An update on Pathophysiology, Epidemiology, Diagnosis and Management Part 6: Medical Treatment of Early and Advanced Parkinson's Disease: Use of Levodopa

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Received: April 2021; Accepted: May 2021; Published: June 1, 2021.
Citation: Abdulrazak Abyad, Ahmed sami Hammami. An update on Pathophysiology, Epidemiology, Diagnosis and Management Part 6: Medical Treatment of Early and Advanced Parkinson's Disease: Use of Levodopa . World Family Medicine. 2021; 19(6): 74-81 DOI:10.5742/MEWFM.2021.94069

Abstract

Despite being the most effective dopaminergic treatment, there is still debate about the optimal way to use levodopa to treat Parkinson's disease (PD). Although there is a wealth of data on levodopa from clinical trials, practical guidance on how to use levodopa optimally throughout the disease is scarce. This article, which is part of a series on Parkinson disease, will discuss the use, benefits, and side effects of Levodopa.

Key words: Levodopa, Parkinson's disease

Introduction

The treatment of Parkinson's disease is symptomatic and does not address the underlying cause of the disease. Although there are no proven neuroprotective treatments for Parkinson's disease, medications are effective at controlling symptoms, particularly in the disorder's early stages. No intervention is widely accepted as disease-modifying in Parkinson's disease at the moment, but some agents, such as rasagiline and coenzyme Q10, have shown promise. These and other agents are currently undergoing clinical trials. Medications are the most frequently used treatment for Parkinson's disease (1-3). The objective is to correct the dopamine deficiency that is causing the symptoms. Typically, pharmacological treatment is initiated when symptoms become incapacitating or interfere with daily activities. Treatment options vary depending on the patient's symptoms, age, and response to specific medications. Often, it takes time to determine the optimal drug combination for each patient.

The majority of Parkinson's disease drug treatments aim to alleviate these symptoms by:

- Increasing dopamine levels in the brain, or
- Stimulating the areas of the brain that produce dopamine;
- Inhibiting the action of additional factors (enzymes) involved in the breakdown of dopamine

PD is currently treated symptomatically and is primarily focused on the dopaminergic pathway; there are no disease-modifying treatments available.

There are medications that are used to treat motor symptoms and medications that are used to treat non-motor symptoms.

Motor symptoms medication

This article discusses the following medications used to treat Parkinson's disease:

1. Carbidopa/Levodopa
2. Agonists for dopamine
3. MAO-B inhibitors
4. Inhibitors of COMT
5. Amantadine
6. Cholinergic antagonists
7. Suggestions for Neuroprotective Therapy
8. Surgical Procedures

The primary goal of any of the medications listed above is to control or manage motor symptoms. Because these symptoms are primarily caused by a depleted supply of dopamine in the brain, the majority of symptomatic medications are designed to replenish, mimic, or enhance this chemical's effect.

Bear in mind that medication is only one component of an overall treatment plan for effectively treating Parkinson's disease. Physical therapy, occupational therapy, speech therapy, holistic practices, nutritional consultation, support groups, education, psychological counseling, and intelligent use of assistive devices are all critical components of the best treatment plan.

Parkinson's Disease in its early stages

When to initiate drug therapy for Parkinson's disease should be determined on an individual basis, taking into account the patient's symptoms, circumstances, and co-morbidities. When symptoms impair one's quality of life, treatment is indicated. There is no evidence to support unnecessary delay in treatment due to concerns about levodopa toxicity or the development of treatment resistance. The objective is to maintain an 'on' state while controlling symptoms. Individuals with early Parkinson's disease who remain untreated may deteriorate not only in motor domains, but also in non-motor domains such as emotional well-being and physical discomfort. Delays in initiating treatment cannot be justified on the basis of concerns about the treatment's limited duration of efficacy or the possibility that L-dopa is neurotoxic and accelerates PD progression.

Which medication should a physician prescribe when a patient with recently diagnosed disease requires symptomatic treatment? Numerous medications provide adequate symptomatic relief, and there is currently debate over which therapy is associated with a lower risk of developing complications as the condition progresses. Medical management of Parkinson disease aims to keep signs and symptoms under control for as long as possible while minimizing adverse effects. Studies demonstrate that if treatment is not initiated immediately upon or shortly after diagnosis, a patient's quality of life rapidly deteriorates. Numerous factors must be considered when determining the optimal treatment option for an individual patient. Among them are the following:

Level of patient disability
If a patient is having significant difficulties with daily living activities or if the patient's ability to work is jeopardized, L-dopa is almost certainly indicated. Patients with mild-to-moderate disability may benefit from dopamine agonists. Amantadine or anticholinergic medications may be considered if symptoms require minimal treatment.

Avoidance of response fluctuation
Initial dopamine agonist treatment may help to reduce the risk of developing dyskinesias, "wearing off," and "on–off fluctuations".

Patient's age
Patients with a younger onset (under the age of 65 years) generally tolerate medications better and may experience fewer side effects. Elderly patients frequently experience greater difficulty with cognitive and psychiatric side effects, and physicians should exercise caution when prescribing anticholinergics and amantadine. Additionally, dopamine agonists may be associated with an increased risk of adverse events in elderly patients.

The adverse effect profile of the drug under consideration
If a patient is concerned about possible drowsiness that could result in the loss of driving privileges, is unable to tolerate a change in mental status, or already has cognitive impairment, a dopamine agonist may not be the best choice. Amantadine or dopamine agonists may exacerbate ankle edema.

Cost
Generic L-dopa/carbidopa and bromocriptine may be the most affordable options for patients without health insurance.

Early Parkinson's disease motor features typically respond well to dopamine replacement therapy. Levodopa may be combined with a dopa-decarboxylase inhibitor, a dopamine agonist, or a monoamine oxidase B inhibitor as a drug therapy option. Rasagiline is an appropriate first-line medication to consider in patients with mild symptoms (4).

Levodopa/Carbidopa

In the 1950s, scientists discovered that experimental depletion of dopamine in the brains of mice resulted in a condition resembling Parkinson's disease in humans, and that dopamine replacement completely eliminated those symptoms. Their efforts to apply these observations to the human condition ultimately resulted in the successful development of levodopa in the late 1960s.

Since its introduction in the 1960s, levodopa has revolutionized the treatment of Parkinson's disease, resulting in dramatic improvements in patient quality of life and disability reductions, and has remained unmatched in terms of symptom control. Levodopa is absorbed into the bloodstream through the small intestine and travels to the brain where it is converted to the active neurotransmitter dopamine. Levodopa that has not been converted has no effect on Parkinson's disease symptoms. Dopamine cannot be used to treat Parkinson's disease because its chemical structure prevents it from crossing the "blood-brain barrier," a physiologic barrier that protects the brain by excluding drugs and other potentially harmful chemicals.

KEY POINT: Forty years after its introduction, levodopa remains the most effective medication available for the treatment of Parkinson's disease's motor symptoms.

Initially, large doses of levodopa were required to alleviate symptoms. As a result, nausea and vomiting were frequently experienced. The development of carbidopa, a levodopa enhancer, was the solution to this inefficient drug delivery. When combined with levodopa, carbidopa allows for an 80 percent reduction in the dose required to achieve the same effect and a significant decrease in the frequency of side effects.

Carbidopa/levodopa significantly alleviates PD symptoms in the majority of individuals with a clinical diagnosis of PD, although the tremor response may lag behind the response to other symptoms. Additionally, the facial expression, posture, speech, and handwriting may improve. Levodopa has a relatively short half-life — the amount of time a drug remains in the bloodstream before being metabolized by the body's tissues — of about 60-90 minutes. This results in fluctuations in dopamine levels in the blood and brain, which accounts for the motor fluctuations that people with Parkinson's disease experience following long-term levodopa use.

The most efficacious agents for motor symptoms are levodopa/dopa-decarboxylase inhibitors, which have a slightly better tolerability profile, particularly when started at low doses. The most straightforward dosing regimen is to initiate a fixed dose at a fixed time and then monitor efficacy in terms of the dose required to relieve symptoms and the duration of that response (5).

Adverse Effect

The most frequently reported side effects of carbidopa/levodopa include the following:

- Nausea
- Vomiting
- Appetite loss
- Lightheadedness
- Lowered blood pressure
- Confusion

Such adverse effects can be minimized by initiating treatment with an antiparkinson drug at a low starting dose and gradually increasing the dose to a satisfactory level. This is especially beneficial for elderly people with Parkinson's disease, who frequently have a lower tolerance for medications than younger people. Additionally, taking medications with meals can help reduce the occurrence and severity of gastrointestinal side effects. For patients with persistent problems, supplementing each dose of carbidopa/levodopa with additional carbidopa (Lodosyn®) may be beneficial.

Diet and levodopa

Levodopa taken with food can occasionally help to alleviate nausea. However, for some individuals, protein (found primarily in meat, fish, eggs, cheese, and beans) appears to impair the way levodopa medication works by impairing the drug's absorption by the body.

Because the body requires protein, it is critical to continue eating it. Certain individuals, however, may benefit from taking their medication at least 30 minutes before eating. Your specialist or Parkinson's nurse can advise you on dose timing, which should be discussed with them when the medication is first prescribed. Additionally, they can assist you in obtaining advice from a dietitian.

Even in the late stages of Parkinson's disease, dopamine replacement therapy (DRT) continues to improve limb bradykinesia, rigidity, and tremor; it is the accumulation of nondopaminergic lesions with disease progression that eventually limits DRT's overall effectiveness (6). Significant evidence now exists against L-dopa neurotoxicity, and experts have emphasized L- dopa's safety (7)

L-dopa and Motor Response Complications

Individuals treated with DRT initially have a stable response throughout the day. They do not perceive any difference in their parkinsonian symptoms from one dose to the next; however, repeated pulsatile stimulation of striatal dopamine receptors with chronic oral L-dopa treatment induces plastic changes in basal ganglia circuits, which can result in the development of motor response complications (MRC) (8). Patients report a marked improvement in their parkinsonian symptoms following a dose of L-dopa (the on period), followed by a recurrence of these symptoms before the next dose has a chance to work (the off period). Involuntary movements (dyskinesia) can occasionally impair the quality of menstruation, and patients can develop off-period dystonia. No other therapy has a more potent antiparkinsonian effect, and nearly

Table 1: Levodopa/carbidopa for Motor Symptoms in PD

Medication (product name in parentheses)	Dosages in Milligrams (mg); tablets unless otherwise noted	Typical Treatmen Regimens*	Potential Side Effects	Indications for Usage (italics = approved by FDA
Levodopa				
Carbidopa/ levodopa immediate-release (Sinemet®)	10/100, 25/100, 25/250	150–1000 mg of levodopa total daily dose (divided 3-4 times)	Low blood pressure, nausea, confusion, dyskinesia	Monotherapy or combination therapy for slowness, stiffness and tremor
Carbidopa/ levodopa oral disintegrating (Parcopa®)	10/100, 25/100, 25/250	150–1000 mg of levodopa total daily dose (divided 3-4 times)	Same as above	Same as above, plus need for dissolvable medication in mouth especially if swallowing is impaired
Carbidopa/ levodopa extended-release (Sinemet CR®)	25/100, 50/200	150–1000 mg of levodopa in divided doses, depending on daily need	Same as above	Monotherapy or combination therapy for slowness, stiffness and tremor
Carbidopa/ levodopa/ entacapone (Stalevo®) (see COMT-inhibitors below)	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200	150–1000 mg of levodopa total daily dose, depending on daily need	Same as above, plus diarrhea and discolored urine (due to entacapone)	Replacement for carbidopa/ levodopa, for motor fluctuations (benefit of entacapone)
Carbidopa/ levodopa extended- release capsules (Rytary™)	23.75/95, 36.25/145, 48.75/195, 61.25/245	855-2340 mg of levodopa total daily dose	Same as above	Monotherapy or adjunct therapy for slowness, stiffness and tremor. Note that dosages of Rytary are not interchangeable with other carbidopa/ Levodopa products.
Carbidopa/ levodopa enteral solution (Duopa™)	Clinician-determined	Up to 2000 mg of levodopa over 16 hours	Same as above	For the treatment of motor fluctuations in patients with advanced Parkinson's disease

all individuals with Parkinson's disease will eventually require L-dopa therapy. However, community-based studies are increasingly indicating that MRC (particularly dyskinesia) may not be the primary source of disability for the majority of people with PD. For example, after ten years of L-dopa treatment, nearly 90% of subjects were spared dyskinesia that could not be controlled through medication adjustment. Similarly, another study found that while approximately 95% of individuals with Parkinson's disease had dyskinesia and/or wear-off by 15 years after diagnosis, these symptoms were not disabling in the majority. Thus, with the exception of children, factors other than the risk of developing MRC should probably weigh more heavily in early treatment decisions.

Initiation of levodopa therapy

Levodopa is the gold standard treatment for Parkinson's disease and the most effective medication for motor symptoms (11). Levodopa passes through the blood–brain barrier and is converted to dopamine by the SNpc's remaining dopaminergic neurons. Levodopa is typically administered multiple times daily via tablet but can also be administered via duodenal infusion in patients with advanced disease.

Levodopa produces peripheral dopaminergic side effects (nausea and hypotension), which can be avoided with the use of a decarboxylase inhibitor (carbidopa or benserazide); other side effects include sleepiness, confusion, hallucinations, and impulse control disorders, such as hypersexuality, compulsive shopping, gambling, and punditry (12). However, its primary limitation is the onset of motor complications such as fluctuations, dyskinesia, dystonia, and wear-off. Complications are believed to be related to the discontinuous phasic stimulation of the striatal dopamine receptors, in contrast to the physiological continuous supply of dopamine (13). The risk of developing motor complications as a result of levodopa is related to the severity of dopaminergic neurodegeneration (the more severe the degeneration, the greater the risk), the dose of levodopa (>400 mg daily), female sex, and low weight (relates to dose/kg) (14). To minimize motor fluctuations, an extended-release carbidopa-levodopa formulation (IPX066) was developed and recently approved (15). In advanced Parkinson's disease, when motor complications become disabling and are unresponsive to conventional pharmacological therapy, levodopa can be pumped directly into the duodenum via a gastrostomy catheter as a levodopa-carbidopa gel; this formulation has been shown to significantly reduce motor fluctuations in advanced Parkinson's disease; potential adverse events are related to the surfactant. Other formulations of levodopa for the treatment of motor fluctuations are currently being investigated, including continuous subcutaneous infusion, an inhaled formulation, a levodopa prodrug (XP21279) (17), and an extended release levodopa (DM1992) formulation (19).

Key POINT: Following several years of a smooth response to levodopa, many people with Parkinson's disease notice the onset of motor fluctuations ("wearing off") and involuntary movements (dyskinesia). Typically, these complications can be managed by adjusting the dose and timing of the medication.

Regardless of the initial therapy, the majority of patients will require levodopa as a supplemental or monotherapy as the disease progresses. Recent research has also demonstrated that, over time, the initial treatment regimen may have no effect on the ultimate risk of developing bothersome dyskinesias once levodopa is initiated(8), or on the incidences of motor complications (19, 20).

Levodopa is given in conjunction with a dopa-decarboxylase inhibitor (DDCI), such as benserazide (Madopar® and Prolopa®) or carbidopa (Sinemet®). Inhibition of dopa decarboxylase (DDC), a key enzyme in peripheral levodopa metabolism, contributes to an increase in levodopa's half-life and bioavailability (21). Despite the fact that this combination improves the pharmacokinetic profile of levodopa, it is still characterized by fluctuations and deep troughs in plasma levodopa levels. Thus, a third pharmacokinetically enhanced formulation of levodopa, LCE (levodopa/carbidopa/entacapone), has been developed recently that inhibits both DDC and catechol-O-methyltransferase (COMT), the second enzyme involved in levodopa's peripheral metabolism (22).

In general, patients should begin with low doses of levodopa and gradually increase to an effective dose. The two most frequently used strategies for initiating levodopa therapy are 50 mg or 100 mg, with variations listed below. Age is a critical factor to consider when determining the optimal strategy for initiating levodopa. Levodopa may be used as first-line therapy in elderly patients (>65 years). In contrast, the first-line therapy for patients with young-onset Parkinson's disease is predominantly dopamine agonists, with levodopa frequently used as an adjunct when symptomatic control fails. As such, lower initial levodopa doses should be used (i.e. 50 mg unit dose may be preferable to 100 mg). Levodopa may, however, be started as first-line therapy in younger patients who experience disabling side effects from dopamine agonists.

Introductory dose of 100 mg levodopa three times daily

This is a frequently used strategy for initiating levodopa in patients who do not have motor fluctuations and are at low risk of developing dyskinesia. Three times daily (tid) dosing may be more convenient for patients because doses can be scheduled around mealtimes, and 100 mg levodopa provides greater symptom control for the majority of patients than lower doses.

50 mg levodopa four times daily

When compared to a three-times-daily regimen, initiating patients on a four-times-daily (qid) regimen may provide better coverage throughout the day. Additionally, this strategy allows for the use of lower individual levodopa

doses in patients at risk of developing adverse events. This strategy is primarily used to minimize the risk of adverse events associated with 100 mg levodopa and to minimize plasma level fluctuations, which may eventually result in pulsatile stimulation of striatal dopamine receptors. However, if 50 mg levodopa doses are insufficient to control symptoms, 100 mg levodopa qid should be considered. There are some drawbacks to this strategy; for example, patients may have a harder time adhering to a four-times-daily dosing regimen that is not centered on mealtimes. Thus, unless the patient is awake for extended periods of time, this strategy may be difficult to follow. Additionally, there is a dearth of clinical evidence to support this strategy's superiority to a three-times-daily regimen.

Slow, gradual titration to levodopa three times daily
Additional variations on the gradual titration to 100 mg levodopa include starting with 50 mg levodopa once daily and gradually increasing by 50 mg every three days until 50 mg tid is reached, or starting with a 100 mg levodopa dose in the morning and two additional 50 mg doses that would be gradually replaced by two 100 mg doses over the course of a week. These strategies may aid physicians in optimizing therapy on an individual basis for each patient, as therapy can be stabilized at any stage based on the patient's response to each step. Additionally, these strategies may be more appropriate for patients at risk of developing poor drug tolerance and may include an intermediate dose of 75 mg levodopa.

Levodopa therapy optimization
Once on levodopa, dose adjustments may be necessary to help maintain optimal symptom control and manage motor complications. Frequently used strategies for symptom control include increasing the total daily dose and unit dose of levodopa, increasing the number of daily doses, switching to controlled-release levodopa, or increasing the number of daily doses. Increased dose strength or frequency of levodopa doses does not completely address the high peaks and low troughs in plasma levodopa levels, although frequent dosing can result in higher plasma levodopa concentrations for longer periods of time (23). Additionally, levodopa at high doses is associated with an increased risk of dyskinesia (24). Controlled-release formulations exhibit an unpredictable pharmacokinetic profile with erratic absorption and a delayed ON-time, and do not significantly reduce the risk of dyskinesia when compared to immediate-release formulations (25). Regardless of this, controlled-release formulations may be beneficial at night.

Stalevo has been shown in studies with healthy subjects and patients with Parkinson's disease to reduce the deep troughs in plasma levodopa levels associated with conventional levodopa (Figure 2), as well as to increase the half-life and bioavailability of levodopa (23, 26). Dual-enzyme inhibition has been shown to increase ON-time, decrease OFF-time, and improve motor scores in patients with advanced wearing-off (27, 28). Additionally, benefits can be seen in patients who exhibit early signs of levodopa wear-off or who require levodopa initiation. Stalevo improves motor function, activities of daily living, patient-reported Clinical Global Impression of Change [CGI-C]), and motor and non-motor wearing-off symptoms in patients with early wearing-off, regardless of whether they previously received levodopa/benserazide or levodopa/carbidopa (29). Additionally, the QUEST-AP study demonstrated that Stalevo improves health-related quality of life when compared to conventional levodopa in patients with Parkinson's disease who have no or few non-disabling motor fluctuations (30).

Finally, using high doses of Stalevo (200 mg levodopa) at night may be beneficial. When given as a single night-time dose, a recent pharmacokinetic study demonstrated that Stalevo has a higher bioavailability and a longer half-life of levodopa than controlled-release levodopa (13).

Neuronet-PD Working Group Recommendations
It is necessary to adjust a patient's levodopa dose in order to maintain symptom control and manage motor complications. To maintain symptom control, the most frequently used modification strategy is to increase the individual levodopa dose, either from 100 to 150 or 200 mg of conventional levodopa or from three to four times daily dosing. Once patients begin to experience wear-off, switching to Stalevo is frequently the best course of action. The switch to Stalevo can be accomplished in a variety of ways, and the most effective strategy is determined by the patient's profile. In general, the number of doses per day should be maintained when switching to Stalevo, unless the patient is receiving five or six doses per day. In this case, a daily dose reduction to four or five is recommended.

Direct connection to Stalevo
For patients with predictable motor fluctuations who are not at risk of dyskinesias, the most frequently used strategy is a direct overnight switch to Stalevo with an equivalent levodopa dose.

Gradual conversion to Stalevo
For patients at risk of dyskinesia or with severe motor fluctuations, a more gradual switch using lower levodopa doses is recommended. The gradual switch can be accomplished by gradually transitioning from conventional levodopa to equivalent doses of Stalevo or by using entacapone. Entacapone requires an additional tablet to be added to each dose of conventional levodopa, which is then replaced by a single, equivalent tablet of Stalevo. Adherence may be a concern with this strategy, as the intermediate stage of the switch results in an increase in the patient's pill burden. While switching to equivalent Stalevo doses would be appropriate for the majority of patients, those receiving high daily doses of levodopa may benefit from a gradual, stepped reduction in Stalevo strength to avoid dyskinesia or worsening of parkinsonian symptoms.

Keeping patients on the most appropriate therapy
Adherence and compliance with medication are critical in Parkinson's disease (PD) to maintain function and avoid the development of motor complications (32). However, studies in patients with Parkinson's disease have revealed low medication compliance, particularly with regard to the

timing of each medication dose. As disease progresses, it has been demonstrated that increasingly complex dosing regimens have a detrimental effect on patient adherence (33,34). Numerous interventions have been proposed to assist patients in remaining on optimal therapy. These include advanced warnings of adverse effects, the addition of an antiemetic during the initiation or dose titration phases, follow-up visits or phone calls by PD nurses/physicians, and computer-based patient information. Notifying the patient of potential adverse events, such as chromaturia (a harmless discoloration of the urine) with Stalevo, may help increase patient compliance if the patient understands that this is a harmless chemical effect of the drug. Active therapy counseling has been shown to improve a patient's timing and adherence to treatment (35). Similarly, a follow-up call has been shown to be beneficial in lowering the rate of discontinuation in patients with Parkinson's disease who had begun treatment with levodopa/DDCI and entacapone. Two weeks after therapy initiation, a phone call significantly reduced discontinuations for up to six months of therapy (36).

Final Thoughts

Levodopa remains the gold standard in the medical treatment of Parkinson's disease. Fear of motor complications, on the other hand, has resulted in its delayed initiation or ineffective administration. Traditionally, levodopa is administered in combination with a DDCI (carbidopa [Sinemet] or benserazide [Madopar]).

Recently, a combined formulation (Stalevo) that inhibits both DDCI and COMT in a single tablet was developed. Stalevo has a better pharmacokinetic profile than conventional levodopa, which translates into clinical benefits. Physicians' strategies for initiating levodopa therapy vary, but most commonly, a 50 or 100 mg levodopa tid dosing regimen is used. Physicians frequently increase the dose or frequency of conventional levodopa or switch to Stalevo as the disease progresses. Switching to Stalevo requires consideration of the patient's profile, levodopa dose, and disease stage. At all stages of disease, it is critical to keep patients on the optimal dose of levodopa and to educate them about potential side effects. This is frequently difficult, and strategies such as patient education and early follow-up may be beneficial in ensuring that patients receive the maximum benefit from their levodopa therapy with the fewest possible side effects.

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