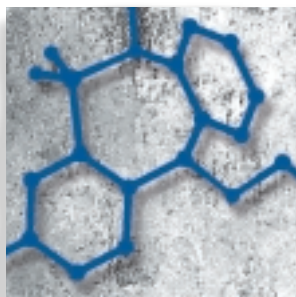


# Pharmacological aspects

## Drug treatment of Parkinson's disease

Amos D. Korczyn, MD, MSc



**P**arkinson's disease (PD) is the second most common neurodegenerative disease, affecting some 30 million patients worldwide. Like Alzheimer's disease (AD), it affects the elderly and causes considerable disability and suffering. The role of dopamine (DA) as a brain neurotransmitter was discovered in the 1960s, and it was noted that there was a loss of this substance in specific brain areas in PD, which was linked to degenerative changes in the substantia nigra, where DA cell bodies are located. This opened the door to the modern treatment of PD. The identification of DA as a key neurotransmitter in the extrapyramidal system and its depletion in PD rapidly resulted in a revolution in the treatment of PD and some related disorders.

### Levodopa

The introduction of dihydroxyphenylalanine (levodopa) to the treatment of PD was a major scientific and clinical breakthrough in the treatment of this devastating disease.

*Parkinson's disease (PD) is a common neurodegenerative disease. While its cause remains elusive, much progress has been made regarding its treatment. Available drugs have a good symptomatic effect, but none has yet been shown to slow the progression of the disease in humans. The most efficacious drug is levodopa, but it remains unclear whether the symptomatic benefit is associated with neurotoxic effects and long-term deterioration. The long-term problem associated with levodopa is the appearance of dyskinesias, which is significantly delayed among patients treated with dopamine agonists as initial therapy. Less clear is the role of other drugs in PD, such as monoamine oxidase inhibitors (MAOIs), including selegiline and rasagiline, the putative N-methyl-D-aspartate (NMDA) receptor antagonists amantadine and memantine, and the muscarinic receptor blockers. All these may be used as initial therapy and delay the use of dopaminergic drugs, or can be added later to reduce specific symptoms (tremor or dyskinesias). Advanced PD is frequently associated with cognitive decline. To some extent, this can be helped by treatment with cholinesterase inhibitors such as rivastigmine. Similarly, hallucinations and delusions affect PD patients in the advanced stages of their disease. The use of classical neuroleptic drugs in these patients is contraindicated because of their extrapyramidal effects, but atypical drugs, and particularly clozapine, are very helpful. The big void in the therapy of PD lies in the more advanced stages. Several motor symptoms, like postural instability, dysphagia, and dysphonia, as well as dyskinesias, are poorly controlled by existing drugs. New therapies should also be developed against autonomic symptoms, particularly constipation.*

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**Author affiliations:** The Sieratzki Chair of Neurology, Sackler School of Medicine, Tel-Aviv University, Ramat-Aviv, Israel

**Address for correspondence:** Amos D. Korczyn, MD, MSc, Sieratzki Chair of Neurology, Sackler School of Medicine, Tel-Aviv University, Ramat-Aviv 69978, Israel  
(e-mail: neuro13@post.tau.ac.il)

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## Selected abbreviations and acronyms

<b>L-AAD</b>	<i>l-amino acid decarboxylase</i>
<b>AD</b>	<i>Alzheimer's disease</i>
<b>COMT</b>	<i>catechol-O-methyltransferase</i>
<b>DA</b>	<i>dopamine</i>
<b>DAA</b>	<i>dopamine agonist</i>
<b>MAOB</b>	<i>monoamine oxidase B</i>
<b>PD</b>	<i>Parkinson's disease</i>

This can be considered in two aspects. First, of course, is the enormous benefit to patients. Second, comes the realization that an understanding of biochemical deficits can provide a clue as to how replacement therapy could be successfully employed in neurodegenerative diseases, providing significant symptomatic benefit, if not a cure. Dopa had an enormous impact on attempts to treat other neurodegenerative disorders, particularly AD. Unfortunately, in spite of miraculous effects on patients with early and advanced PD and the motor benefits afforded to them, it soon became clear that dopa does not slow the neurodegenerative process and its effects are purely symptomatic. Consequently, the dopa dose required to control the motor manifestations must be gradually increased as the disease progresses. It quickly became clear also that, of the two dopa isomers, only the levorotatory stereoisomer, levodopa, produced therapeutic benefits, and chemical means to separate the two isomers were developed. In practice, only levodopa is now used in the treatment of PD, resulting in an improved safety profile. Soon after came the recognition that some of the adverse effects associated with the drug were the result of peripheral—rather than central—conversion of levodopa into DA, which, unlike levodopa, has significant autonomic activity.<sup>1</sup> Since DA does not cross the blood–brain barrier (BBB), any DA produced in the peripheral nervous system does not contribute to the clinical benefits afforded by levodopa, and actually causes significant adverse events, particularly gastrointestinal and other autonomic disturbances. The enzyme involved in the transformation of levodopa to DA, ie, *l*-amino acid decarboxylase (L-AAD, initially called dopa decarboxylase) is widespread in the body, with high concentrations in the liver. Two agents were developed that could inhibit it, and both are still in use: carbidopa and benserazide. At present, practically all patients who require treatment with levodopa receive it as a fixed-dose combination with one of these inhibitors. Of course, it is essential that levodopa be converted into DA in the brain, and so the L-AAD inhibitor should not cross the BBB.

The inhibition of peripheral L-AAD has another result, which was initially unappreciated: it prolongs the biological half-life of levodopa (and therefore also of DA in the brain). This effect is important in advanced PD. Early on in PD, there is a dramatic beneficial effect of levodopa, described as the “honeymoon.” As the disease advances and additional DA neurons are being lost, there is a need to compensate for this by increasing the daily dose of levodopa. This is first manifested by shortening of the duration of action of individual levodopa doses, called “end-of-dose” effect or wearing off. Later on, other manifestations appear, including “peak of dose” dyskinesias and erratic responses to levodopa (so-called unexpected “on-off,” or yo-yoing) (*Table I*). While the exact mechanism responsible for this erratic response is still elusive, it is at least partly dependent upon pharmacokinetic factors such as plasma levels of levodopa. In particular, the phenomenon of wearing off, where the initial prolonged response to individual doses of levodopa is no longer maintained,<sup>2</sup> limits the patients’ independence. Wearing off probably results from impaired capacity of the nigrostriatal DA neurons and their terminals to uptake, store, and release DA. This problem becomes more severe as more and more ter-

### Parkinson's disease

Adult-onset, progressive, predominantly motor disorder

Combining 2 or more of the following:

- Resting tremor
- Bradykinesia
- Limb rigidity
- Gait instability (late)

Dramatic response to levodopa

Accepted associated phenomena:

- Depression (early or late)
- Cognitive decline (early or late)
- Autonomic dysfunction (mainly constipation)

### Advanced Parkinson's disease

Chronic progressive disease

With deterioration of:

- Gait and balance
- Motor manifestations
- Nonmotor problems (eg, dementia, autonomic dysfunction)

Variable response to therapy:

- Fluctuations and/or drug-induced complications
- Short duration response: delayed or partial “on,” wearing off, dyskinesias

**Table I.** Clinical definition of Parkinson's disease and advanced Parkinson's disease.

minals degenerate.<sup>3</sup> Blockade of peripheral L-AAD, which prolongs the biological half-life of the drug, can only incompletely compensate for this.

Levodopa remains the “gold standard” of PD therapy. It is the most potent antiparkinsonian drug available.<sup>4</sup> However, several key symptoms of PD fail to respond to levodopa, or have a limited or unsatisfactory response (*Table II*). As discussed above, the long-term use of levodopa often leads to complications later in the disease; wearing-off, dyskinesias, freezing episodes, and unpredictable “on-off” fluctuations are the most problematic.<sup>5</sup> The pathogenesis and pathophysiology of these complications remain unclear, but it has been suggested that they are related to the toxicity of levodopa or its metabolites. The pharmacokinetic and pharmacodynamic changes that take place as the disease progresses may be major contributors. It has also been speculated that the complications may derive, at least in part, from the toxic effects of levodopa or DA oxidative metabolites.

Since levodopa alleviates the symptoms of the disease, accurate assessment of the patient's real condition and monitoring of disease progression are problematic. At present, the only way to assess progression or deterioration is by withdrawing levodopa for a period exceeding 2 weeks. Obviously, this is not a practical solution particularly in the advanced stages of the disease and therefore our ability to monitor the rate of disease progression is limited. Biological surrogate markers are constantly being sought. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) techniques are being developed and have shown significant correlations with global severity of PD.<sup>6</sup>

### COMT inhibitors

Catechol-*O*-methyltransferase (COMT) is a ubiquitous enzyme that breaks down levodopa before it can be converted to DA, as well as DA itself. COMT inhibitors prolong the availability of a single dose of levodopa, without delaying the onset of its effects, frequently reducing the total amount of levodopa needed. The present indication

Posture and gait problems, speech problems, freezing
Autonomic dysfunction
Cognitive disorders
Affective disorders
Sleep problems

**Table II.** Symptoms unresponsive to levodopa.

for COMT inhibition is as an adjunctive therapy to levodopa in advanced PD patients who have developed wearing off or “on-off” fluctuations.<sup>7,8</sup> However, COMT treatment in the earlier stages of PD may also be worthwhile by preventing or delaying motor complications. COMT inhibition as a new treatment strategy for PD has been recently comprehensively reviewed.<sup>9,10</sup>

Two COMT inhibitors have been widely tested so far: tolcapone and entacapone. Although motor fluctuations such as “off” periods are frequently reduced or eliminated by the use of tolcapone or entacapone, peak dose dyskinesias can be enhanced or precipitated, requiring a reduction in individual doses of levodopa. Both drugs were shown to improve the patients' quality of life. Tolcapone was recently removed from the market in most countries due to presumed hepatic toxicity. However, the exact relationship to drug exposure is still ambiguous. On the basis of the rarity of these adverse events, some practitioners believe that its withdrawal was premature, arguing that the drug is possibly superior to entacapone (although a direct comparison between the two has not been performed).

Entacapone has a brief duration of action of approximately 2 h, ie, it has to be consumed with each levodopa dose (or even more frequently). Preparations containing levodopa, entacapone, and a decarboxylase inhibitor in a single tablet or capsule could be beneficial, especially for patients who are treated with other drugs as well. Long-acting derivatives or sustained-release formulations of entacapone could also be advantageous.

### DA agonists

DA agonists (DAAs) have been an important tool in the treatment of PD for almost 40 years.<sup>11</sup> The first study of DAAs by Calne et al<sup>12</sup> constituted a milestone in PD therapy. These drugs were introduced shortly after the discovery of levodopa and were initially thought to represent second- or even third-line agents. This was because they were effective in patients who had developed intolerance to—or side effects of—levodopa. Their initial use demonstrated not only their efficacy against rigidity and tremor, but also their dopa-sparing effects. The possibility of reducing the dose of levodopa gradually became more important as the complications of chronic levodopa therapy were recognized, particularly dyskinesias and motor fluctuations. The ability to replace some of the levodopa dose with a DAA resulted in amelioration of these

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motor disturbances, also proving that they are not necessarily an unavoidable development in chronic PD.

Attempts to use a DAA as monotherapy in advanced cases of PD were deserted due to poor efficacy and the existence of side effects, while the trend toward using a DAA as early therapy increased: by delaying the initiation of levodopa treatment, motor complications can be prevented. Several novel DAAs were tested and their utility was unquestionably demonstrated, although these studies proved that DAAs are less efficacious than levodopa (with the notable exception of apomorphine). This may not be very important in the initial stages of PD. However, as the disease progresses, stronger DA stimulation is required and, as increased DAA dosages become limited by side effects, supplementation with levodopa becomes necessary, albeit again with the danger of the development of motor complications.<sup>13,14</sup>

Although there is no doubt that DAAs can be used initially as monotherapy, the number of patients in whom this treatment can be maintained over long periods remains unclear. According to available data, levodopa will be added over 3 years in about 20% of patients, and in 50% after 5 years.<sup>15</sup>

While the ergot derivatives are clearly efficacious in PD, their use has been complicated by several side effects. It was realized that ergots are “dirty” drugs, with the potential to interact with several types of receptors in the central nervous system, as well as in the periphery. The development of the synthetic DAAs piribedil, ropinirole, and pramipexole was an important further step. However, these agents shared a number of side effects. It thus became clear that, while pleuropulmonary fibrosis may be specific to ergot derivatives, most of the complications of these therapies are class effects. Cardiac valve changes were recently ascribed to pergolide.<sup>16,17</sup>

The motor fluctuations that characterize prolonged levodopa therapy are thought (but not proven) to be related to the short plasma half-lives of individual levodopa doses ( $t_{1/2}$ =90 min). The clinical benefit from individual doses is longer, at least in early stages of the disease, due to the buffering capacity of surviving DA neurons, which transform levodopa to DA, store it, and then release it in a tonic, rather than phasic, pattern. The fact that DAAs do not depend on DA neurons is a theoretical advantage, particularly at advanced stages of the disease when very few DA neurons survive. However, this advantage is related to their longer duration of action, typically 4 to 6 hours (and much longer for cabergoline). If the nonsus-

tained level of DA stimulation is responsible for the development of motor fluctuations, these complications should be significantly delayed if cabergoline is to be used in de novo cases.

Several studies have suggested that DAAs have additional beneficial properties, such as antioxidant or antiapoptotic effects.<sup>12</sup> Notably, all these studies were performed in vitro, and therefore had a very short duration and used doses with unclear relationship to the clinical situation. There are no available data indicating that DAAs have relevant antioxidant or antiapoptotic effects in routine clinical use in humans, or indeed that oxidative stress plays a major role in the pathogenesis of PD. The early addition of a DAA prevents (or at least delays) the appearance of motor complications, but whether this should be regarded as a neuroprotective effect is questionable. Furthermore, even if DAA can slow the progressive loss of DA neurons in the substantia nigra, it would be very difficult to prove it.

If DAAs do slow the progression of PD, a possible mechanism could be stimulation of presynaptic DA receptors. Probably all DA terminals contain receptors that mediate the synthesis and release of DA by negative feedback. Endogenous DA can be metabolized to produce toxic reactive oxygen species. Reduction in the rate of DA synthesis can thus be expected to slow the ongoing damage to DA neurons. Most (and probably all) DAAs reduce the rate of DA synthesis, but there is limited information on their relative efficacy in this regard. Theoretically, a drug with relatively strong presynaptic stimulation (relative to postsynaptic D<sub>2</sub> stimulation), such as talipexole, should be preferred, although it is difficult to see how that advantage can be demonstrated in PD patients.

Currently used DAAs include the “ergot-derived” or “ergoline” drugs bromocriptine, cabergoline, lisuride, and pergolide, with chemical structures based on ergot, a plant alkaloid. The newer, “non-ergot” synthetic DAA, piribedil, pramipexole, and ropinirole—chemically unrelated to ergot—are being promoted vigorously.

Side effects typical of all DAAs (as well as levodopa) include nausea, vomiting, dizziness, and orthostatic hypotension.<sup>11,15,18-20</sup> At higher doses, DAAs may induce confusion, hallucinations, and psychosis, although these usually appear in the advanced stages of the disease.<sup>21</sup> Sedation and insomnia are other reported side effects of some DAAs, as well as of levodopa, and are probably not associated with any specific agonist.

Attention has recently been drawn to somnolence as a possible adverse effect of DAAs (including levodopa). Events of a compelling urge to sleep (so-called “sleep attacks”) have been observed in patients treated with DAAs.<sup>22-26</sup> This is a serious side effect that may cause driving accidents. This needs to be considered and explained to the patient, particularly if he or she is involved in activity in which the somnolence, even if not excessive, could endanger them or others.

Some of the side effects specifically linked to the ergot derivatives include digital or coronary vasospasm, as well as pleuropulmonary and retroperitoneal fibrosis. These are not associated with the newer and safer non-ergot DAAs piribedil, ropinirole, and pramipexole.<sup>27</sup>

A transdermal formulation of the experimental D<sub>2</sub> selective agonist rotigotine is currently in development.<sup>28</sup> It has been found to reduce daily levodopa doses by 30% in a multicenter phase 2b trial in mild-to-severe PD.

Apomorphine is the most potent DAA, and the only one that stimulates effectively both DA D<sub>1</sub> and D<sub>2</sub> receptors (as does DA itself). However, its therapeutic effect is hampered by its complex interindividual pharmacokinetics and pharmacodynamic variability and its narrow therapeutic range. Apomorphine cannot be used as an oral drug, but subcutaneous injections are very helpful, particularly for patients with prolonged “off” episodes. Continuous delivery of apomorphine subcutaneously through a pump is available, but is technically complex to use and expensive.<sup>29</sup> In order to overcome these difficulties, several attempts to create individualized controlled delivery systems for apomorphine are being explored, eg, transdermal iontophoresis and sublingual delivery of the drug. This will be particularly useful for a rapid effect to control fluctuations.<sup>30</sup> In a recent study, a carboxymethyl cellulose powder of apomorphine was tested as intranasal sustained-release formulation. These newer delivery systems will hopefully enhance its use as a rescue medication in severe cases.<sup>30</sup>

There are at least five types of DA receptors, namely D<sub>1</sub>, D<sub>2</sub>, D<sub>3</sub>, D<sub>4</sub>, and D<sub>5</sub>. The role of D<sub>1</sub> stimulation in the therapy of movement disorders, and particularly PD, has been debated for years. Bromocriptine is a D<sub>1</sub> antagonist, pergolide a D<sub>1</sub> agonist, while ropinirole and pramipexole do not interact with D<sub>1</sub> receptors at all. Since all these DAAs have similar efficacy in PD, the role of D<sub>1</sub> receptors in PD therapy is questionable. However recent reports suggest that the specific D<sub>1</sub>-stimulating drug, ABT-431, is also effective in PD.<sup>31</sup> Thus, there are several remaining issues in DAA therapy (*Table III*).

## Other drugs

The efficacy of selegiline in the treatment of PD is based on the assumption that inhibition of the monoamine oxidase B (MAOB) enzyme may prevent DA neurotoxicity.<sup>32,33</sup> The extensive DATATOP (Deprenyl And Toco-pherol Antioxidative Therapy Of Parkinsonism) study demonstrated the safety and beneficial symptomatic effects of selegiline in early PD, but not necessarily its neuroprotective effect.<sup>34</sup> It is possible that at higher therapeutic doses, MAOB inhibitors will not only ameliorate disease symptoms, but could also provide neuroprotection, which has been demonstrated in vitro with equivalent drug concentrations. Several MAOB inhibitors are at various stages of development. A new formulation of selegiline dissolves instantly in the mouth, eliminating the first-pass effect in the liver, so that therapeutic levels are reached at an eighth of the daily regular dose of selegiline. This reduces the concentrations of amphetamine, the unwanted metabolite of selegiline, which otherwise limits the maximal tolerated dose.

Rasagiline, another MAOB inhibitor, is presently being evaluated in clinical trials in the USA, Europe, and Israel. At doses up to 2 mg/day, rasagiline shows good safety and tolerability.<sup>32</sup> It has a similar pharmacological profile to selegiline, but without amphetamine as a metabolite. Amantadine has been used for the treatment of PD for several decades, even though its mechanism of action is obscure.<sup>35,36</sup> Recently, it was shown to function by inhibiting *N*-methyl-D-aspartate (NMDA) receptors and found to be effective in reducing dyskinesias.<sup>37,38</sup> Memantine, a related drug, also functions as a neuroprotective agent through this mechanism. Memantine is used in Germany as an antispastic drug and also to treat dementia, and is presently being evaluated for its effectiveness in PD, on the basis of preliminary results.<sup>39</sup> The antilglutamatergic

Functional significance of dopamine receptor subtypes D <sub>1</sub> , D <sub>2</sub> , D <sub>3</sub> , D <sub>4</sub> , and D <sub>5</sub>
Neuroprotection by DAA: does it exist? (If yes, what are the mechanisms?)
Possible advantages and complications of long-term DAA monotherapy.
Is the prevention of dyskinesias afforded by DAAs due to their long half-life, or is it related to pharmacodynamic factors?
What is the mechanism responsible for tolerance to the peripheral side effects of DAAs?

**Table III.** Remaining issues in dopamine agonist (DAA) therapy.

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effect of amantadine and memantine also suggests a neuroprotective action, and memantine is now actively promoted in AD.

## Treatment of nonparkinsonian symptoms

Although motor symptoms are the cardinal features of PD, most if not all patients will also manifest symptoms in other spheres. Depression is particularly common and frequently antedates the motor disorder.<sup>40</sup> Clinical experience shows that tricyclic antidepressants and selective serotonin reuptake inhibitors are very efficacious in this condition, with a dose and adverse event profile similar to that of other patients. Amitriptyline, which has a marked antimuscarinic action, may adversely affect the constipation, while reducing the severity of parkinsonian tremor.

Cognitive deterioration in PD may start even before motor symptoms appear (and is then trendily termed “dementia with Lewy bodies”), but more frequently characterizes the advanced stages of the disease. The underlying mechanism probably relates to cholinergic loss<sup>41</sup> and is thus similar to AD. It is therefore not surprising that treatment with acetylcholinesterase inhibitors is effective in demented patients with PD.<sup>42</sup> Interestingly, the motor manifestations are not made worse. Although data are still meager, they seem to favor rivastigmine over donepezil.

Delusions and hallucinations, usually visual, are frequent in advanced PD, particularly in demented patients. Obviously, classical neuroleptics cannot be used since by blocking DA receptors the parkinsonian symptoms would be exacerbated. The new generation of antipsychotics offers an important advance. Clozapine in particular is

helpful in this situation, though its side effects and particularly the need for hematological monitoring are disadvantageous.<sup>43</sup> Quetiapine may be as useful,<sup>44</sup> but other so-called “atypical neuroleptics,” and particularly olanzapine, are quite likely to induce motor exacerbation.

The autonomic dysfunction in PD is another frequently problematic area. The most significant of all is constipation, which commonly antedates the diagnosis and is frequently exacerbated by the antiparkinsonian drugs.<sup>43</sup> Clinical experience again suggests that the usual therapies (eg, sildenafil for penile erectile dysfunction) are useful.

## Conclusion

The management of PD is quite easy at the initial stages of the disease, where all dopaminomimetic drugs, as well as amantadine or selegiline (or an antimuscarinic agent if tremor is the main problem), can be very efficacious. As the disease advances, however, the motor complications become increasingly more severe and difficult to control, and require expertise and individual tailoring. At this stage, it is sometimes necessary to resort to functional neurosurgery.

Unfortunately, no drugs are yet available that slow the rate of progression of PD. The initial therapy for the motor symptoms should constitute a DAA, which all have similar efficacy, though non-ergot DAAs are probably safer. As the disease progresses and these agents become insufficient, levodopa can be added. There is no clear role for selegiline and amantadine. In spite of the fact that these drugs are definitely effective and relatively safe, their efficacy is lower than that of the previously mentioned drugs. Several new modalities are presently under investigation. □

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### **Tratamiento farmacológico de la enfermedad de Parkinson**

La enfermedad de Parkinson (EP) es una enfermedad neurodegenerativa frecuente. A pesar de que su causa permanece sin aclararse, se ha realizado bastante progreso en su tratamiento. Los fármacos disponibles tienen un buen efecto sintomático, pero ninguno de ellos ha demostrado que pueda retrasar la progresión de la enfermedad en el ser humano. El fármaco más eficaz es la levodopa, pero aun no se aclara si el beneficio sintomático está asociado con los efectos neurotóxicos y el deterioro a largo plazo. El problema a largo plazo asociado con la levodopa es la aparición de disquinesias, la cual está significativamente retardada en los pacientes que reciben agonistas dopaminérgicos como terapia inicial. El papel de otros fármacos en la EP parece menos claro, como ocurre con los inhibidores de la monoamino-oxidasa (IMAOs) que incluyen la selegilina y la rasagilina, los antagonistas del receptor putativo de N-metil-D-aspartato (NMDA) amantadina y memantina, y los bloqueadores del receptor muscarínico. Todos estos fármacos pueden utilizarse como terapia inicial y retardar el empleo de fármacos dopaminérgicos, o se pueden adicionar más adelante para reducir síntomas específicos como el temblor o las disquinesias. La EP avanzada se asocia frecuentemente con una declinación cognitiva. En parte esta declinación se puede tratar con inhibidores de la colinesterasa como la rivastigmina. Del mismo modo, las alucinaciones y los delirios afectan a los pacientes con EP en estados avanzados de la enfermedad. El empleo de neurolépticos clásicos en estos pacientes está contraindicado debido a sus efectos extrapiramidales, pero los neurolépticos atípicos, y especialmente la clozapina, resultan muy útiles. El gran vacío en el tratamiento de la EP radica en las etapas más avanzadas. Algunos síntomas motores, como la inestabilidad postural, la disfagia y la disfonía, como también las disquinesias son escasamente controlados por los fármacos existentes. Se deben desarrollar nuevos tratamientos contra síntomas autonómicos, especialmente la constipación.

### **Traitement médicamenteux de la maladie de Parkinson**

La maladie de Parkinson (MP) est une maladie neurodégénérative fréquente. Alors que sa cause reste difficile à trouver, beaucoup de progrès ont été faits en ce qui concerne son traitement. Les médicaments disponibles agissent bien sur les symptômes, mais aucun n'a encore montré qu'il ralentissait la progression de la maladie chez l'homme. Le médicament le plus efficace est la lévodopa, mais l'on se demande si l'effet favorable sur les symptômes n'est pas associé à des effets neurotoxiques et une détérioration à long terme. Le problème à long terme de la lévodopa est la survenue de dyskinésies, qui est significativement retardée chez les patients recevant des agonistes dopaminergiques comme traitement initial. Le rôle d'autres médicaments dans la MP, tels que les inhibiteurs de la monoamine-oxydase (IMAO), dont la sélégiline et la rasagiline, les présumés antagonistes du récepteur N-méthyl-D-aspartate (NMDA), l'amantadine et la mémantine, et les agents bloquant le récepteur muscarinique, est moins clair. Tous peuvent être utilisés en première intention et retardent l'utilisation des médicaments dopaminergiques, ou peuvent être associés plus tard afin de diminuer des symptômes spécifiques (tremblement ou dyskinésies). La MP évoluée est fréquemment associée à un déclin cognitif. Les anticholinestérasiques comme la rivastigmine peuvent l'empêcher, jusqu'à un certain point. De la même façon, les hallucinations et délires concernent les patients parkinsoniens aux stades évolués de leur maladie. L'utilisation de neuroleptiques classiques chez ces patients est contre-indiquée à cause de leurs effets extrapyramidaux, mais des médicaments atypiques, et en particulier la clozapine, sont très utiles. Le grand vide dans le traitement de la MP se situe aux stades les plus évolués. Plusieurs symptômes moteurs, comme l'instabilité posturale, la dysphagie, la dysphonie, ainsi que les dyskinésies, sont mal contrôlés par les médicaments existants. De nouveaux médicaments devraient aussi être développés contre les symptômes liés au système nerveux autonome, en particulier la constipation.

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