

## PARKINSON'S DISEASE: THERAPEUTIC OPTIONS

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*[Malattia di Parkinson: opzioni terapeutiche]*

### ABSTRACT

Parkinson's disease is an idiopathic, relentlessly progressive, neurologic disorder manifested clinically by tremor, bradykinesia, rigidity, and postural instability. After completing the diagnostic procedure and having verified the need to start drug treatment, we follow the criteria for therapy aimed at maximum benefits with minimal side effects in the short and long term.

This paper examines, step by step, the different treatment options.

**Key words:** Parkinson's disease, parkinsonism, l-dopa, dopamine agonist therapy.

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### Introduction

Parkinson's disease is an idiopathic, slowly progressive disease, characterized by tremor, rigidity, akinesia and postural instability.

Due to the existence of multiple clinical conditions with parkinsonism and to the lack of a certain diagnostic method for the disease, it is crucial to understand all of the clinical nuances in order to correctly diagnose it<sup>(1)</sup>.

Evidence of an akinetic-rigid syndrome, associated or not with tremor, leads a diagnosis of Parkinson's disease. It should be borne in mind that some anatomo-clinical correlation studies have shown that as much as 20-25% of patients, diagnosed in vivo as suffering from idiopathic Parkinson's disease, actually had different diseases and in particular multiple system atrophy (MSA), PSP, vascular encephalopathy, etc.<sup>(2)</sup>.

Therefore, it is necessary to make the effort to identify those symptoms that enable us to orient the diagnosis as safely and accurately as possible towards one of the degenerative diseases that have parkinson-like symptomatology. Clinical tool at our disposal is observation at the time of the first visit

and longitudinal observations in the course of the disease, associated with data of instrumental exams, where appropriate, such as MRI, SPECT, and neurophysiology.

Many clinical data are useful for the differential diagnosis of akinetic-rigid degenerative syndromes (Parkinson's disease, PSP, MSA, corticobasal degeneration, Lewy body dementia).

In the initial phase of the disease, some clinical findings are of particular importance to suspect a disease other than Parkinson's disease:

- early impairment of the autonomic nervous system directs the diagnosis toward MSA.
- presence of ataxia when walking, cerebellar signs or nystagmus should lead you to think of an MSA like sporadic OPCA
- instability of balance and tendency to fall from the first year of illness should raise the suspicion of PSP<sup>(3,4)</sup>
- a marked stiffness of a limb, especially the upper ones, with dystonic contraction, is typical of corticobasal degeneration; this symptom should not be confused with the acute painful symptoms of rare diseases<sup>(5)</sup>
- rapid development of an akinetic-rigid, sym-

metrical picture raises the suspicion of nigrostriatal MSA

- early cognitive impairment suggests widespread Lewy body dementia, Alzheimer's disease with extrapyramidal symptoms or finally an association of Parkinson's disease and Alzheimer's disease<sup>(6)</sup>

- osteotendineal hyperactivity or a prevalence of symptoms only in both lower limbs: it is the typical picture of vascular parkinsonism associated with small-step gait and sphincter disturbances<sup>(7,8)</sup> or demyelination<sup>(9)</sup>.

- when symptoms are asymmetrical, tremor is present, the course is slow, there is a good response to dopaminomimetic substances, and hypomimia (10) and MRI are normal, a diagnosis of idiopathic Parkinson's disease can be made

- when in the same generation two or more people are affected, the response to L-dopa is good, the onset is early and the course is slow, one can assume Parkinson's disease due to parkin alteration.

## Therapy

The first treatment of the disease dates back to early 20th century and was suggested by the observation and the attempt to treat one of the most common symptoms: hypersalivation.

The mechanism of *Atropa belladonna* extract in inhibiting the salivation was known: this treatment proved surprisingly effective not only for the hypersalivation, but also for the other symptoms of the disease. This observation led later to the hypothesis of the acetylcholine-dopamine balance, which still retains some validity.

In recent years, accurate treatment guidelines<sup>(11)</sup> have been defined to keep the symptoms of Parkinson's disease under control as long as possible and in the presence of reduced side effects. Knowledge of the disease and clinical experience must be accompanied by knowledge of the patient who should be assessed and treated as a single case and the staging of the patient's disease becomes a key point of reference in defining the therapy.

A simple staging of Parkinson's disease is shown in Table 1.

The choice between the various options for drug treatment is subject to the knowledge of the precise location that the many currently available drugs (Table 2) have in the therapeutic algorithm of Parkinson's disease, as indicated in Table 3.

This knowledge is essential to avoid the use of certain drugs at an inappropriate stage of the dis-

ease, thereby wasting therapeutic options and exposing patients to side effects without any effective therapeutic benefit.

In the early stage of disease, a therapeutic treatment should be started only when clinical signs of functional impairment appear, namely when patients are unable to perform common daily activities or do their work. The functional deficit should therefore be assessed individually and in the context of the lifestyle of the individual patient.

At the onset of functional deficit, treatment with I-MAO B<sup>(8)</sup> can be started or, after careful titration, dopamine agonists can be administered. Compared to L-dopa, these have a minor symptomatic effect but determine motor complications with lesser frequency, and allow postponing the use of levodopa to the time when the dopaminergic drugs alone are no longer able to control the symptoms of Parkinson's disease. Advanced age (> 70 years) and a higher functional demand make the delay of the use of L-dopa less stringent. In these cases, it is appropriate to use initially L-dopa in the slow-release formulation and switch to fast-acting L-dopa in case of poor therapeutic response.

Therefore, the treatment options available in the initial stage of the disease are:

- monotherapy with a dopamine agonist;
- combination of L-dopa and dopaminergic agent;
- monotherapy with L-dopa.

Key factors in the choice of treatment are age and functional demands of the patient.

In the intermediate stage of the disease, therapy should be continued unchanged if the patient is compensated. If the patient is not compensated and reaches this stage in monotherapy with a dopamine agonist, the strategy of first choice is the introduction of L-dopa/carbidopa in controlled release formulation, starting with the minimum effective dose (tablets of slow-release L-dopa/carbidopa at a dose of 100/25 mg once a day), in order to reach, over a period of one month, the optimal dose (one 100/25-mg tablet three times a day), in association the dopaminergic agonist. Failure to resolve the symptoms or their worsening requires the association of immediate-release formulations, starting with the minimum effective dose (half a tablet of L-dopa/carbidopa at a dose of 100/25 mg once a day), to reach, in a period of one month, the optimal dose (half tablet four times a day or one tablet three times a day) and possibly increasing, the single dose or the number of daily administrations in the

STAGE	EARLY	INTERMEDIATE	ADVANCED
YEARS AFTER DIAGNOSIS	3-5	5-10	>10
CLINICAL PICTURE	mild motor signs	Impaired balance, on-off cycles, difficult walking, difficulty to initiate movement, postural instability	Severe dyskinesias, long off periods
MOTOR COMPLICATIONS	Relatively infrequent	50 to 70% of patients	70 to 80 % of patients
RESPONSE TO LEVODOPA OR DOPAMINE AGONISTS (DA)	Excellent	decreased yet present	Heavily decreased
QUALITY OF LIFE	normal or almost	decreased	Severely affected
DAILY ACTIVITIES	normal or almost	possible request for assistance	Assistance needed

**Table 1:** Staging of Parkinson's disease<sup>1</sup>.

event of persistent functional deficit. The daily dosage of L-dopa should be kept below 500 to 600 mg for as long as possible, by administering higher doses only if the control of the symptoms is not otherwise achievable.

There is no standard dosage ceiling and some patients may require up to 1500 mg or more of L-dopa a day. The principle is always to use the lowest dose capable of keeping symptoms under control without any side effects not tolerated by the

patient. L-dopa and DA agonists have an excellent action on bradykinesia and rigidity, while tremor is poorly responsive to these drugs. Only if the tremor causes functional disability and in the absence of contraindications (glaucoma, heart rhythm disorders, cognitive impairment, prostatic hypertrophy, constipation ...), an anticholinergic drug may be used. Another theoretically feasible treatment option before switching to treatment with L-dopa is to change DA agonist.

Dopamine precursors: L-dopa associated with peripheral dopa decarboxylase inhibitor (carbidopa, benserazide)
Dopamine agonists: bromocriptine*, apomorphine, dihydroergocryptine*, pergolide*, lisuride*, cabergoline*, ropinirole, pramipexole
Adamantane derivatives: amantadine
Monoamine oxidase type B inhibitors (MAO-B): selegiline, rasagiline
Inhibitors of catechol-O-methyltransferase (iCOMT): entacapone, tolcapone **
Anticholinergics: orphenadrine, biperiden, biperidine, metixene, procyclidine, trihexyphenidyl
Antidepressants: Tricyclic antidepressants (amitriptyline, and others), serotonin reuptake inhibitors (fluoxetine, escitalopram, sertraline, and others)
Antipsychotics: clozapine, quetiapine, olanzapine

\* Not recommended due to side effects, \*\* suspended from sale in November 1998 due to the occurrence of fatal cases of hepatitis; to date it can be prescribed under close monitoring by a specialist

**Table 2:** Classes of drugs used in the therapy of Parkinson's disease

If the patient is being treated with L-dopa and DA agonist begins to show a suboptimal response, a decrease in efficacy in controlling the symptoms or signs of end-of-dose deterioration, it is possible to increase the dosage of the DA agonist leaving unchanged the dose of L-dopa or vice versa. If the first option is chosen, the dose of DA agonist should be increased until an adequate improvement in symptoms is gradually achieved and in some cases by resorting to premedication with domperidone (up to 60 mg/day in three separate doses) 30 to 60 minutes before taking the DA agonist. In the absence of an effective response or in the presence of side effects, it is possible to change DA agonist according to three different possible modes:

➤ Rapid change of the DA agonist from one day to another

➤ Reduction (by about 20%) in the first days of the dosage of the new DA agonist and subsequent increase until reaching an optimal therapeutic response

➤ Gradual reduction of the first DA agonist at the same time as the association of the new DA-agonist.

In case of the second option, the dose of the individual doses of L-dopa must be increased gradually until a good response is achieved while maintaining or possibly reducing the dose of the DA agonist. Alternatively, you can increase the number of daily doses of levodopa, administering the next dose before the end of the effect of the previous dose. An age of over 70 years, episodes of psychosis or orthostatic hypotension, signs of cognitive impairment, presence of autonomic or cardiovascular comorbidities should point to the use of L-dopa alone.

If the patient reaches the intermediate state on monotherapy with L-dopa and starts to have a reduced response to treatment or signs of end-of-dose deterioration, the single doses or the number of daily doses should be increased (at this stage no more than 4-5 doses a day). Patients in non-advanced age and not at risk of side effects can be treated with a DA agonist, whose dose should be increased gradually until the effective dose is reached without exceeding the maximum dosage allowed

The therapeutic path indicated above is intended to ensure a dopaminergic pharmacological stimulation like the physiological one of tonic nature for the longest possible span of time, in order to delay the onset of motor complications associated with

pulsatile stimulation provided by the pharmacological treatment. In the advanced stage of the disease, however, in most patients, motor and non-motor complications related with the progression of the disease and treatment with L-dopa occur. A reduced response to L-dopa should be treated by increasing the dose possibly by adding DA agonists, i-COMT or i-MAO-B. End-of-dose deterioration can be fought by manipulating the number of doses of L-dopa or increasing them, by increasing the dose of the DA agonist while maintaining a constant dose of L-dopa, by associating an i-COMT, entacapone at a dose of 200 mg in combination with each dose of L-dopa, or by using formulations of L-dopa-retard or i-MAO-B (selegiline), or, finally, through surgical treatment. On-off phenomena can be treated with the following treatment options:

- I-comt (entacapone, 200 mg) in combination with each dose of immediate-release L-dopa

- Use, in combination with L-dopa, of a DA agonist at the highest dose allowed in the absence of side effects

- liquid preparations of L-dopa (Levomet) in two daily doses when the number of off episodes is limited

- subcutaneous administration of apomorphine by penject, at the average dose of 2-4 mg/dose in 3 to 4 daily boluses

- infusion of apomorphine with programmable pumps when there are numerous daily off episodes requiring too many of boluses

- the intake of L-dopa on an empty stomach and moving the protein meal to the evening may facilitate the absorption of L-dopa to a certain extent.

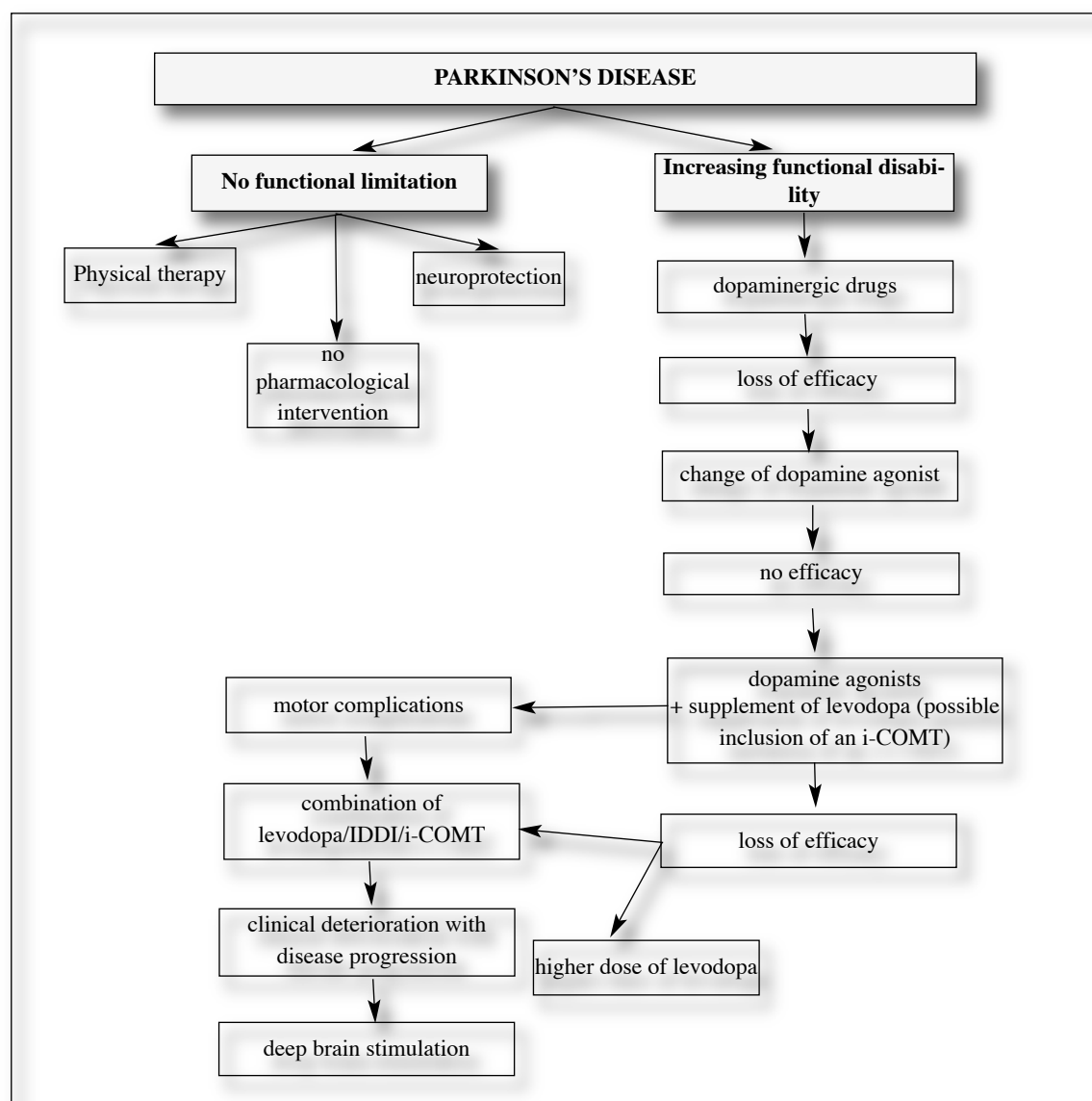
The treatment of the various medical conditions possible in the advanced stage of the disease (such as sudden motor block, the so-called peak or end-of-dose dyskinesias, dystonias) is susceptible to a specific drug treatment chosen and personalized for each individual case.

With regard to the treatment of dystonia in the morning, it coincides with that of akinesia at night and at wake up and recognizes the following treatment options:

- use of controlled-release L-dopa/IDD at bedtime, possibly in association with entacapone

- use as the first dose of the morning of rapid-release or liquid L-dopa before getting up.

In addition to motor complications, a number of non-motor complications and comorbidities may affect the advanced stage of the disease and require



**Table 3:** Treatment algorithm of Parkinson's disease<sup>(11)</sup>.

a specific drug treatment, such as depression, anxiety, insomnia, orthostatic hypotension, urinary incontinence, and disorders of the memory and other cognitive activities<sup>(12-16)</sup>.

In an advanced stage of Parkinson's disease, despite the best drug therapy possible, the response may become poor and the clinical picture very serious. The last possibility that remains in this condition is that of surgical treatment. Possible surgical treatments are:

- the lesion or high-frequency deep brain stimulation of the ventral intermediate nucleus of the thalamus, indicated in the forms of the disease involving tremor
- pallidotomy or high-frequency bilateral deep brain stimulation of the postero-ventral region of the pallidum, indicated when the main problem is

dyskinesia

- deep brain stimulation of the subthalamic nucleus of Luys, which is currently the most effective treatment for the significant improvement in terms of rigidity, tremor, and bradykinesia.

The indications for surgical treatment<sup>(17)</sup> are age <70 years, the absence of significant internal diseases and psychiatric disorders, a very serious clinical picture in a patient with Parkinson's disease at an advanced stage, a good response to L- dopa in the early stages and finally a normal brain MRI.

Another therapeutic approach is finally the transplantation of embryonic mesencephalic neurons, but after the first studies that claimed positive results, a long series of large-scale prospective, randomized clinical trials has followed. These have registered only a moderate benefit in some patients

following transplantation of embryonic mesencephalic neurons, with modest functional improvement during the off period and a minor reduction of dyskinesias.

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