

Common Myths and Misconceptions That Sidetrack Parkinson Disease Treatment, to the Detriment of Patients



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Abstract

Parkinson disease symptoms become apparent when there has been substantial loss of brain dopamine. That is the consequence of the slow progression of the Lewy body neurodegenerative process. Replenishment of brain dopamine with levodopa therapy dates back approximately a half century and continues to be the most efficacious symptomatic treatment. Understanding the fundamentals of levodopa treatment is crucial to therapeutic success. Various myths over the years have sabotaged treatment outcomes and have discouraged primary care physicians from managing patients with Parkinson disease. That is unfortunate because in some regions, neurologists, and in particular movement specialists, are in short supply. The long history of these persistent levodopa myths and the counterarguments are the focus of this article.

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The fundamentals of Parkinson disease (PD) medical treatment have been established for a number of decades. New medications have come and gone; some have remained available but may not necessarily provide unique benefits to our patients. The treatment strategies for PD are relatively straightforward and should be in the armamentarium of internists and primary care physicians. This is especially relevant in communities where neurologists are in short supply and appointments are hard to come by. Neurologists continue to have an important role and especially when complications surface in later PD or if clues to an atypical condition become apparent (parkinsonism-plus disorder).

Compromising PD treatment are many myths still commonly present online and sometimes verbalized by clinicians unaware of their origins or veracity. In my practice, I frequently devote a substantial portion of counseling time with patients to disabuse them of advice they have read or heard and that would impede their treatment. The purpose of this article is to highlight these myths and point out their fallaciousness

using evidence-based medicine, confirmed with experience in the clinic.

BACKGROUND AND CHRONOLOGY

The most important discovery for PD treatment, to date, was the recognition that striatal dopamine deficiency was the substrate for many of the symptoms of PD. Scientists recognized that dopamine does not cross the blood-brain barrier (BBB), but the immediate precursor, levodopa, is transported across the BBB. Specifically, a molecular transporter at the BBB picks up L-neutral amino acids, including levodopa, and carries them into the brain. Within the brain, levodopa is converted to dopamine by the enzyme dopa decarboxylase. This research in the 1960s led to the approval of levodopa therapy by the US Food and Drug Administration (FDA) in 1969.

In the early levodopa era, very high levodopa doses were necessary for a therapeutic response, and nausea and vomiting were common. Scientists recognized that these problems were due to the ubiquitous *peripheral* dopa decarboxylase; this enzyme was prematurely converting levodopa to



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ARTICLE HIGHLIGHTS

- Primary care clinicians should feel comfortable managing routine Parkinson's disease (PD).
- Carbidopa/levodopa is the single drug crucial to optimum PD management. Deferring levodopa or limiting the dose confers no long-term benefit.
- Sub-optimal levodopa responses are often due to meal-time dosing.

dopamine in the circulation. Levodopa, peripherally converted to dopamine, was prevented from entering the brain. Moreover, a related mechanism accounted for the nausea/vomiting. The increased circulating dopamine was entering the brain stem nausea center (area postrema; chemoreceptive trigger zone), one of very few regions where the BBB is patent. Thus, drugs were designed that blocked peripheral dopa decarboxylase but could not cross the BBB: carbidopa (in the Americas) and benserazide (in Europe). Carbidopa/levodopa was FDA-approved in 1975 and has been the mainstay of PD treatment in the United States ever since.

Approved Medications for Symptomatic Treatment of PD

Primary care clinicians may defer PD treatment to specialists because of the numerous available drugs. General neurologists may also be challenged by the proliferation of PD drugs. Parenthetically, discussion regarding drug choice has often been influenced by commercial interests.

Carbidopa/levodopa is the most efficacious medication for symptomatic treatment of PD. Regular (immediate-release) 25 mg/100 mg carbidopa/levodopa has been the primary formulation used at most medical centers.¹ It is the appropriate formulation for initiation and maintenance for nearly all patients with PD. Carbidopa/levodopa is also available in a 10 mg/100 mg formulation, which is not recommended because of insufficient carbidopa for some patients. The 25 mg/250 mg formulation also has

proportionately less carbidopa, plus the large fixed amount of levodopa makes dose adjustment difficult. Carbidopa/levodopa is also available in 2 sustained-release formulations, which are used in special circumstances (Sinemet CR and Rytary).

Dopamine agonists behave like synthetic forms of dopamine, and they tend to have quite variable affinities for the 5 primary dopamine receptor subtypes.² Currently available oral dopamine agonists include pramipexole and ropinirole. The oral ergot dopamine agonists, bromocriptine and pergolide, are no longer used because of the potential for inflammatory-fibrotic cardiopulmonary reactions. A dopamine agonist patch, rotigotine, is now available.

Monoamine oxidase (MAO) B inhibitors increase brain dopamine concentrations and are mildly efficacious for symptomatic PD treatment. They inhibit one route of brain dopamine degradation, via MAO-B. Because they do not block MAO-A in the recommended doses, they do not have the risk of the serious adverse effects of the nonselective MAO inhibitors used to treat refractory depression. They do not require dietary restrictions.

Each of the 2 available MAO-B inhibitors, selegiline and rasagiline, have been advocated as slowing PD progression, but this view has been very controversial³ and not proven. The FDA has not approved either of these drugs for that specific indication.

Catechol-O-methyltransferase (COMT) inhibitors block an enzyme that degrades levodopa. Entacapone is a peripherally acting COMT inhibitor that prolongs the levodopa effect in the circulation by up to about an hour. The purpose is to prolong short-duration levodopa responses and reduce wearing-off of the levodopa effect in patients with advancing PD. It has a short half-life and is typically administered concurrently with each dose of carbidopa/levodopa, either as separate pills or the combination drug Stalevo. An older COMT inhibitor, tolcapone, has both a peripheral and a central effect with a longer half-life, allowing 3 times per day dosing. Soon after it was FDA approved

and launched, serious liver toxicity surfaced, and it now is rarely prescribed. Neither of these drugs has an antiparkinsonism effect when used in the absence of levodopa.

Other medications with different pharmacologies have been used for symptomatic PD treatment but with modest benefits. These drugs include anticholinergic medications, the benefit of which are often overshadowed by adverse effects. The newly approved adenosine A_{2A} antagonist istradefylline has modest benefits as an adjunct to carbidopa/levodopa compared with placebo but with limited overall efficacy.^{4,5} Amantadine has mild symptomatic PD benefit but with utility primarily restricted to attenuation of levodopa-induced dyskinesia.^{6,7} These other medications will not be discussed further in this article.

Speculation About the Cause of PD and How It Influenced Levodopa Treatment

With the remarkable clinical response to carbidopa/levodopa treatment in the 1970s, speculation about the etiology of PD focused on the dopaminergic neurons in the substantia nigra. What was it about this dopaminergic nucleus that caused it to degenerate? Researchers' attention soon focused on the neurotransmitter dopamine and its potential for oxidative metabolism. Cytotoxic oxidative stress linked to dopamine metabolism was proposed as a primary cause of PD.^{8,9} By the early 1990s, dopamine oxidative stress as an important causative factor had many advocates. Implicit in this hypothesis was that levodopa treatment potentially fueled cytotoxic oxidative processes, facilitating nigrostriatal degeneration.^{10,11} By the mid-1990s, this hypothesis was predominant and strongly influenced PD treatment. Thus, clinicians were advised to defer levodopa, use alternatives whenever possible, and limit the levodopa dose. Alternate views were published¹²⁻¹⁴ but represented a minority view.

Pharmaceutical companies developing alternative PD drugs undoubtedly contributed to this discussion. Their substantially less efficacious PD medications with more adverse effects and greater expense required

clever marketing. Thus, a generation of clinicians and patients learned about PD treatment through this background.

Dopamine Oxidative Stress Is Not Etiologically Important in PD: Evidence

Vestiges of this hypothesis still surface in my PD practice, voiced by patients who have encountered it online or by word of mouth. Clinicians should be knowledgeable about appropriate counterarguments to put these concerns to rest, including the following.

- Oxidative neuropathology is not unique to PD. It is ubiquitous in most neurodegenerative disorders.¹⁴
- Parkinson disease Lewy body neuropathology spares some dopaminergic nuclei. In fact, within the substantia nigra, the dorsal regions are consistently spared.¹⁵ The nearby A8 dopaminergic neurons are modestly affected in PD^{16,17} or not affected at all.¹⁸
- Conversely, it has been known for decades that Lewy body pathology is found in many nondopaminergic nuclei/neurons.¹⁹ The elegant PD neuropathologic studies of Braak et al,^{20,21} initially published about 15 years ago, subsequently brought this fact into full view.

In the scheme developed by Braak et al, involvement of dopaminergic neurons represents an intermediate PD stage, which is clinically very apparent because of the seminal role that the dopaminergic nigrostriatal system plays in modulating movement. The symptoms of the earliest PD stages, such as rapid eye movement sleep behavior, constipation (dysautonomia), or olfactory deficits, reflect involvement of nondopaminergic regions, as do the later PD states in which dementia, hallucinations, or levodopa-refractory symptoms may surface. The Braak et al scheme elucidated the relationship between evolving Lewy body neuropathology and the broad range of PD symptoms over a lifetime.²⁰⁻²² A major component of Lewy body pathology and the current target of PD research is α -synuclein, which has no special association with dopamine.

Levodopa Is Not Toxic: Evidence

If dopamine oxidative stress is not a cause of PD neurodegeneration, might dopamine neurotoxicity still be a concern? Multiple lines of evidence have argued against that hypothesis.

- Longevity among patients with PD has been assessed just before and soon after the introduction of levodopa therapy in 1969. In all, 7 independent studies documented substantially increased life spans time-locked to levodopa availability.¹⁴
- Early levodopa era patients had varied durations of PD before treatment because of prior unavailability of levodopa. Among 4 large PD cohorts starting levodopa therapy around 1969, longer delays before starting levodopa were associated with significantly worse age-adjusted mortality rates.²³ The University of California, Los Angeles PD study group also found that the disability score and dementia risk were related to the duration of parkinsonism and not the duration of levodopa treatment.²⁴
- If levodopa was toxic, the neuropathology should document evidence. However, Yahr et al²⁵ reported that in patients with PD, the substantia nigra pathology was unchanged following the use of levodopa.
- Finally, a small number of patients without PD underwent long-term treatment with high doses of levodopa without subsequent postmortem evidence of substantia nigra damage.^{26,27}

Clinical Evidence: Levodopa Therapy Does Not Accelerate PD Neurodegeneration

The preceding evidence was not an easy sell to clinicians or researchers. Thus, the strong concerns about levodopa toxicity were ultimately assessed in a large National Institutes of Health–funded, randomized, controlled trial of long-term administration of carbidopa/levodopa vs placebo spanning 40 weeks.²⁸ The expectation was that if levodopa treatment was toxic, it should be evident in the PD scores following a 2-week drug washout compared with baseline. In fact, the results were just the opposite.

With the levodopa dosage of 600 mg daily, parkinsonism scores remained significantly *improved* over these patients' baseline scores after 2 weeks of drug abstinence. This outcome might have been anticipated from a prior smaller study comparing nearly 14 months of carbidopa/levodopa treatment to the dopamine agonist bromocriptine after a 7-day washout phase.²⁹ Specifically, the levodopa group's postwashout parkinsonism motor scores did not significantly decline below baseline and, in fact, were better than those of the group receiving bromocriptine (not significant). These studies were instrumental in reducing concerns about levodopa toxicity.

THE NEW MILLENNIUM: CLINICIANS STILL ADVISED TO SPARE LEVODOPA

With the seeds planted to discourage or to question levodopa therapy, clinicians continue to experience “levodopa anxiety/phobia.”³⁰ As recently as a decade ago, well-known experts still recommended initiating PD treatment with nonlevodopa products.^{31–33} Clinicians were advised to start symptomatic treatment with an MAO-B inhibitor (eg, selegiline, rasagiline) or a dopamine agonist (eg, pramipexole, ropinirole, rotigotine). Recently, experts tempered this advice—“best to use low doses of l-dopa when possible”³⁴—but still conveyed reluctance about using levodopa therapy. Thus, the guiding term “levodopa-sparing” strategies was perpetuated.

These concerns tend to legitimize myths about levodopa still communicated to patients: “it stops working after a few years,” “it should be saved for later,” “the dose should be restricted,” “levodopa dyskinesia is worse than PD.” Other problematic myths include “levodopa causes nausea and should be taken with food,” “levodopa disrupts sleep,” and “50% of people with PD experience hallucinations.”

This 45-year-old drug, carbidopa/levodopa, should be easy to initiate, but currently it often requires a major allocation of clinic time to address levodopa myths. Moreover, primary care physicians, who could easily manage routine PD care, now

are confronted with a morass of misinformation and disparate advice; hence, they delegate PD treatment to specialists.

Levodopa Myths That Still Sabotage PD Treatment: What Clinicians Should Know

Myth: Levodopa Stops Working After a Few Years. In PD, levodopa never stops working, although in “parkinsonism-plus” disorders, such as progressive supranuclear palsy or multiple system atrophy, it may stop working or never work at all. Also, in elderly adults, the responses are not as prominent because of brain aging, which affects basal ganglia motor systems.³⁵⁻³⁷

The dynamics of the levodopa response change with progressing PD. In the early years, the response to levodopa is long-lasting, building up over a week on a stable dose (the so-called long-duration effect). Years later, the beneficial effect becomes partly time-locked to each dose, termed the *short-duration response* and leading to “wearing-off phenomena.”³⁸ This change reflects the duration of PD rather than levodopa treatment duration.³⁹

After 10 to 20 years of PD, the levodopa response is not as robust as it was initially. This decline reflects the progression of the Lewy body neurodegenerative process affecting nondopaminergic basal ganglia circuitry, wired in series with the nigrostriatal system.^{20,40,41}

Myth: Levodopa Should Be Saved for Later. Parkinson disease is a progressive disorder that slowly advances over decades, often starting with dream-enactment behavior (rapid eye movement sleep behavior disorder), constipation, or olfactory loss and typically, years later, as motor parkinsonism. The motor signs of parkinsonism do not surface until 50% to 80% of the striatal dopaminergic terminals are lost.⁴²⁻⁴⁵ However, the neurodegenerative loss of these terminals continues, and when nearly depleted, synaptic dopamine can no longer be regulated. Presynaptic terminals are responsible for stable, persistent dopamine synaptic concentrations. When these presynaptic terminals are depleted, synaptic

dopamine tends to mirror circulating levels. Thus, synaptic dopamine concentrations may be excessive or short-lived, resulting in dyskinesia or clinical fluctuations, respectively. This process reflects the natural history and progression of the Lewy body neurodegenerative progression, and it cannot be avoided by deferring levodopa treatment.⁴⁶

Longer durations of parkinsonism before levodopa treatment were common when this drug was first introduced (about 50 years ago); this time lapse allowed separating the effect of PD duration from levodopa treatment duration. Such analyses documented that both disability and dementia risks were related to parkinsonism duration rather than levodopa treatment duration.²⁴ Moreover, it was found that the age-adjusted mortality rates worsened with longer levodopa delays.²³

As noted previously, the initially very robust levodopa benefit tends to decline as the Lewy body neurodegenerative process progresses beyond dopaminergic circuitry into neighboring basal ganglia circuits. This decline cannot be avoided by deferring levodopa.

Deferring levodopa treatment is acceptable if it does not compromise activities of daily living and the capacity to be active and exercise.⁴⁷ However, if quality of life is compromised by lack of treatment, such good years are lost; they cannot be retrieved.

Myth: Limit the Levodopa Dose to Avoid Later Dyskinesia. Typical levodopa-induced dyskinesia consists of choreiform movements. It follows individual doses of levodopa and is dose related (ie, there is a dose threshold). It should be distinguished from cramplike dystonias, such as foot inversion or toe curling, which typically are due to PD per se and are not a medication effect. Such PD-related dystonias usually resolve with adequate levodopa doses.

Early levodopa-induced dyskinesia was common when levodopa was first introduced in the late 1960s. This issue reflected the longer durations of parkinsonism before levodopa became available.⁴⁶ In the current

era, dyskinesia tends to be uncommon in the early years of levodopa treatment. Moreover, the risk relates to age. Patients with young-onset PD (onset before age 40 years) nearly always experience at least some dyskinesia within the first 5 years of levodopa treatment.^{48,49} In older patients, dyskinesia incidence after 5 years of levodopa is uncommon (eg, 16% 5-year risk among levodopa-treated patients older than 70 years⁵⁰).

Importantly, dyskinesia can be abolished easily by levodopa dose reduction. It reflects the size of *each individual* dose. A supra-threshold levodopa dose provokes dyskinesia that lasts a few hours, then resolves. If the next dose is reduced to below the dyskinesia threshold, it does not occur. Dyskinesia is not directly related to the total daily levodopa dose, as opposed to the individual doses.

In a PD incidence cohort in Olmsted County, Minnesota, after 10 years of levodopa treatment, only 43% of patients had development of dyskinesia severe enough to require medication adjustments.⁵¹ Only 12% of the entire 10-year cohort had dyskinesia that could not be controlled with medication adjustment (ie, levodopa reduction resulted in troublesome parkinsonism).⁵¹ In the current era, these patients would be candidates for deep brain stimulation.

Myth: Limit the Levodopa Dose to Avoid Later Fluctuations. “Fluctuations” with levodopa treatment reflect “short-duration” levodopa responses, ie, a given dose reverses parkinsonism for only a few hours. Such short-duration pharmacodynamics tend to develop after several years of PD and presumably reflect the continued loss of dopaminergic terminals. When the aggregate terminals can no longer modulate dopamine concentrations within the synapse, the response tends to reflect circulating concentrations of levodopa.

These short-duration levodopa responses are treatable but require patients’ insight into what is occurring. Often, the affected patient will report that levodopa is “no longer working,” when, in fact, it *does* work but only for

a few hours after each dose. The strategy for treatment is 2-fold. First, identify the levodopa dose that produces the best response. Second, administer it at intervals that match the duration of the response.

An online myth advises such patients to use lower individual levodopa doses if taking it more often; however, this will impair the responses. Another myth is that there is an absolute limit to the number of levodopa tablets or doses per day. There is no limit, except as limited by common sense. Some institutional pharmacies arbitrarily subscribe to the 4 times a day, 200-mg (8 tablets) dose limit for carbidopa/levodopa, further contributing to the “maximum levodopa” myth.

Myth: The Dopamine Agonist Drugs Are Nearly as Efficacious as Levodopa. The oral dopamine agonist medications available in the United States are pramipexole and ropinirole. These drugs have been advocated as an alternative to carbidopa/levodopa for the past couple of decades. Some patients with PD will have sufficient improvement with one of these agonists to allow them to defer levodopa for up to a few years. Generally, however, the responses are not nearly as robust as with therapeutic doses of levodopa. This deficiency is not surprising for these oral agonists given their limited in vitro dopamine receptor-binding affinities in human striatal tissue. Thus, these 2 drugs have high affinity for 1 of the 5 primary dopamine receptors (D₃) but little affinity for the other 4 dopamine receptors in this in vitro striatal model.²

Often overlooked with these 2 oral dopamine agonist drugs is the adverse effect spectrum. Pathologic compulsive behaviors develop in about a quarter of patients taking therapeutic doses of pramipexole or ropinirole.⁵² Hallucinations are about 3 times more common with these 2 agonists compared with carbidopa/levodopa in controlled trials.⁵³⁻⁵⁶ In these same trials, somnolence was also substantially more frequent, and this factor may be sufficient to result in sleep-related automobile accidents.⁵⁷ Edema refractory to treatment also infrequently occurs with pramipexole or ropinirole.

Rotigotine is a dopamine agonist available only as a patch, changed once daily. It is an expensive medication, and in the available patch sizes of 2 mg to 8 mg, the responses are mild to moderate.

Of note, published head-to-head comparative studies of a dopamine agonist vs carbidopa/levodopa typically limit the levodopa dosage in 2 ways. First, the carbidopa/levodopa dose is not increased above 2 of the 25 mg/100 mg tablets taken 3 times daily, and second, patients are never instructed to take carbidopa/levodopa on an empty stomach at least 1 hour before meals and at least 2 hours after the end of meals¹. Experience in the clinic indicates that these issues substantially limit carbidopa/levodopa efficacy.

Myth (Television): Around 50% of People With PD Will Experience Hallucinations. As someone who sees patients full-time in the neurology outpatient clinic, I have a different view of this topic than what is communicated in television ads. When hallucinations occur among my patients, most resolve with elimination of PD medications other than carbidopa/levodopa. These medications include dopamine agonists, MAO-B inhibitors, and amantadine, as well as centrally acting anticholinergics (most often used for hyperactive bladder). Maintenance of carbidopa/levodopa monotherapy typically is tolerated in patients susceptible to hallucinations. Other contributors to hallucinations include opioids and muscle relaxants. Whereas hallucinations can be a primary component of Lewy body dementia in PD, centrally acting drugs are often provocative.

Myth: Carbidopa/Levodopa Should Be Taken With Meals. It was recognized a half century ago that nausea from levodopa monotherapy was due to the premature conversion of levodopa to dopamine in the circulation. Although the BBB is impervious to circulating dopamine, it does enter the brain stem nausea center, the chemoreceptive trigger zone (area postrema), where the BBB is patent. The peripherally acting dopa decarboxylase inhibitor carbidopa (or

benserazide outside the United States) was subsequently added to levodopa, typically preventing nausea.

Despite use of carbidopa (or benserazide), nausea occasionally occurs. It is usually mild and dissipates with continued carbidopa/levodopa use, but rarely, it can be treatment-limiting. This problem has been the basis for advising patients to take carbidopa/levodopa with food. It continues to be advised routinely but is rarely necessary.

Unfortunately, dietary protein effectively blocks the levodopa benefit if carbidopa/levodopa is taken around the time of meals or snacks (except for fruit). The inhibition of levodopa benefit by dietary amino acids is primarily mediated at the BBB, where an amino acid transporter (specific for L-neutral amino acids) carries levodopa into the brain.⁵⁸ This transporter has a finite number of binding sites and is easily saturated with dietary amino acids, generated from protein digestion.⁵⁸ Thus, typical meals (which contain substantial protein) block the levodopa effect.⁵⁹⁻⁶¹ Patients with short-duration levodopa responses report that if their carbidopa/levodopa dose is taken around a meal, it fails to “kick in.” Such patients can define the safe times for taking carbidopa/levodopa. From them, we have learned that to guarantee a response, carbidopa/levodopa must be taken at least 1 hour before meals and at least 2 hours after the end of meals. To avoid an attenuated levodopa response, it seems wise to advise all patients to follow the rule of not eating until at least an hour after taking carbidopa/levodopa and waiting at least 2 hours after the end of a meal to take another dose of carbidopa/levodopa. This is an inconvenience but not as much of an inconvenience as a blocked or attenuated levodopa response. A few patients can “cheat” on this timing and still experience their full levodopa response. However, if patients wish to “cheat,” they should first obey this empty stomach rule to establish a reference point.

Whereas absorption at the gut level and passage into the circulation can influence the levodopa response, the primary effect of meals is at the BBB.⁵⁹

Myth: Carbidopa/Levodopa Disrupts Sleep.

Insomnia is a common disorder. When it newly surfaces in the context of PD, it often relates to an inability to become comfortable in bed because of the parkinsonism per se (eg, akathisia, inability to turn over easily, stiffness). Treating the parkinsonism often improves sleep. Among patients with newly diagnosed PD, the daytime doses of carbidopa/levodopa typically result in long-duration pharmacodynamics,³⁸ which carry over to the nighttime. With longer-standing PD and development of “short-duration” levodopa responses,³⁸ a full carbidopa/levodopa dose an hour before bedtime may allow sleep. If recurrence of parkinsonism occurs during the night with awakening, another full carbidopa/levodopa dose should allow a return to sleep (30-60 minutes later, once it has taken effect). “Full dose” implies taking the same dose found to produce the best daytime response. Of note, insomnia is common among people in general; other causes may be present, but this is a very treatable cause.

Myth: Sustained-Release Carbidopa/Levodopa Is the Preferred Formulation When Starting Treatment. The carbidopa/levodopa formulation with the most predictable and consistent responses is regular (immediate-release) carbidopa/levodopa.¹ To minimize the potential for nausea and facilitate easy dose adjustments, the 25 mg/100 mg regular carbidopa/levodopa tablet is preferred, as opposed to the 10 mg/100 mg pill.

The controlled-release formulation of carbidopa/levodopa (Sinemet CR) was developed a couple of decades ago and proved to have only limited advantages and several disadvantages. Thus, the effect only lasted about 60 to 90 minutes longer and often took twice as long to take effect.⁶² It proved to be incompletely bioavailable⁶³ and required larger doses, which were often difficult to estimate when converting from the regular formulation (ie, not a milligram to milligram correspondence to regular carbidopa/levodopa).⁶²

A new delayed-release formulation of carbidopa/levodopa was approved a few years ago with the brand name Rytary. This capsule

has combinations of carbidopa/levodopa with varying release rates, which ultimately translate into a 1-hour longer response after each dose compared with regular carbidopa/levodopa tablets. Note that the conversion from regular carbidopa/levodopa requires a 2:1 increase in levodopa. Rytary is advantageous for patients with short-duration levodopa responses (ie, responses that last only about 3 hours). However, Rytary is not appropriate for patients with newly diagnosed PD just starting carbidopa/levodopa treatment. It is substantially more expensive and is unnecessary in early PD.

Optimized Levodopa Is Crucial to the Well-Being of People With PD

The purpose of this article was to address the myriad of myths that have impeded optimal use of carbidopa/levodopa. A detailed discussion of how to initiate and dose carbidopa/levodopa is beyond the scope of this writing but can be found in an article published nearly a decade ago.⁶⁴ A more extensive PD treatment text has been published since and remains appropriate for current needs.¹

CONCLUSION

Levodopa has been available in the United States for a half century. Long-term use is common and has not been associated with any late-occurring adverse consequences. Unstable levodopa responses and dyskinesia appear to reflect the continued loss of dopaminergic innervation within the striatum, with loss of a dopamine storage effect and buffering capacity. A later decline of motor function, development of cognitive impairment, and dysautonomia are the consequences of continued Lewy body neurodegeneration, invading nondopaminergic systems. Saving levodopa for later or limiting the dose does not confer later benefits. Rather, such strategies potentially impair function during the early to middle years of PD, when optimum treatment may come close to normalizing function; thus, years of good-quality life may be lost. Among the available PD medications, carbidopa/levodopa produces the most robust

symptomatic responses with the fewest adverse effects and least expense.

Abbreviations and Acronyms: BBB = blood-brain barrier; COMT = catechol-O-methyltransferase; FDA = Food and Drug Administration; MAO = monoamine oxidase; PD = Parkinson disease

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