Pharmacological management of Parkinson's disease motor symptoms: update and recommendations from an expert

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Introduction. Parkinson's disease (PD) is a neurodegenerative multisystemic disorder that affects approximately 1% of the population over 55 years old, with the mean age of onset at 60 years old, and the prevalence of the disease constantly growing.

Development. PD is a progressive disease characterized by motor and non-motor symptoms that compromise patients' daily activities. It has a variable profile of onset and clinical evolution. Although currently available treatments have failed to clinically demonstrate neuroprotective properties, most motor symptoms are acceptably managed with dopaminergic medication. More than 50 years after launching levodopa, it remains the most effective treatment of motor symptoms in PD, able to provide sustained benefit throughout the entire course of the disease. Nevertheless, after two to three years of treatment, certain fluctuations start to appear in motor and non-motor responses to different doses of levodopa. Early identification and treatment of these fluctuations have a strong positive impact on the quality of life of the patient. Frequently accompanied by involuntary movements, proper control of fluctuations requires periodical adjustments of the medication and expert supplementation with dopaminergic and non-dopaminergic adjuvants.

Conclusions. The main purpose of this work is to offer a practical, updated guideline for neurologists regarding the use of dopaminergic agents from the initial stages of PD. Special emphasis is placed on the critical period after the end of the 'honeymoon' phase when variations in the symptomatology presented by each patient appear, forcing re-adjustment of the medication to fit their individual needs.

Key words. Algorithm. Levodopa. MAO-B inhibitors. Motor fluctuations. Parkinson's disease. Treatment.

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Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disorder pending a cure [1,2]. Therefore, the primary aims of PD treatment are keeping the patient functionally independent as long as possible, trying to improve both motor and non-motor symptoms, and striving for a balance between the most efficient and least harmful options. The ultimate goal of any management program is to improve the quality of life of the patient [3].

It is becoming increasingly clear that PD is not a single clinical pathological entity but a syndrome consisting of multiple disease states with different underlying mechanisms of neurodegeneration [4,5]. Accordingly, the development of more personalized therapies is facilitated [6]. Beyond specific genetic variants showing characteristic phenotypes (including age at onset, dystonia, motor complications, dyskinesias, and cognitive impairment) [7], different motor subtypes have been delineated in sporadic PD [6,8-10]. These include the tremor dominant, and the postural instability and gait difficulty subtypes [11-13].

Another classification of PD subtypes, based on cluster analysis of clinical features and biomarkers of initial PD patients (patients at the initial stages of the disease), defined three variants according to disease presentation, the effect of dopaminergic medication on motor symptoms and disease progression [8]. 'Mild motor-predominant' appears as the more frequent subtype (49-53%), characterized by young age at onset, good response to treatment, and slow disease progression. Next is the 'intermediate' subtype (35-39%), characterized by intermediate age at onset, moderate motor and non-motor

symptoms, moderate to good dopaminergic response, and moderate progression. Finally, the 'diffuse malignant' subtype seems less frequent (from 9 to 16%), presenting a variable age at onset, REM sleep behavior disorder, mild cognitive impairment, orthostatic hypotension, severe motor symptoms, early gait problems, and rapid progression of motor and cognitive deficits [6]. These patients also showed a profound dopaminergic deficit, increased atrophy in PD brain networks, and a more Alzheimer's disease-like cerebrospinal fluid profile [6].

Although dopaminergic denervation is essential in the appearance and progression of motor and non-motor symptoms [14], abnormalities in other neurotransmitters are also key in the development of these symptoms and can be detected from early stages of PD. Both, alterations in cholinergic innervation and serotonin and noradrenergic deficiency are associated with several non-motor symptoms such as anxiety, depression, cognitive impairment, psychosis, and sleep disorders [15-18]. Glutamatergic hyperactivity following dopaminergic denervation is also implicated in the appearance of these symptoms, in addition to motor complications, development of levodopa-induced dyskinesia, and excitotoxic cell death of dopaminergic neurons in the *substantia nigra pars compacta* [19,20]. Therefore, it is simplistic to consider that PD therapy should be limited to trying to only restore the corticobasal ganglia circuit to normal by addressing dopaminergic deficit alone.

While therapies for people with PD (PwP) carrying hereditary genetic mutations have entered into clinical trials targeting kinase inhibitors in *LRRK2*-associated PD or enhancement of glucocerebrosidase activity in *GBA*-associated PD [21, 22], it is not clear whether sporadic PD subtypes should be treated differently.

A better understanding of underlying disease mechanisms, as well as identification of different phenotypes with implications for diagnosis, expected treatment response and prognosis, will help clinicians to incorporate personalized treatments into daily practice [6].

Meanwhile, it is key to acknowledge that PD is a highly heterogeneous disorder, and there is no such thing as 'one-size-fits-all' [8]. Thus, treatment should be: a) individualized, based on age, presumed motor phenotype, cognitive and mental status, degree of functional impairment, expectations, social and working conditions; and b) periodically adapted and corrected, based on the initial response to treatment and eventual side effects [3].

Initial treatment for motor symptoms

Neuroprotective approach

Neuroprotective treatments aim to prevent or arrest disease progression and secondary injuries by halting or delaying the loss of neurons. The development of a neuroprotective treatment that changes the natural course of a disease with an intervention is the goal for any neurodegenerative disease [3]. Common mechanisms behind neurodegeneration include oxidative stress, excitotoxicity, mitochondrial dysfunction, iron accumulation, apoptosis, deficit of neurotrophic factors, inflammation, and accumulation of aggregated pathogenic proteins [23-26]. Different mechanisms of neuroprotection have been hypothesized for monoamine oxidase-B (MAO-B) inhibitors such as selegiline and rasagiline [27]. These include preventing reactive oxygen species production and increasing neurotrophic and anti-apoptotic factors [28]. However, clinical studies have been unable to prove such beneficial effects [27]. A delayed start design trial with rasagiline showed some interesting indirect results, but these were not considered enough evidence of neuroprotection [3,29].

None of the compounds recently developed have conclusively been proven to modify the progression of PD. Clinical trials targeting α-synuclein accumulation with immunotherapy seemed to be promising [3,30]. Although more studies are ongoing, recent failures in achieving primary objectives (significant changes versus placebo in total Movement Disorder Society-Sponsored–Unified Parkinson's Disease Rating Scale score) have somewhat diminished the initial enthusiasm for this strategy [31]. Actually, a common limitation of any disease-modifying strategy in PD is the lack of reliable biomarkers that are able to link the mechanisms of action of the intervention to the pathophysiology of the disease [3,32].

Pharmacologic interventions

First-choice treatment for PwP focuses on pharmacological dopamine replacement, which improves symptoms and quality of life [3]. Although there is no conclusive evidence that earlier symptomatic treatment may modify the course of the disease, there is no compelling reason to delay dopaminergic treatment in a patient exhibiting some disability. As was shown in the LEAP study, early initiation of treatment is potentially associated with positive

effects on the quality of life of PwP, even when disability is negligible. Nevertheless, it is not mandatory to initiate a symptomatic treatment in those subjects exhibiting detectable symptoms without accompanying disability [29].

For those who need drug therapy, treatment can be started with any of the available medications: MAO-B inhibitors, dopamine agonists, and levodopa/carbidopa or levodopa/benserazide preparations. According to numerous guidelines and evidence-based reviews, several different strategies can be effective; but presently, there is no official consensus favoring any specific strategy [33]. Since there is insufficient comparative data to support one particular line of treatment, individualized therapies should be applied to PwP [3].

Monotherapy with MAO-B inhibitors is usually well tolerated in *de novo* PD, but it is limited to short periods of time in individuals with very mild disability. Dopamine agonists –such as the oral preparations of ropinirole or pramipexol and the transdermal rotigotine patch– exhibit a more robust and prolonged symptomatic effect [27,33]. It has been shown that PwP who tolerate monotherapy with dopamine agonists in their first years of treatment present fewer incidences of motor fluctuations and dyskinesias than those initially treated with levodopa, but with disease progression their efficacy decreases and most, if not all, PwP will need levodopa after three to five years of treatment [27]. By re-examining pivotal comparative studies of dopamine agonists vs. levodopa in initial PD, it was recently suggested that rather than delaying dyskinesias, dopamine agonists were mostly incapable of extending their effect beyond a relatively short period of time, providing less overall benefit than levodopa, although the levodopa-treated group had significantly more dyskinesias [34,35]. At the highest tolerable dose, dopamine agonists showed lower efficacy in improving motor symptoms and quality of life, had a less safe side effect profile than levodopa, and may have induced or worsened dyskinesias once PwP needed concurrent oral levodopa [27,34,35]. Although we should not overreact and demonize this valuable group of drugs, the use of dopamine agonists to improve symptoms of initial PD should be balanced against their relative lower potency and higher overall risk of side effects when compared to levodopa [27], specifically, psychosis, excessive daytime somnolence, leg edema, and impulse control disorders [36,37]. PwP should be carefully monitored as these side effects may lead to a risk of catastrophic financial, legal and psychosocial consequences, and severe withdrawal symptoms, such as anxiety and drug craving when PwP attempt to discontinue drug use [38].

Until recently, clinical guidelines for management of PD recommended a preferential use of dopamine agonists over levodopa as initial therapy. This was mainly based on the unsubstantiated belief that levodopa might promote oxidative stress and accelerate both motor complications and progression of the disease. Despite the recent guidelines recommending levodopa as the most effective therapy for the treatment of PD [33,39], the tendency to avoid initiating levodopa due to 'levodopa phobia' is still present in clinical practice and may be harmful or cause unnecessary delays in improving parkinsonian symptoms and quality of life [29,40]. Related to this, three large studies (ELLDOPA, PD-MED and LEAP) evaluated levodopa as a *de novo* treatment for PD, and none provided significant evidence against it [4, 27,29,41]. Moreover, observations on sub-Saharan African PD patients who had difficulties accessing the medication and remained untreated showed that delaying treatment did not reduce the likelihood of having motor complications and dyskinesias [34]. Thus, there is no contraindication in prescribing levodopa to newly diagnosed PwP, nor is there an indication to consider levodopa as the last treatment option after other dopaminergic drugs have proven insufficient for controlling motor symptoms.

Since fluctuations and dyskinesias are related to the disease duration rather than cumulative levodopa exposure, delaying levodopa treatment is no longer recommended [34]. Nevertheless, chronic treatment with high doses of short half-life preparations of levodopa are still associated with the development of dyskinesias, especially in younger PwP [42], and should be avoided to unnecessarily increase the risk of motor complications [4, 29,34].

Non-pharmacological interventions

There is growing evidence supporting the role of physical and mental activities, such as aerobic exercise, cognitive training, mindfulness and yoga, dance, and balance training, in improving both motor (gait, posture, balance, speech and swallowing) and non-motor outcomes (mood, cognition) in PD. These activities should be considered an integral part of the multidisciplinary management of PD and are useful and advisable from the early stages of PD [43-47].

Treatment of specific symptoms in initial Parkinson's disease: tremor

Although trying anticholinergic agents such as trihexyphenidyl has been recommended for relatively young PD patients with predominant tremor symptoms, there is not enough evidence of their utility, and their use can be associated with adverse side effects, particularly related to cognition [48,49].

Based on newly uncovered inter-individual differences in the response of resting tremor to dopaminergic therapy, showing dopamine-responsive and dopamine-resistant resting tremor in PD, it is important not to force excessive doses of dopaminergic medication during treatment of PwP [50].

Algorithm of treatment for initial Parkinson's disease

There are many approaches to initiating symptomatic treatment in PD. Published algorithms merely represent assistance guidelines that risk excluding PwP from the decision-making process. PwP should be informed of the various possibilities and advised that, in PD therapeutics, there is no such thing as 'one-size-fits-all' [8]. The driving force is quality-of-life improvement and maintenance, with a continuous effort to balance pragmatism with evidence-based rigor. PwP should also be cautioned that the combination of drugs of different classes to attain complementary benefits is a common practice in PD and does not necessarily correlate with the severity of the disease.

All antiparkinsonian drugs have side effects that can significantly reduce the quality of life of PwP. Thus, it is very important to assess the health conditions of PwP, and to recognize and adequately address the specific side effects of the type of drug or the combination of drugs used. Starting the treatment with levodopa allows substantial improvement of quality of life compared to symptomatically less predictable drugs [27,29]. Among available dopaminergic agents, levodopa promotes better functional response but increased risk of causing dyskinesias at high doses [27,34]. For this reason, a useful strategy could be to start with low doses of levodopa (no more than 300 or 400 mg/day) titrating to the therapeutic threshold, and reserve other drugs as adjunctive treatments for later in the disease course [51]. Most initial PD patients, regardless of their degree of disability, will exhibit a consistent motor benefit and good tolerance to medication when slowly titrated (during a period of two to three weeks) to levodopa 100 mg three times a day (Figure). Patients can be advised to take domperidone for a few days if they experience nausea. Doses above 30 mg/daily should only be prescribed after careful consideration of its potential cardiotoxic effects [52].

For those patients exhibiting minimal disability, a test with a MAO-B inhibitor may be justified. Patients exhibiting mild disability who have no history of cardiovascular diseases, psychosis, depression, renal or hepatic insufficiency [53] and are aware of the higher risks of side effects of dopamine agonists, and still prefer not to take three daily doses of levodopa, could be offered a test with dopamine agonists (Figure).

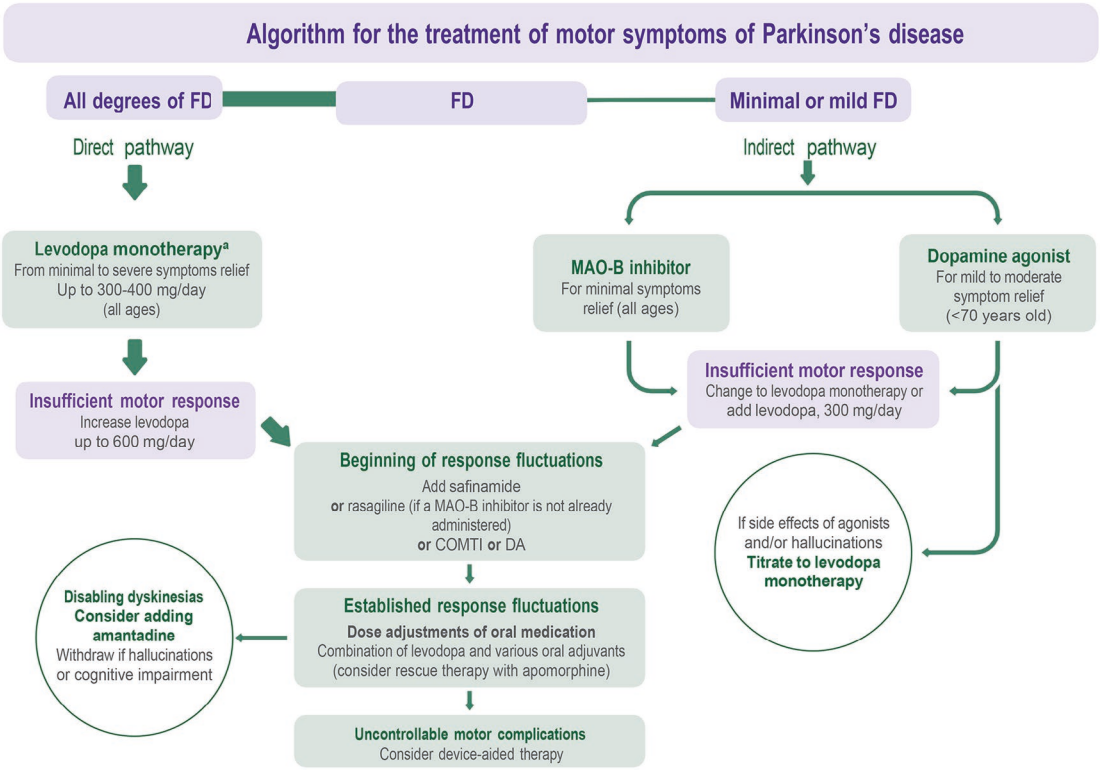
If the progression of the disease results in an insufficient motor response, both levodopa- and non-levodopa-treated patients could replace or combine their current therapies with doses of levodopa not higher than 600 mg/day. Depending on the patient's disability, it would be possible to administer a MAO-B inhibitor and/or a dopamine agonist plus up to 300 mg/day of levodopa (Figure). Although some side effects are idiosyncratic, the probability of experiencing adverse events increases with the amount of medication taken (especially at high doses of dopamine agonists) [53]. As such, if side effects from dopamine agonists are reported, levodopa monotherapy should be implemented instead.

Once response fluctuations are noticed for the first time, a combination of the previous treatments with safinamide, COMTI (catechol-o-methyl transferase inhibitors) or dopamine agonists is suggested. Administration of rasagiline in combination with levodopa is also possible, if a MAO-B inhibitor has not been prescribed before. Intensification and increased frequency of the response fluctuations will require an adjustment of the oral medication, and could include levodopa combined with adjuvant drugs. At this point, a rescue therapy with apomorphine should be considered. If disabling dyskinesias occurs, administration of amantamide should be carefully considered while taking into account its side effects.

Progression of disease and narrowing of the therapeutic window

Newly diagnosed PwP initiated on dopaminergic therapy typically experience a 'honeymoon' phase of three to five years, during which time the symptoms of the disease are not too disabling [54,55]. However, PD is a clinically heterogeneous disease with

Figure. Treatment algorithm. MAO-B: monoamine oxidase-B; COMTI: catechol-o-methyl transferase inhibitors; DA: dopamine agonist; FD: functional disability. [a]At the present state of knowledge, sooner or later, all subjects with PD will need levodopa treatment; there is no compelling reason to avoid prescribing levodopa from the early stages of the disease or to delay its introduction at the expense of the subject's functionality.



much inter-individual variation, which includes rapidly and slowly progressive forms [34,56]. Motor phenotype and motor response to medication is not fixed and can change with disease progression, with an increase over time in the percentage of cases with a non-tremoric motor phenotype [57].

With the progression of PD, non-levodopa preparations like MAO-B inhibitors and dopamine agonists, both alone or in combination, generally show limitations in providing a good motor response. Thus, after two to three years of treatment, most patients will require initiation with levodopa [33]. These patients, and those who until then had only taken levodopa, will typically notice a decline in the duration of benefits from each dose with time [35,58,59]. Although levodopa provides a therapeutic benefit over the entire course of PD [60], higher and more frequent doses of levodopa are eventually needed. Levodopa-induced dyskinesia is frequently seen, typically occurring at the time of maximal levodopa concentrations in the brain [4,34].

When prescribed for the first time, levodopa is typically dosed three times daily, which provides adequate dopamine concentrations across daytime hours [61,62]. Gradual deterioration in the motor response to each dose of levodopa, accompanied by the re-emergence of motor symptoms between doses (tremor, bradykinesia, rigidity and gait problems) is commonly termed 'wearing off' or 'end-of-dose deterioration' [63,64]. Non-motor symptoms may also appear, including anxiety, fatigue, sadness, sweating, dyspnea, pain, restless legs, paresthesia and other symptoms that are more difficult for the patient to define or recognize as fluctuating [60,65].

All these issues are mainly related to the pharmacokinetics and pharmacodynamics of long-term

levodopa use [58,59,62]. The progression of the disease is associated with a decrease in the so-called 'long-duration response' to levodopa and an inability to store the excess dopamine accumulated from repeated doses of dopaminergic medication [58,59]. Once this long-duration response is substantially diminished or lost, short plasma half-life of current levodopa preparations is insufficient to cover the so-called 'short-duration response' (antiparkinsonian response that parallels plasma levels of levodopa) [58].

During a dopamine-depleted state of PD, intermittent levodopa doses result in marked fluctuations in striatal dopamine, contrary to stable levels found under normal conditions [66]. Pulsatile synaptic availability of dopamine leads to molecular and neurophysiologic changes that underlie the appearance of motor fluctuations [58,66]. Further complicated by erratic gastric emptying of levodopa, this phenomenon is considered responsible for the 'wearing-off' response [58,66]. In turn, progressive receptor and neurotransmitter changes that occur in the brain, associated with phasic dopaminergic stimulation, are considered responsible for dyskinesias [34,67]. Several preclinical and clinical studies show improvement of dyskinesias with antiglutamatergic drugs [68-70], demonstrating that hyperfunction of the glutamatergic pathways and N-methyl-D-aspartate receptors on striatal efferent neurons are also associated with chronic non-physiologic dopaminergic stimulation that contributes to the pathogenesis of dyskinesias [34,54,71].

Conversely, evidence provided by studies such as COPPADIS or CamPaIGN showed that motor complications are relatively common after two years of PD and do not necessarily confer a negative prognosis [72,73]. Thus, after a variable period of good response to dopaminergic therapy, generally between two to five years [54,55], and disregarding the modality of treatment initiation, a progressive narrowing of the therapeutic window of levodopa doses occurs in up to 50% of patients, who typically develop fluctuations in response to dopaminergic pharmacotherapy accompanied or not by dyskinesias [59,60].

Recognizing fluctuations in the levodopa response

The first signs of a re-emergence of parkinsonian symptoms are neither well established nor the same for all PwP who experience the 'wearing-off' phenomenon [60]. While for some, the first signs are characterized by a return of classic parkinsonian motor symptoms, for others, non-motor symptoms could also emerge independently or in combination [60,65]. Clinicians should routinely inquire about the recurrent presence of these signs close to or coinciding with the time of the next dose of medication [60]. Clinical research studies using appropriate scales have shown that these fluctuations can even occur subclinically in patients who otherwise deny suffering from them when asked [61,74].

A tool to identify and quantify a parallelism between neuropsychiatric and motor fluctuations has been proposed to facilitate self-assessment by PwP of their PD state during 'on-off' conditions [75]. For this, a detailed clinical history should be recorded by patients and their caregivers to identify different problems, such as underdosing, motor and non-motor signs, fluctuations, and side effects to medication [54]. Additionally, the use of self-reporting diaries and wearables could help analyze recurrent PD symptoms in individual PwP.

Treatment of response fluctuations

Several strategies can be applied when the 'honeymoon' phase ends and patients begin to experience a 'wearing-off' response to dopaminergic medication [1,3,76]. The most commonly used ones are a) fragmentation of levodopa dosing to adjust the timing and dosing of oral levodopa; and b) increasing the half-life of levodopa between doses using adjunctive drugs [1,3,54,76].

Fragmentation of levodopa dosing could help during a limited period of time –for instance, taking four instead of three doses of levodopa– as the patient generally requires modification of the total amount of daily levodopa to avoid ineffective doses and dyskinesias [77,78]. Regarding the use of adjunctive medication, stable delivery of levodopa to the brain might help restore physiological levels of dopamine and reduce the risk of motor fluctuations [34]. Combination therapies of levodopa with MAO-B inhibitors, COMTI or dopamine agonists enhance dopaminergic transmission, reduce doses of levodopa and show better control of motor complications that may arise as a consequence of the poor pharmacokinetic profile of conventional levodopa [56,58,79]. Additionally, double-effect agents such as safinamide, a MAO-B inhibitor and glutamatergic modulator, should help reduce levodopa-induced dyskinesias in patients with moderate to severe PD [69,80].

A practical, useful option for patients who start to exhibit either motor or non-motor fluctuations, or both, is the use of adjunctive medication (Figure) [54]. This may help maintain a limited number

of daily doses (three or four), with less risk of ineffective doses and a relatively low amount of total daily levodopa, although it does not avoid augmenting the risk of dyskinesias [76]. Adjunctive medications include the use of MAO-B inhibitors (selegiline, rasagiline), COMTI (entacapone, opicapone), dopamine agonists (ropinirole, pramipexole, transdermal rotigotine patch), or combined drugs such as safinamide (MAO-B inhibitors + glutamatergic modulator) [33,69,77]. A recent study has found using dopamine agonists or MAO-B inhibitors as initial adjuvant therapy was preferable to using COMTI. Considering MAO-B inhibitors presented disease control equivalent to dopamine agonists, more importance should be given to the use of these inhibitors [81].

Large double-blind and observational studies have shown that safinamide is well tolerated and has a beneficial effect on some of the accompanying non-motor symptoms of PD as well as a possible long-run beneficial effect on dyskinesias related to its anti-glutamatergic properties [69,82]. It can also be used in combination with amantadine [69,82].

New preparations of levodopa are in progress to optimize oral levodopa therapies and overcome the limitations of conventional formulations, while providing effective symptomatic control [62,74,83,84].

Different preparations of levodopa have been tested in patients with advanced PD [62,84]. Still, future studies should try to correlate stable plasmatic levels of levodopa with a protective effect against fluctuations.

There may come a time when medication taken as tablets, capsules or patches no longer works well to control motor fluctuations and dyskinesias. This is when other possible solutions may be considered, such as deep brain stimulation, continuous levodopa-carbidopa intestinal gel, and continuous subcutaneous apomorphine infusion [85,86].

Conclusions

Currently, available therapies aim to preserve the autonomy of PwP as long as possible. For this reason, PwP in the initial stage of PD should start their treatment as soon as any disability is detected, regardless of the medication of choice. With the progression of the disease, different combinations of levodopa, MAO-B inhibitors or safinamide, dopamine agonists and amantadine are routinely prescribed to properly control motor and non-motor PD symptoms, and reduce to a minimum any potential side effects. Unfortunately, avoiding the 'wearing-off' phenomena is hardly possible for those PwP under levodopa treatment for several years. Although there is a global effort to extend levodopa bioavailability, clinicians should pay close attention to the onset of any PD symptom fluctuations by routinely checking on their patients. For now, the use of adjunctive medication should help regain a stable state. Based on the increasing evidence of patient-dependent responses to therapy, further clinical investigations are required to assist in defining personalized algorithms of treatment.

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Tratamiento farmacológico de los síntomas motores de la enfermedad de Parkinson: actualización y recomendaciones de un experto

Introducción. La enfermedad de Parkinson (EP) es un trastorno neurodegenerativo multisistémico que afecta aproximadamente al 1% de la población mayor de 55 años, con una edad media de aparición a los 60 años y una prevalencia en rápido crecimiento.

Desarrollo. La EP es una enfermedad progresiva, caracterizada por presentar síntomas motores y no motores combinados que afectan a la vida diaria de los pacientes. Sin embargo, tanto la presentación como la progresión clínica de la enfermedad son muy variables. A pesar de que ningún tratamiento ha demostrado clínicamente un efecto neuroprotector convincente, la mayoría de los síntomas motores son aceptablemente manejados con fármacos dopaminérgicos. Más de 50 años después de su introducción, la levodopa sigue siendo el tratamiento más eficaz para tratar los síntomas motores de la EP, que mantiene los beneficios a nivel motor durante todo el curso de la enfermedad. Sin embargo, después de un período variable de entre dos y cinco años desde el inicio del tratamiento, suelen aparecer fluctuaciones en la respuesta motora y no motora a las distintas dosis de la medicación. La identificación precoz y el tratamiento adecuado de estas fluctuaciones tienen un fuerte impacto positivo en la calidad de vida de los pacientes. El control de las fluctuaciones, frecuentemente acompañadas por movimientos involuntarios, requiere ajustes periódicos de la medicación y el uso de adyuvantes con acción dopaminérgica y no dopaminérgica, siguiendo las recomendaciones de un experto.

Conclusiones. El objetivo principal de este artículo es ofrecer una guía práctica actualizada para neurólogos sobre el uso de agentes dopaminérgicos desde la etapa inicial de la EP. Sobre todo, durante el período crítico después de la fase de 'luna de miel', cuando la aparición de variaciones en los síntomas presentados por cada paciente requiere el ajuste personalizado de la medicación existente.

Palabras clave. Algoritmo. Enfermedad de Parkinson. Fluctuaciones motoras. Inhibidores de la MAO-B. Levodopa. Tratamiento.