Management della malattia di Parkinson in fase iniziale

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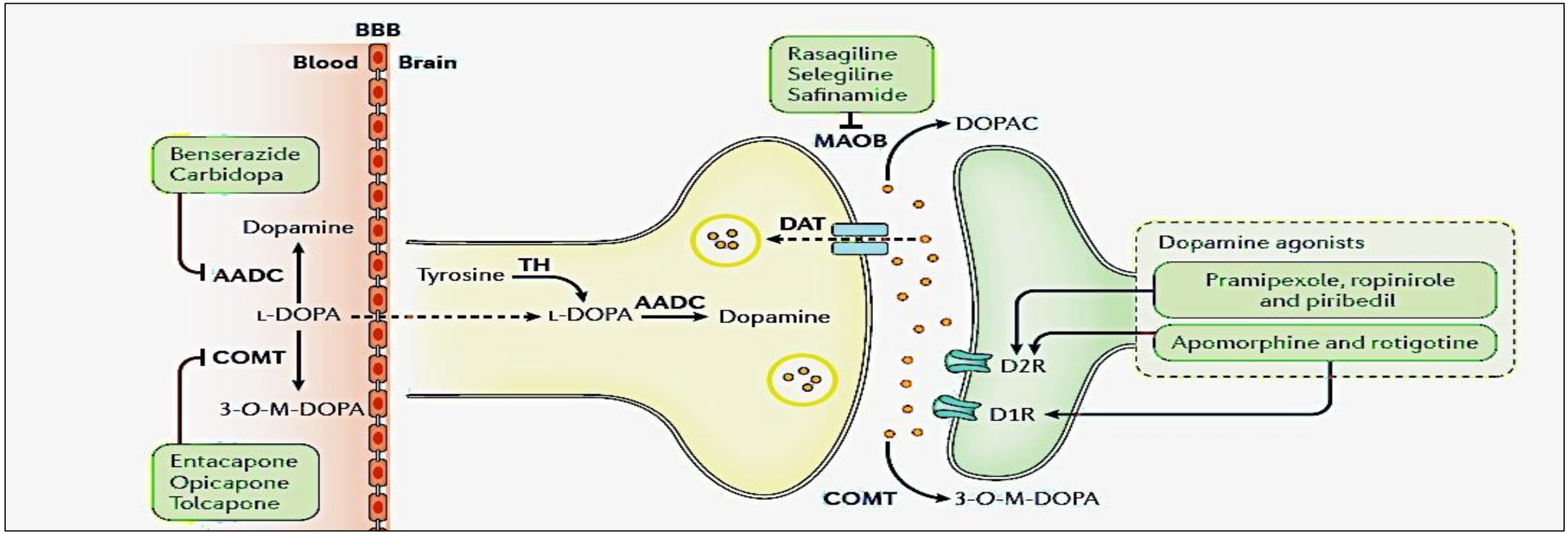
Terapia farmacologica malattia di Parkinson



Poewe et al.2017

Farmaci utilizzati per la MP

Levodopa + inibitori DOPA decarbossilasi	**Levodopa/Carbidopa** **Levodopa/Carbidopa (ER)** **Levodopa/Benserazide** **Levodopa/Benserazide (ER)** **Melevodopa**
Inibitori delle Catecol-O-metilltransferasi (I-COMT)	**Entacapone** **Tolcapone** **Opicapone**
Inbitori delle Monoamino ossidasi B (IMAO-B)	**Rasagilina** **Selegilina**
IMAO-B + modulazione rilascio Glu	**Safinamide**
Dopamino-agonisti	**Pramipexolo** **Pramipexolo - RP** **Ropinirolo** **Ropinirolo - RP** **Rotigotina cerotto** **Apomorfina s.c.**
Inibitori recettore NMDA	**Amantadina**
Anticolinergici (solo per tremore prominente in pazienti molto giovani)	**Biperidene** **Triessifenedile**

Levodopa

- **L-dopa (diidrossifenilalanina)**
- **Precursore biosintesi dopamina**
- **Aumenta dopamina nell'encefalo**
- **Principale terapia per migliorare i sintomi motori**

- **Assorbita nel duodeno prossimale**

- **Dieta a basso contenuto proteico**
- **No co-somministrare Vit B6**

Levodopa
Effetti collaterali

- **Nausea e vomito**
- **Ipotensione ortostatica**
- **Aritmie**
- **Effetti psicotici**
- **Effetto sedativo, agitazione, disturbi psichici, sogni vividi o incubi**
- **Euforia**
- **Sovradosaggio: discinesie**

Caratteristiche farmacocinetiche delle diverse formulazioni di Levodopa

FORMULAZIONE	T_{max} (m)	$T_{1/2}$ (h)	Biodisponibilità(%)
L-dopa +ID SINEMET/MADOPAR	30-120	1 - 3	99
L-dopa + carbidopa RM	120-180	4 - 5	70
L-dopa + benserazide HBS	120-240	6 - 8	60
Melevodopa SIRIO	20-60	0,2-0,6	99
L-dopa+carbidopa + Entacapone STALEVO	30-120	1- 5	99

Dopaminoagonisti. Rispetto alla levodopa:

- **minore efficacia nel controllo dei sintomi parkinsoniani**
  maggiore incidenza di effetti collaterali

- **minore incidenza di complicanze motorie**

Gruppo	Farmaco	Interazione recettori dopamina (famiglie)	Emivita (h)	Dosaggio medio giornaliero (mg)
Ergot-derivati	Bromocriptina	D2	6	25-45
	Lisuride	D2	1-7	0,8-0,16
	Pergolide	D2>D1	15-27	1,5-5,0
	Cabergolina	D2	65	2-6
	Diidroergocriptina	D2 (±D1)	12	60-80
Non ergot-derivati	Pramipexolo	D2	8-12	0,375-4,5
	Ropinirolo	D2	3-10	6-18
	Apomorfina	D2/D1	0,5	1,5-6,0 per ogni bolo
	Rotigotina	D2/D1	3-7	8-16

Dopaminoagonisti
Effetti collaterali

- **Periferici:**
  - **nausea, vomito**
  - **ipotensione ortostatica**
  - **edemi periferici**
  - **aumento della pressione oculare**
  - **reazioni cutanee in sede di posizionamento del cerotto (rotigotina)**

- **Centrali:**
  - **discinesie**
  - **psicosi dopaminergica (allucinazioni, stati confusionali, deliri)**
  - **sonnolenza/attacchi improvvisi di sonno**
  - **disturbi del controllo degli impulsi (gambling o gioco d'azzardo patologico, sessualità compulsiva, alimentazione compulsiva, shopping patologico, punding)**
  - **sindrome da disregolazione dopaminergica (auto-somministrazione di farmaci dopaminergici fino alla dipendenza)**

Anticolinergici
Tremore resistente ai farmaci dopaminergici

- **Effetti collaterali**

- **Periferici:**
  - **ritenzione urinaria**
  - **Stipsi**

- **Centrali:**
  - **Deficit cognitivi**

Controindicazioni:
- **glaucoma ad angolo chiuso**
- **tachicardia**
- **ipertrofia prostatica**
- **occlusione intestinale**

Possibile rebound del tremore alla sospensione

Treatment Strategies in Early Parkinson's Disease

Luca Marsili*,†, Roberto Marconi†, Carlo Colosimo‡,1

International Review of Neurobiology, Volume 132 **2017**

The appropriate choice of pharmacological therapy for early Parkinson's disease depends on many factors:

- **patient's age at onset**
- **employment-related features**
- **lifestyle**
- **phenomenology and severity of motor symptoms**
- **presence of nonmotor features such as cognitive or behavioral abnormalities**
- **comorbidities**

However, even when all these variables have been considered, the question of when pharmacological therapy should be initiated remains controversial

There are two different approaches:

1) **“watch-and-wait” strategy (delaying treatment until the patient’s clinical condition is such that pharmacological therapy is indispensable)**

1) **initiation of treatment as soon as the diagnosis is made**

Luca Marsili*,†, Roberto Marconi†, Carlo Colosimo‡,1

International Review of Neurobiology, Volume 132 **2017**

- **Early initiation of therapy in PD allows the motor symptoms of the disease to be controlled more effectively and the quality of life to be improved**

- **No studies have unequivocally shown that early PD therapy slows down the clinical progression of PD**

- **Delayed initiation of PD treatment instead has other advantages, which include reduced adverse effects of anti-PD medication and lower costs for health services**

- **Unfortunately, delayed initiation of therapy is also associated with a greater disability and a higher likelihood of loss of productivity, which have consequences for both patients and society in the long term**

There is thus a widespread consensus among neurologists that delayed initiation of therapy cannot be considered a successful strategy because the primary goal of treatment should be the improvement in patients' function and quality of life

Luca Marsili*,†, Roberto Marconi†, Carlo Colosimo‡,1
International Review of Neurobiology, Volume 132 **2017**

- **The question of when and how pharmacological therapy should be initiated remains controversial, with no general consensus being reached in international guidelines**

- **As a practical suggestion, we recommend that treatment in younger patients (i.e., younger than 70) or in those without high functional requirements be started with DAs and/or MAO-B I**

- **By contrast, treatment in older patients or in those with high functional requirements should start directly with low doses of levodopa**

Marsili et al. 2017

Initial treatment of Parkinson's disease in 2016:
The 2000 consensus conference revisited

REVUE NEUROLOGIQUE 172 (2016) 512–523

C. Laurencin [a,c,*], T. Danaila [a], E. Broussolle [a,b,c], S. Thobois [a,b,c]

Timing of treatment initiation: early or late?

The question of timing needs further study, whereas the current consensus is that the treatment remains symptom-based and should be started as soon as functional impairment occurs

Which treatment is used first when patient disability is present?

- **When functional impairment is limited, rasagiline could be proposed as monotherapy for its symptomatic effects and potential disease-modifying action, even though evidence of its neuroprotective action remains to be demonstrated**
- **When patients need a more powerful treatment two major options are possible: DAs and LD**
- **LD sparing could still be advised as a first-line treatment for young patients, although the cut-off point in terms of age remains arbitrary (? < 70, < 65, < 60 years)**
- **The advantage of delaying the occurrence of motor complications and dyskinesias is particularly important for younger patients, and goes with delaying LD initiation, although LD itself is not the cause of motor complications**

- **DA monotherapy should be considered carefully and with clear information as regards the patient and caregivers, especially in "at-risk" subjects (young, single and male). Earlier than was thought in 2000, clinicians should consider adding LD to Das even in young-onset patients and not push the DA monotherapy strategy too far**

- **LD remains the most effective treatment for motor symptoms in PD, and should be added to early-stage PD treatment when symptoms are not sufficiently relieved by DAs**

- **In older patients (? > 70, > 65 years), LD is still recommended as the first-line treatment**

- **With LD, as motor complications are related to dosage, LD should be kept at the lowest dose effective for controlling motor symptoms**

Laurencin et al. 2016

- **Nowadays, other characteristics of PD patients should also be taken into account: are there risk factors for ICD, which will make us more cautious about DAs? Are there prominent non-motor symptoms that will be more responsive to DAs than to LD? Thus, the decision will have to be tailored to the given patient**

- **For younger patients with severe tremor, anticholinergic treatments are not superior to LD or DAs and, indeed, are responsible for more frequent and serious side effects. Therefore, their prescription should remain limited even in younger patients, and should be clearly avoided in older ones**

- **The level of evidence for amantadine efficacy is poor**

- **COMT-Is have not shown any additional benefits compared with LD in early PD**

Laurencin et al. 2016

Pharmacological management of motor symptoms

Before starting treatment for people with Parkinson's disease, discuss:

- **the person's individual clinical circumstances, for example, their symptoms, comorbidities and risks from polypharmacy**
- **the person's individual lifestyle circumstances, preferences, needs and goals**
- **the potential benefits and harms of the different drug classes**

	Levodopa	Dopamine agonists	MAO-B inhibitors
Motor symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of daily living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

NICE National Institute for Health and Care Excellence
NICE guideline
Published: 19 July 2017
nice.org.uk/guidance/ng71

- **Antiparkinsonian medicines should not be withdrawn abruptly or allowed to fail suddenly due to poor absorption (gastroenteritis, abdominal surgery) to avoid the potential for acute akinesia or neuroleptic malignant syndrome**

- **The practice of withdrawing people from their antiparkinsonian drugs (so called 'drug holidays') to reduce motor complications should not be undertaken because of the risk of neuroleptic malignant syndrome**

First-line treatment

- **Offer levodopa to people in the early stages of PD whose motor symptoms impact on their quality of life**

- **Consider a choice of dopamine agonists, levodopa or monoamine oxidase B (MAO-B) inhibitors for people in the early stages of PD whose motor symptoms do not impact on their quality of life**

- **Do not offer ergot-derived dopamine agonists as first-line treatment for PD**

NICE National Institute for Health and Care Excellence
NICE guideline
Published: 19 July 2017
nice.org.uk/guidance/ng71

Information and support

When starting treatment for people with PD, give people and their family members and carers (as appropriate) oral and written information about the following risks, and record that the discussion has taken place:

- **Impulse control disorders with all dopaminergic therapy (and the increased risk with dopamine agonists)**
- **Excessive sleepiness and sudden onset of sleep with dopamine agonists**
- **Psychotic symptoms (hallucinations and delusions) with all treatments (and the higher risk with dopamine agonists)**

NICE National Institute for Health and Care Excellence
NICE guideline
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Predictors for the development of impulse control disorders

- **Impulse control disorders can develop in a person with PD who is on any dopaminergic therapy at any stage in the disease course**

- **The following are associated with an increased risk of developing impulse control disorders:**

  - **Dopamine agonist therapy**

  - **A history of previous impulsive behaviours**

  - **A history of alcohol consumption and/or smoking**

NICE National Institute for Health and Care Excellence
NICE guideline
Published: 19 July 2017
nice.org.uk/guidance/ng71

Information and support

When starting dopamine agonist therapy, give people and their family members and carers (as appropriate) oral and written information about the following, and record that the discussion has taken place:

- **The increased risk of developing impulse control disorders when taking dopamine agonist therapy, and that these may be concealed by the person affected**
- **The different types of impulse control disorders (compulsive gambling, hypersexuality, binge eating and obsessive shopping)**
- **Who to contact if impulse control disorders develop**
- **The possibility that if problematic impulse control disorders develop, dopamine agonist therapy will be reviewed and may be reduced or stopped**
- **Discuss potential impulse control disorders at review appointments, particularly when modifying therapy, and record that the discussion has taken place**
- **Be aware that impulse control disorders can also develop while taking dopaminergic therapies other than dopamine agonists**

Managing dopaminergic therapy in people who have developed an impulse control disorder

If a person with PD has developed a problematic impulse control disorder, seek advice from a healthcare professional with specialist expertise in PD before modifying dopaminergic therapy

Discuss the following with the person and their family members and carers (as appropriate):

- **How the impulse control disorder is affecting their life**
- **Possible treatments, such as reducing or stopping dopaminergic therapy**
- **The benefits and disadvantages of reducing or stopping dopaminergic therapy**
- **When managing impulse control disorders, modify dopaminergic therapy by first gradually reducing any dopamine agonist. Monitor whether the impulse control disorder improves and whether the person has any symptoms of dopamine agonist withdrawal**
- **Offer specialist cognitive behavioural therapy targeted at impulse control disorders if modifying dopaminergic therapy is not effective**

International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease

Susan H. Fox, MRCP, PhD,[1,2*] Regina Katzenschlager, MD,[3] Shen-Yang Lim, MD, FRACP,[4] Brandon Barton, MD, MS,[5,6] Rob M. A. de Bie, MD, PhD,[7] Klaus Seppi, MD,[8] Miguel Coelho, MD,[9] Cristina Sampaio, MD, PhD,[10,11]

Movement Disorders, Vol. 00, No. 00, 2018

Treatments That May Delay/Prevent Disease Progression

- **To date, no intervention has shown efficacy or is designated as being useful in clinical practice as a means of preventing or slowing PD disease progression**
- **Dietary/nutritional supplements, including coenzyme Q10, creatine, and vitamin D remain popular among PD patients because of widespread availability, ease of use, and good tolerability, but the EBM review shows that there is no evidence of clinical benefit**
- **Overall, the area of slowing and preventing disease progression in PD remains a large unmet need**

Treatments for Symptomatic Monotherapy (Including Strategies to Delay/Prevent Motor Complications)

- **There are a number of factors that need to be considered when deciding which intervention to offer an early PD patient requiring treatment for motor symptoms**
- **These include the level of disability, the relative efficacy of the therapy, potential side effects, and the need to prevent the development of long-term motor complications**
- **There are several options for monotherapy in early PD. Both levodopa and all DAs improve motor symptoms when compared with placebo**
- **The relative efficacy of the different DAs appears to be similar. The choice of DA may thus depend on the duration of action (e.g., shorter duration with IR vs longer acting ER)**

FOX ET AL **2018**

Treatment of initial phase

- **The clinical equipoise has consistently been whether a patient with early PD should be started on levodopa or a "levodopa-sparing" option such as a DA or an MAO-B inhibitor to delay the emergence of motor fluctuations and dyskinesia**

- **In longer term follow-up, the available evidence suggests that there is no clinically relevant difference on motor function, troublesome motor complications, or mortality according to the choice of initial therapy**

- **MAO-B inhibitors (selegiline and rasagiline) improve motor symptoms in early PD, but the effect size has been smaller than with levodopa and DAs**

- **The evidence for delaying motor fluctuations with rasagiline or selegiline remains "investigational" ; selegiline is "not useful" for delaying dyskinesia**

FOX ET AL **2018**

Treatment of initial phase

- **Overall, the choice of treatment in early disease thus depends on the need for relief from motor symptoms and tolerability/side effects both over the short and long term**

- **Factors to be taken into account include the higher risk of motor complications in younger onset patients and personal circumstances**

- **These may include the need for rapid improvement for reasons of employment (which would favor initial levodopa) or the predominant need or desire to delay dyskinesia for as long as possible (which favors levodopa-sparing initial treatments)**

FOX ET AL **2018**

Dopamine-agonists

- **The major issue with DAs (at all disease stages) remains side effects**
- **The ergot DA-related side effects (including fibrosis/restrictive heart valve changes) have reduced the use in most areas of the world**
- **Overall, nonergot DAs have similar profile of side effects (sleepiness, postural hypotension, peripheral edema, and neuropsychiatric issues). Rotigotine has additional side effects related to the transdermal administration**
- **In clinical practice, a significant side effect is the high risk of impulse control disorders (ICDs) with DAs compared to levodopa**
- **Although lower rates of ICDs associated with long-acting or transdermal Das have been reported, to date there has been no interventional study evaluating the relative risk of ICDs between the DAs, and this remains an important area of research**

FOX ET AL **2018**

Grazie