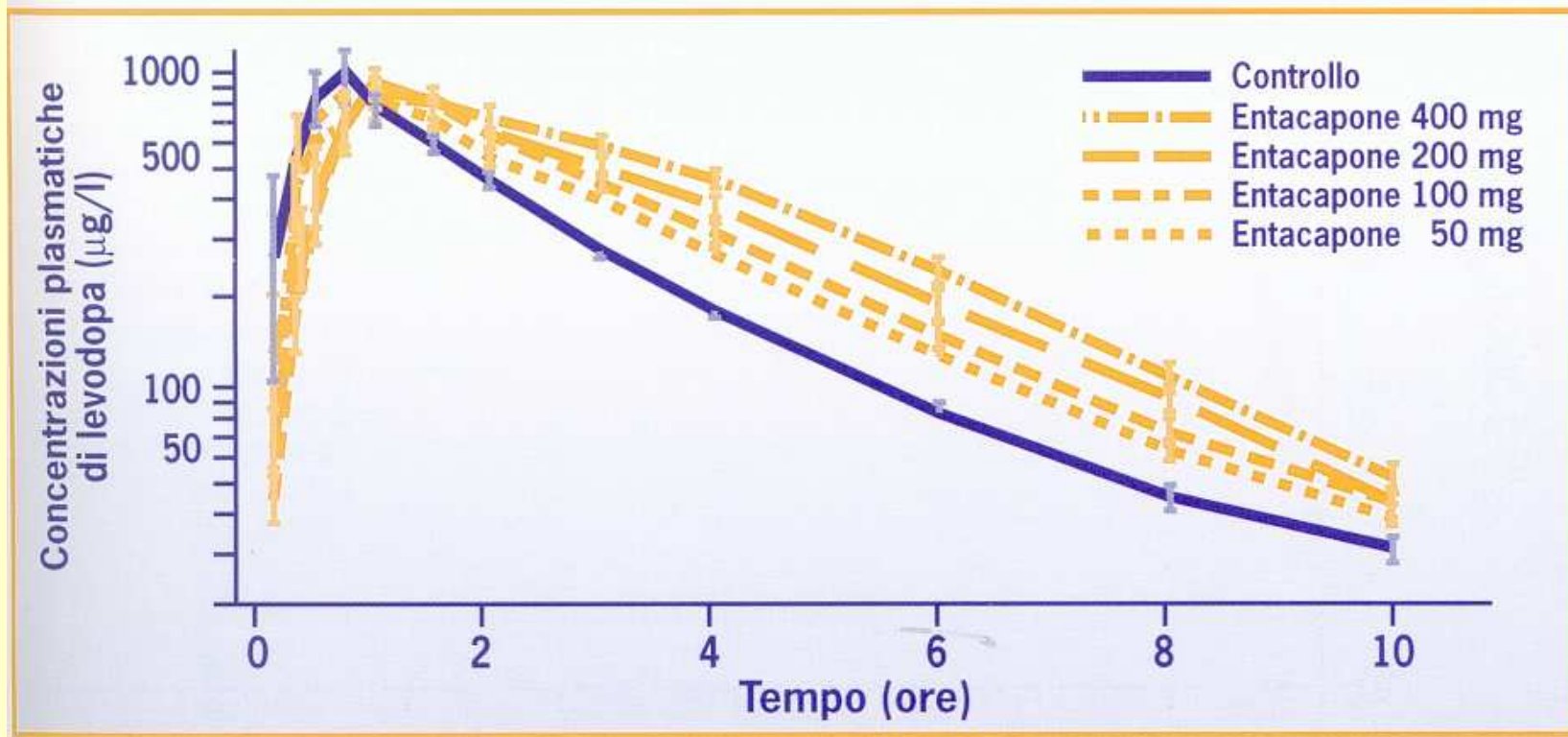


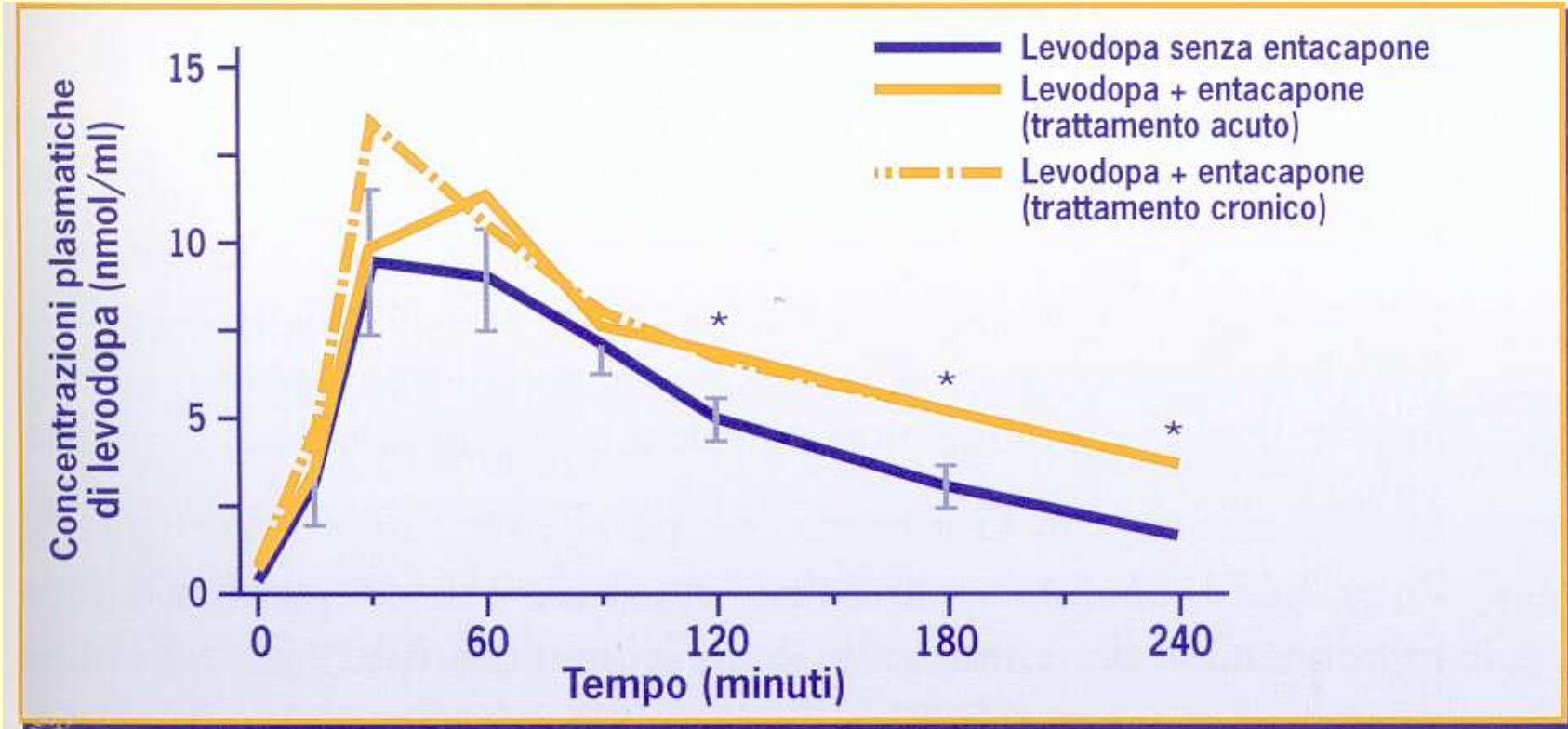


L'uso dei COMT-inibitori nella pratica clinica

Prof. Marco Onofrj

Farmacologia clinica di entacapone





Studio dei paesi nordici ("Nomecomt")

- › Morbo di Parkinson idiopatico
- › Stadi di Hoehn e Yahr 1,5-4 in periodo "ON"
- › Responsivo alla levodopa
- › Fluttuazioni motorie "wearing-off"
- › Trattamento stabile con levodopa (4-10 dosi/die)
- › Preparazioni standard di levodopa/carbidopa o levodopa/benserazide
- › Consentiti altri farmaci antiparkinsoniani
- › Periodo medio di "ON" dopo una singola dose di levodopa < 4 ore

Studio nord americano ("Seesaw")

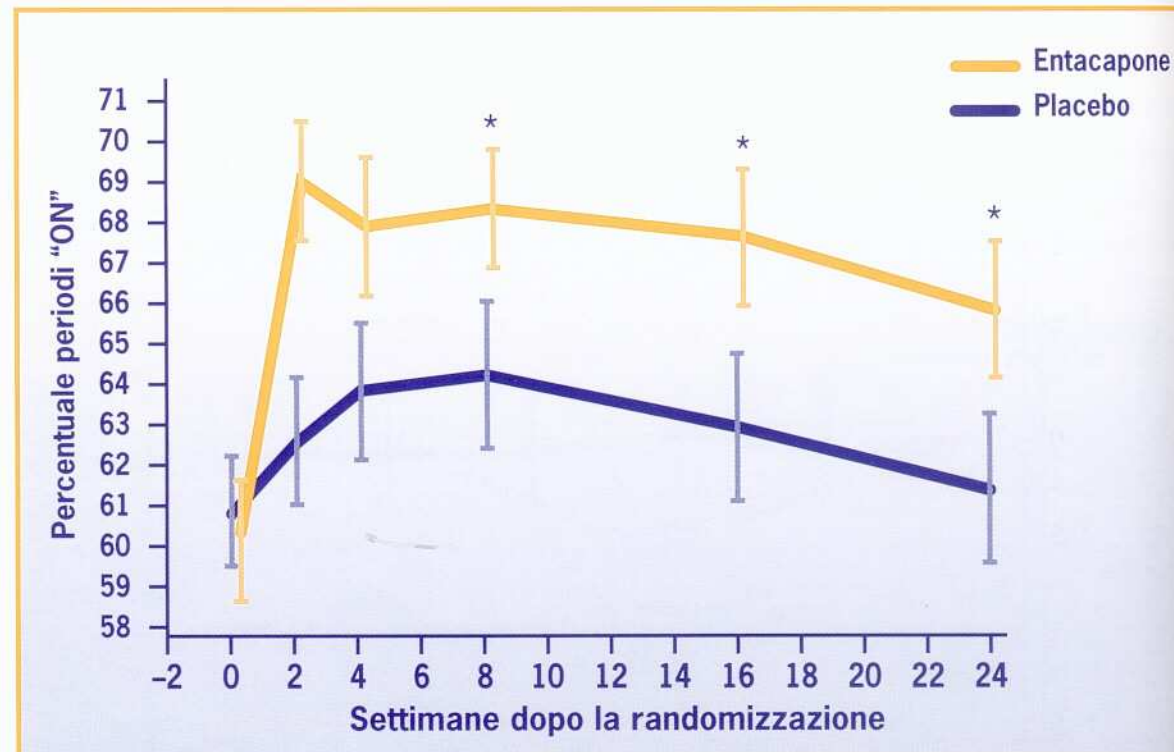
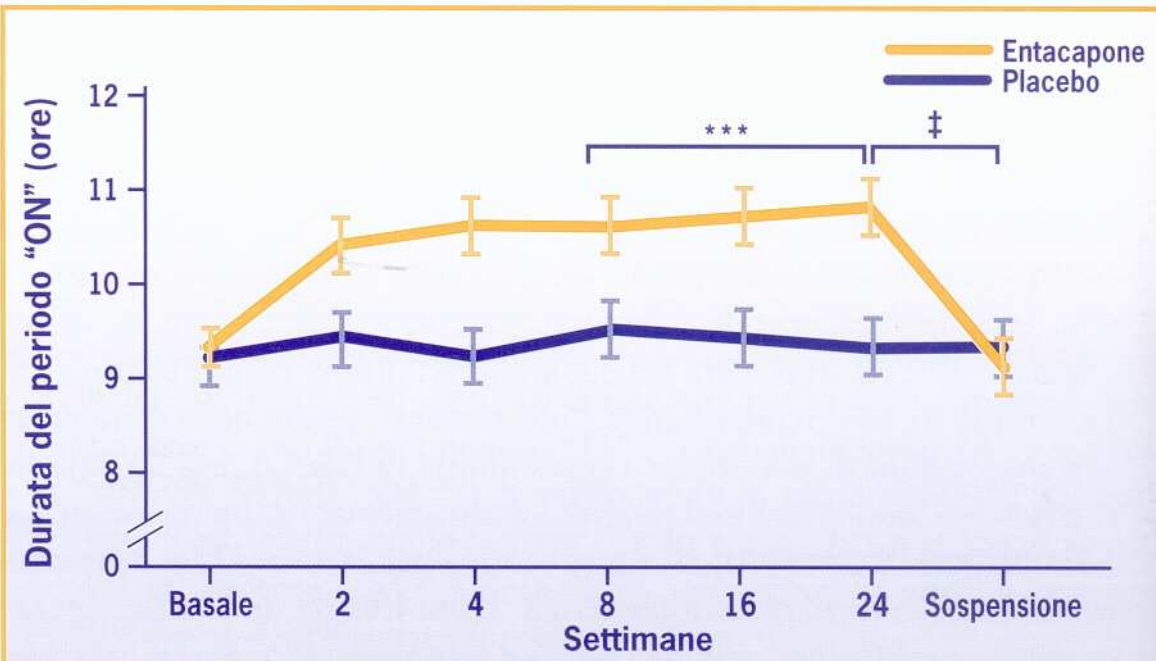
- › Morbo di Parkinson idiopatico
- › Stadi di Hoehn e Yahr 1,5-4 in periodo "OFF"
- › Responsivo alla levodopa
- › Fluttuazioni motorie "wearing-off"
- › Trattamento stabile con levodopa (4-10 dosi/die)
- › Preparazioni standard di levodopa/carbidopa
- › Consentiti altri farmaci antiparkinsoniani
- › Periodo "OFF" ≥ 3 ore

Studio Seesaw

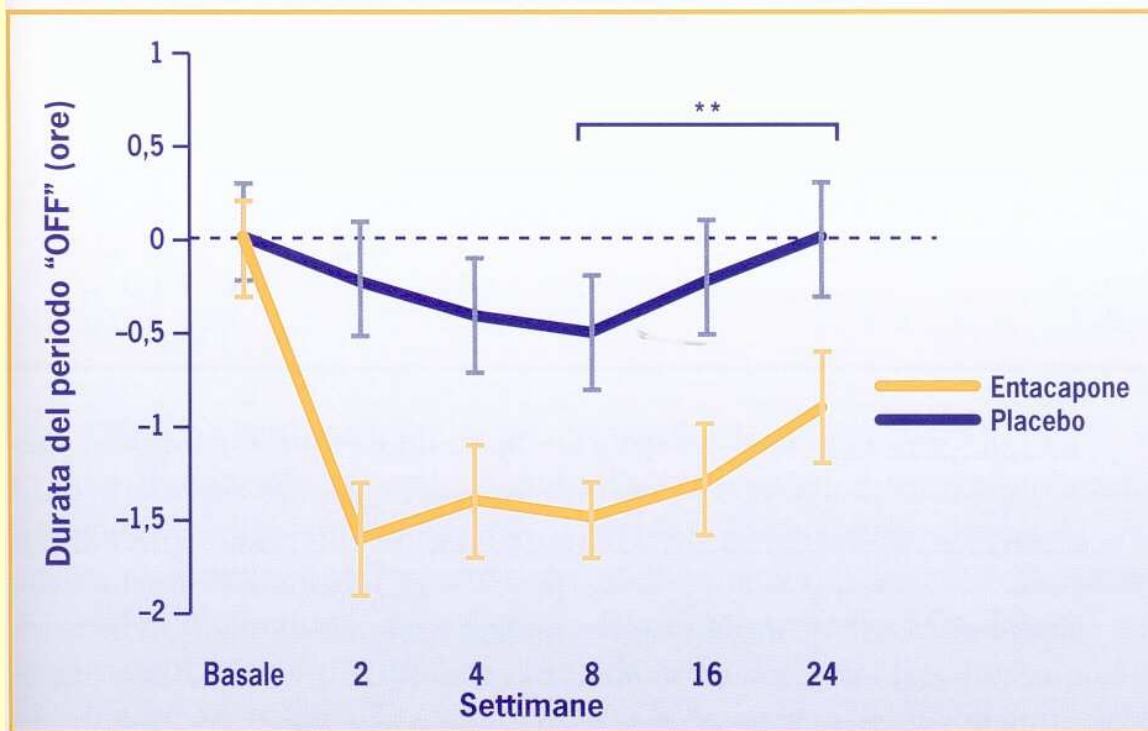
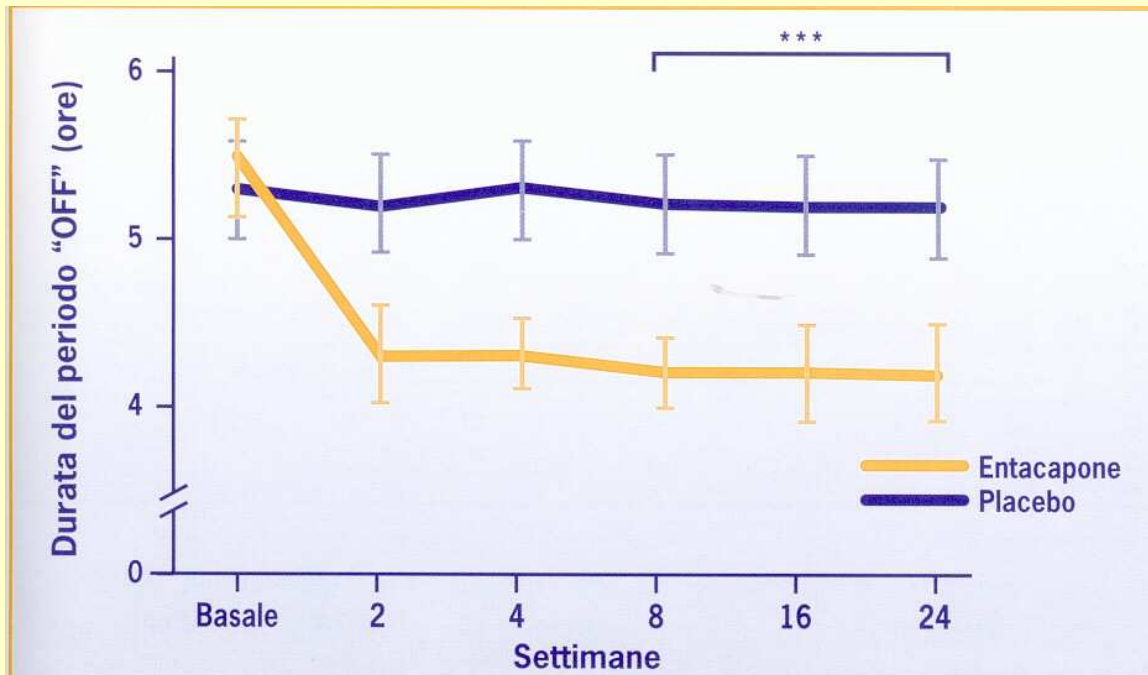
Studio Nomecomt

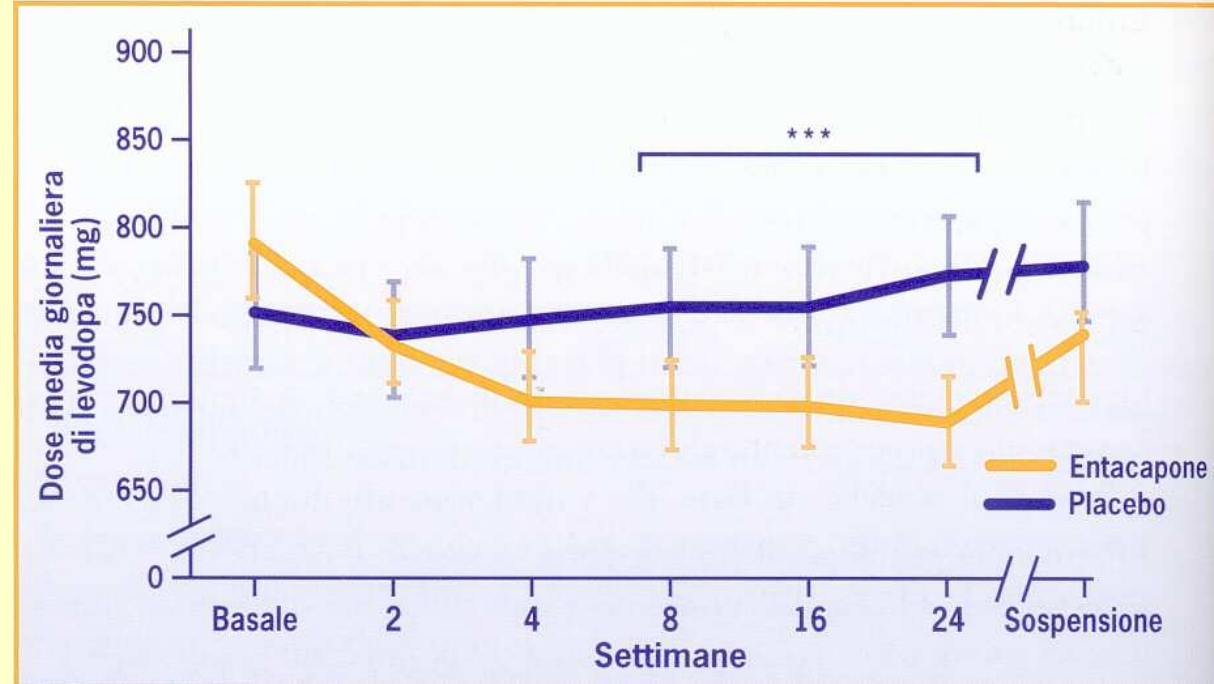
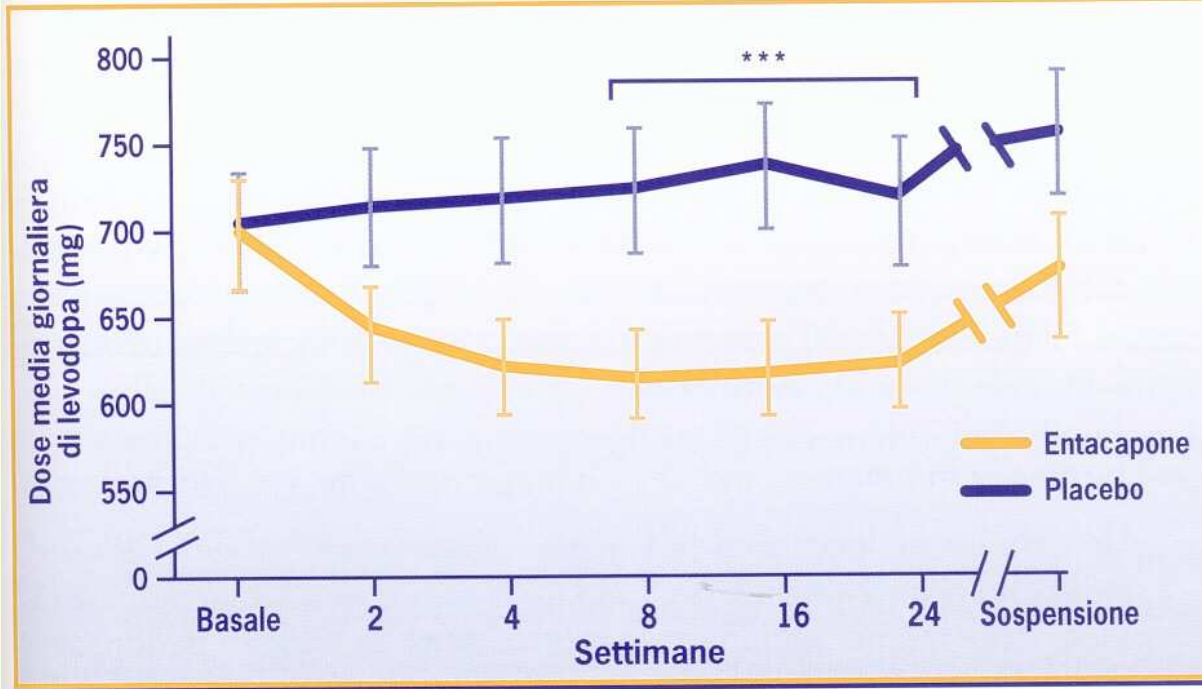
	Entacapone 200 mg (n = 103)	Placebo (n = 102)	Entacapone 200 mg (n = 85)	Placebo (n = 86)
<u>UPDRS sezione I</u>				
- basale	1,3 ± 1,2	1,5 ± 1,7	1,8 ± 1,4	2,0 ± 1,5
- media settimane 8-24	1,5 ± 1,2	1,8 ± 1,8	1,8 ± 1,4	2,2 ± 1,7
<u>UPDRS sezione II</u>				
- basale	11,9 ± 6,2	11,7 ± 6,7	11,2 ± 5,0	11,0 ± 4,5
- media settimane 8-24	11,5 ± 6,4*	12,1 ± 6,8	9,5 ± 5,4**	10,6 ± 4,8
<u>UPDRS sezione III</u>				
- basale	22,0 ± 11,7	22,6 ± 12,0	25,5 ± 13,1	24,6 ± 12,3
- media settimane 8-24	21,1 ± 11,2*	22,9 ± 11,9	22,5 ± 13,8*	28,8 ± 12,7
<u>UPDRS sezione I-III</u>				
- basale	35,1 ± 15,9	35,6 ± 17,2	38,5 ± 16,8	37,4 ± 15,8
- media settimane 8-24	34,1 ± 16,1**	36,6 ± 17,7	34,1 ± 17,7**	36,3 ± 16,6

“ON”



“off”





Indicazioni:

- **Deterioramento fine dose**
- **Fluttuazioni imprevedibili**

Posologia:

1 cp per ogni

somministrazione di L-DOPA

Esempio 1

Ore 6	Madopar Dispersibile 1 cp + Madopar HBS 1 cap	+	1 Comtan
Ore 9	Madopar Divisibile ½ cp	+	1 Comtan
Ore 12	Madopar Divisibile ½ cp	+	1 Comtan
Ore 15	Madopar Dispersibile 1 cp + Madopar HBS 1 cap	+	1 Comtan
Ore 18	Madopar Divisibile ½ cp	+	1 Comtan
Ore 22	Madopar HBS 2 cap	+	1 Comtan

Esempio 2

Ore 6	Madopar Dispersibile 1 cp	+	1 Comtan
Ore 9	Requip 5 mg		NO !
Ore 11	Madopar Divisibile 1/2 cp	+	1 Comtan
Ore 13	Requip 5 mg		NO !
Ore 15	Madopar Dispersibile 1 cp	+	1 Comtan
Ore 16	Levomet Sol 2 spruzzi		NO ! ?
Ore 18	Madopar Divisibile 1 cp	+	1 Comtan
Ore 21	Requip 5 mg		NO !
Ore 23	Madopar HBS 3 cap	+	1 Comtan

Precauzioni:

**Ridurre la dose di L-DOPA del 25%
prima di introdurre Comtan**



**Peggioramento UPDRS
Motorio**



Riaumentare Madopar



**aumento UPDRS
Dysk o Mental**



Ridurre ancora Madopar

o

Ridurre numero di somministrazioni

Effetti collaterali:

Dopamino simili → **ridurre Madopar**

Diarrea → **sospendere Comtan**

Dolori addominali → **sospendere Comtan**

Urine scure → **Normale !**

Xerostomia → **?**

Psicosi e allucinazioni → **ridurre Madopar o dopaminoagonisti**

Switch-Over from Tolcapone to Entacapone in Severe Parkinson's Disease Patients

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Key Words

Tolcapone · Entacapone · Parkinson's disease

Abstract

Forty patients affected by severe Parkinson's disease (PD) were treated with tolcapone as an adjunctive therapy to L-DOPA, for 3–7 months, until this drug was discontinued because of side-effects (2 diarrhoea, one of them with orthostatic hypotension, 2 increments of liver enzymes) or because of mandatory indications of the European drugs authority. All patients, after 3–6 months of L-DOPA therapy adjustments, received entacapone for 3 months again followed by withdrawal. L-DOPA daily dosage was significantly reduced by tolcapone and entacapone ($p = 0.01$ and 0.05). 'On' time was increased by 15% during tolcapone treatment ($p < 0.05$), and by 8% during entacapone treatment. 'Off' time was decreased by 16% during tolcapone and by 7% during entacapone treatment. Entacapone was withdrawn in the same patient who experienced diarrhoea and orthostatic hypotension during tolcapone because of recurrence of side-effects, in 6 patients because of increment of dyskinesias (with hallucinations) and in 1 patients because of rhythmic, jerking myoclonus.

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Introduction

On November 12, 1998, the European Agency for the Evaluation of Medical Products (EMEA) recommended the suspension of the marketing authorisation for tolcapone, a nitrobenzophenone catechol-O-methyl transferase (COMT) inhibitor inducing increments of 'on' time and decrements of 'off' time in fluctuating Parkinson's disease (PD) [1], as 3 cases of acute, unpredictable, hepatitis were reported [2]; because of this mandatory indication, several patients had to suddenly quit this adjunctive therapy.

Since entacapone, a nitrocatechol COMT inhibitor [3] was granted marketing authorisation in the European Union in September 1998, it became technically possible to switch over to entacapone some of the patients who had been treated with tolcapone.

In this report, we describe the effect of tolcapone/entacapone switch-over in 40 patients affected by severe PD, with unpredictable fluctuations and psychiatric complications (table 1).

In 4 of these patients, tolcapone treatment had already been withdrawn several weeks before the indications by EMEA because of side-effects (diarrhoea in 2 patients, one of them with orthostatic hypotension, and increment of liver enzymes in 2 patients).

The tolcapone/entacapone switch-over was performed in all the 40 patients in order to reduce the impact of selec-

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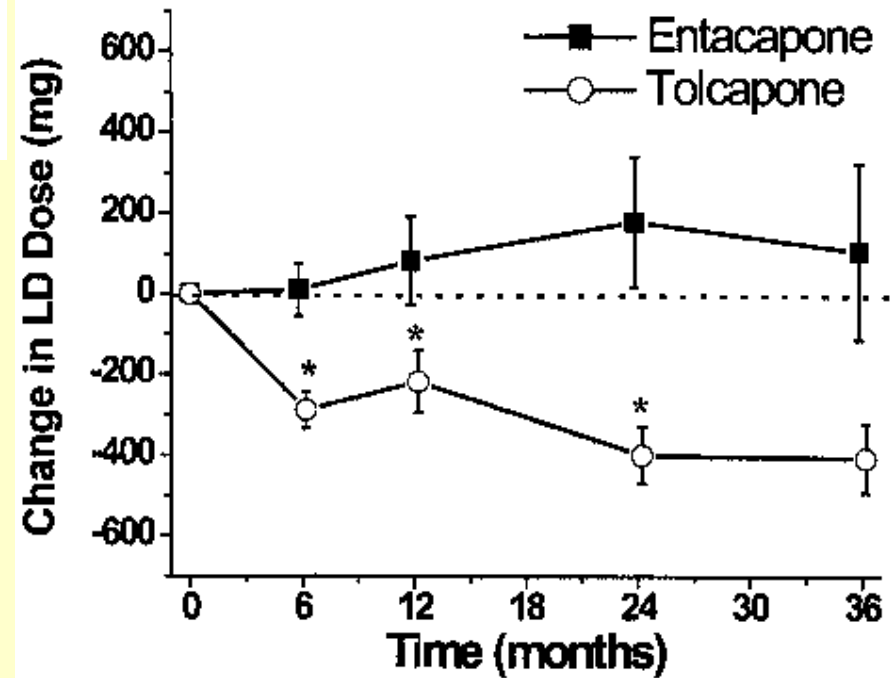
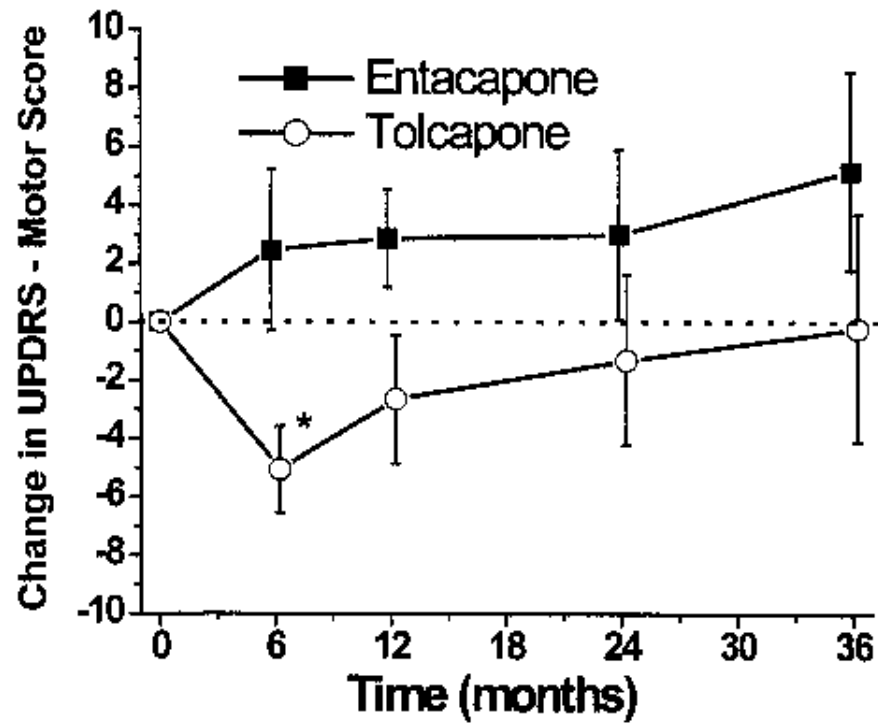
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Long-Term Comparative Experience with Tolcapone Entacapone in Advanced Parkinson's Disease

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*Departments of Neurology and *Neurosurgery, Albany Medical Center, Albany, New York, USA*

Summary: The objective of this study was to compare the long-term tolerability and efficacy of tolcapone and entacapone in patients with fluctuating Parkinson's disease (PD). Tolcapone and entacapone are two currently available catechol-*O*-methyltransferase inhibitors that have demonstrated efficacy in the treatment of advanced PD. There are little published data on long-term experience and no direct comparisons. We compared the results of two separate, simultaneous, long-term open label extensions, one for tolcapone and the other for entacapone. The inclusion/exclusion criteria were similar. Data were collected prospectively at 6, 12, 24, and 36 months. Efficacy measures included the Unified Parkinson's Disease Rating Scale (UPDRS) total score, subscores, items 32 (duration of dyskinesia) and 39 (duration of "off" time), and levodopa dose. The two groups were compared using a Mann-Whitney *U* test for change from baseline and analysis of variance. Tolerability was defined as the ability of patients to maintain therapy and was compared using a Kaplan-Meier analysis. Eleven patients enrolled in the entacapone study and 14 in the tolcapone study. The tolcapone group had more severe disease with significantly higher UPDRS motor score, duration of "off," and levodopa dose requirement. Tolcapone was more effective in lowering UPDRS motor and complication subscores, duration of "off" time, and levodopa doses. UPDRS motor scores and change in levodopa dose in the tolcapone group remained below baseline level for 36 months; however, they were above baseline in the entacapone group from 6 months on. Tolerability was the same for both treatments. Tolcapone appears to have greater and longer efficacy with regard to motor symptoms, "off" time, and change in levodopa requirements than entacapone. These findings indicate that tolcapone continues to have a place in the treatment of advanced PD. However, the risks associated with this drug, particularly hepatic injury, and the requirement for rigorous blood monitoring, need to be considered when choosing an appropriate treatment for patients with advanced PD. **Key Words:** Parkinson's disease—Catechol-*O*-methyltransferase inhibitors—Tolcapone—Entacapone



Reported side effects	Tolcapone n=40	DO	Withdrawals n=40	Entacapone n=40	DO
Dyskinesia*	12		22	24°	6
Nausea*	5		0	5	
Dystonia*	0		1	4	
Insomnia (sleep disorders)*	1		0	1	
Orthostatic Hypotension*	1		0	1	
Muscle cramps*	3		6	5	
Confusion*	0		1	3	
Hallucinations*	2		3	10	3
Vomiting*	0		0	1	
Agitation/restlessness*	1		2	6	
Cardiovascular collapses*	0		0	0	
Diarrhoea	2	2	0	1	1
Constipation	0		0	1	
Abdominal pain	0		0	2	
Headache	0		1	3	
Increased sweating	0		0	5	
Chest pain	0		0	1	
Xerostomia	0		0	1	
SGOT/sGPT increments	2	2	0	0	
Myoclonus	0		0	1	
Total Drop outs		4			8

Ahtila S, Kaakkola S, Gordin A, Korpela K, Heinavaara S, Karlsson M, Wikberg T, Tuomainen P, Manisto PT. Effect of entacapone, a COMT inhibitor, on the pharmacokinetics and metabolism of levodopa after administration of controlled-release levodopa-carbidopa in volunteers. Clin Neuropharmacol. 1995 Feb;18(1):46-57.

Piccini P, Brooks DJ, Korpela K Pavese N, Karlsson M, Gordin A The catechol-O-methyltransferase (COMT) inhibitor entacapone enhances the pharmacokinetic and clinical response to Sinemet CR in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2000 May;68(5):589-94

PRE-FRI-008**L-dopa neurotoxicity—the role of the COMT pathway**P. Werner,^{1,2*} A. Di Rocco,¹ S. Bressman,¹ M.D. Yahr²

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L-dopa is standard therapy for Parkinson's disease (PD). However, L-dopa may be neurotoxic, possibly due to catechol-oxidation. O-Methylation of catechols by catechol-O-methyltransferase (COMT), an S-adenosylmethionine (SAM) consuming reaction, can prevent the initiation of catechol autoxidation. We hypothesized that COMT activity ameliorates L-dopa neurotoxicity, if sufficient SAM or SAM precursors are provided. This was tested in primary mesencephalic cultures treated with 200 μ M L-dopa with 2 mM methionine or 1 mM dimethionine or 0.5 mM SAM with or without 0.2 μ M of the COMT-inhibitor 2', 5'-dinitrocatechol (DNC). L-dopa was neurotoxic, and surviving dopamine neurons had fewer and shorter processes. Methionine, dimethionine and SAM all ameliorated L-dopa toxicity to DA neurons, and neither SAM itself nor its metabolic precursors were neurotoxic. However, DNC completely abolished protection effect against L-dopa toxicity. We conclude that supplementation with SAM, methionine or dimethionine may be beneficial for Parkinson's disease patients, while inhibition of catechol-O-methylation (i.e. COMT) may aggravate or unmask L-dopa neurotoxicity. This is further supported by an open-label clinical study, where SAM given orally at 0.5–3 g/d improved depression in PD patients without affecting the efficacy of the antiparkinsonian medication, supporting the notion that an active SAM/COMT pathway in the CNS is beneficial, rather than detrimental, in PD.

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