

Parkinson Disease Treatment in Hospitals and Nursing Facilities: Avoiding Pitfalls

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CME Activity

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Abstract

The unique needs of patients with Parkinson disease challenge staff when such patients are admitted to hospitals or nursing facilities. Prolongation of the hospital stay, falls with injuries, fainting, or declining motor function may result from therapeutic misadventures or failure to anticipate common problems. Staff familiarity with Parkinson disease, and especially carbidopa-levodopa dosing and dynamics, may prevent such problems and streamline hospital and nursing home care.

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Parkinson disease (PD) is a common condition, estimated to affect about 1 million people in the United States. People with PD have unique problems and special medication needs. This can be a challenge to clinicians and nurses caring for them when they are hospitalized or admitted to a nursing facility. The consequences of therapeutic misadventures due to staff unfamiliarity with PD are potentially substantial. Prolongation of hospital stays due to PD-related problems is common but often avoidable. Patients with PD who are admitted to nursing facilities may experience major upheaval in their medication

management. Fortunately, a little knowledge can be quite helpful, and that is the focus of this article, which is directed to doctors, mid-level health care professionals, and nurses.

BACKGROUND

Parkinson disease is a neurodegenerative disorder that notoriously causes slowness (bradykinesia), stiffness (rigidity), and a walking disorder typified by a stooped, shuffling gait with reduced arm swing; most, but not all, patients have a resting tremor. Unrecognized by many clinicians, however, are the nonmotor features of PD, which include anxiety, akathisia, depression,



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dysautonomia, as well as insomnia and other sleep disorders, to name a few.

Neurodegenerative disease with loss of the brain neurotransmitter dopamine underlies many of the motor and nonmotor symptoms of PD. The recognition that replenishment of brain dopamine with levodopa alleviates many PD symptoms was a revolutionary discovery. Despite 4 decades since the discovery of levodopa therapy, it still remains the most efficacious treatment for PD (as carbidopa-levodopa).

With advancing PD, the Lewy body neurodegenerative process extends beyond dopaminergic systems, causing dysautonomia (eg, orthostatic hypotension), cognitive impairment, and motor symptoms refractory to carbidopa-levodopa and related medications. Nonetheless, carbidopa-levodopa remains the foundation of treatment throughout the lifetime of those with PD, necessary for optimal quality of life. Basic knowledge of levodopa dosing and dynamics is crucial when caring for patients with PD who are hospitalized or admitted to nursing facilities.

CARBIDOPA-LEVODOPA

Dopamine cannot cross the blood-brain barrier, whereas the amino acid precursor levodopa crosses via an amino acid transporter. When levodopa was initially introduced without carbidopa, nausea and vomiting were common adverse events, and extremely high levodopa doses were necessary. These problems were related to the conversion of levodopa to dopamine before entering the brain, ie, in the bloodstream. Prematurely converted dopamine in the circulation is excluded from the brain. However, it crosses in one limited region where the blood-brain barrier is patent: the brainstem nausea/vomiting center. The addition of carbidopa solved that problem. Carbidopa blocks the enzyme that converts levodopa to dopamine; it does this only outside the brain because it does not cross the blood-brain barrier. Carbidopa-levodopa remains the most efficacious drug for symptomatic PD treatment.

The antiparkinsonian effect from carbidopa-levodopa occurs in 2 patterns, termed the *long-duration response* and the *short-duration response*. The levodopa long-duration benefit builds up over about a week with stable dosing. This is typically the primary pattern during the first several years of PD. Patients treated with a stable

carbidopa-levodopa dosing scheme can be early or late with their doses or occasionally even skip a dose without consequence. If the carbidopa-levodopa is stopped, the deterioration may be delayed for days up to a week.

After several years of PD, a second response pattern superimposes, the short-duration response. This presumably occurs because of the progressive loss of dopamine neurons, ie, the cumulative beneficial effect cannot be “stored,” and the responses increasingly mirror the levodopa concentrations in the circulation. For example, those with a short-duration levodopa response may be unable to walk in the morning before taking their medications, only to note a normal gait an hour after carbidopa-levodopa administration. The short-duration effect typically spans 2 to 6 hours, with the response duration typically shortening over time. Higher levodopa doses do not substantially prolong the response. An appropriate treatment strategy for such short-duration responses is to identify the optimal dose (the individual dose producing the best effect 60-90 minutes later) and administer that dose at intervals matching the response duration. It is important to recognize that there is no arbitrary ceiling on the number of doses or tablets per day.^{1,2}

Carbidopa-levodopa has few adverse effects, and they tend to reflect short-duration dynamics. Involuntary movements (chorea), known as dyskinesias, represent an excessive levodopa effect, typically appearing about an hour after a dose and lasting 2 to 4 hours. A sudden drop in the standing blood pressure (BP) may be provoked by individual doses of carbidopa-levodopa, with potential for syncope. Because of the short-duration levodopa dynamics, the BP may vary dramatically, depending on the time since the last carbidopa-levodopa dose. Nausea may be induced by levodopa, and like the other levodopa adverse effects, it tends to be time locked to the doses.

OTHER DRUGS FOR PD

Drugs for the treatment of PD are listed in Table 1; all work through dopamine mechanisms, except for the anticholinergic medications and amantadine. Although amantadine pharmacology was initially linked to dopamine, the primary activity is now recognized

TABLE 1. Parkinson Disease Medications for Long-term Use^a

Drug class	Medication	Comments
Dopamine precursor	Carbidopa-levodopa ^b	Generates brain dopamine
Dopamine agonist	Pramipexole (Mirapex) Ropinirole (Requip) Rotigotine (Neupro patch)	Primarily bind to the dopamine D3 receptors ^c
MAO-B inhibitor	Selegiline (deprenyl) Rasagiline (Azilect)	The B form of monoamine oxidase is one route of brain dopamine degradation ^d
COMT inhibitor	Entacapone (Comtan) Carbidopa-levodopa plus entacapone (Stalevo)	Peripheral COMT degrades circulating levodopa; entacapone prolongs the levodopa effect by 30-60 min ^{5,6}
Amantadine	Generic	Primarily used to reduce levodopa dyskinesias
Anticholinergic	Benzotropine (Cogentin) Trihexyphenidyl (Artane)	No longer advised for PD treatment due to adverse effects

^aCOMT = catechol-O-methyltransferase; MAO-B = monoamine oxidase B; PD = Parkinson disease.

^bOutside the United States, benserazide is formulated with levodopa; benserazide-levodopa is interchangeable with carbidopa-levodopa.

^cThere are 5 classes of dopamine receptors; these agonists have affinity primarily for the D3 class.³

^dRasagiline and selegiline MAO-B inhibition has a 40-day half-life.⁴

to be blockade of *N-methyl-D-aspartate* glutamate receptors. A few useful points about drugs other than carbidopa-levodopa follow.

Dopamine Agonists

The dopamine agonist drugs for long-term treatment (Table 1) are much less efficacious than carbidopa-levodopa and are approximately 3 times as likely to induce hallucinations.⁷⁻⁹ Uncommonly, they may induce extensive lower limb edema. Pramipexole and ropinirole are available in a once-daily sustained-release formulation as well as a 3-times daily regular formulation. They are conventionally administered with meals, but they can be taken on an empty stomach if no nausea occurs.

Monoamine Oxidase B Inhibitors

Selegiline and rasagiline have been advocated as medications for slowing PD progression; however, this benefit is unproven and not uniformly accepted.¹⁰ They mildly improve PD symptoms. Because of their long half-life (40 days), they may be stopped abruptly if necessary.

Catechol-O-methyltransferase Inhibitors

Catechol-O-methyltransferase is one route of levodopa degradation. Entacapone (Comtan) blocks catechol-O-methyltransferase outside the brain and mildly prolongs the levodopa effect in patients with short-duration levodopa responses (by 30-60 minutes^{5,6}). Entacapone does

not improve parkinsonism if administered without carbidopa-levodopa. It is administered with each carbidopa-levodopa dose. An entacapone dose of 200 mg captures the full effect, and higher individual doses do not add either benefit or adverse effects. Entacapone also makes each dose of carbidopa-levodopa slightly more potent, and by that mechanism, it may provoke dyskinesias. If levodopa dyskinesias are prominent, entacapone can be stopped abruptly, on at least a trial basis.

Carbidopa-Levodopa-Entacapone

Entacapone is also formulated with carbidopa-levodopa as Stalevo; each tablet contains 200 mg of entacapone. The dose of levodopa is given by the Stalevo number; thus, Stalevo-100 contains 100 mg of levodopa and Stalevo-150 contains 150 mg of levodopa. The amount of carbidopa in each tablet is in the same proportion as in the regular carbidopa-levodopa 25/100-mg tablets and need not be adjusted in most cases. If entacapone is to be stopped, plain carbidopa-levodopa could be substituted, eg, Stalevo-200 could be switched to 2 of the 25/100-mg immediate-release carbidopa-levodopa tablets.

Amantadine

Amantadine only mildly improves PD symptoms and is used primarily to reduce levodopa dyskinesias (see "Dyskinesias" section). Its effect on dyskinesias is dose related. It can be

started in a dose of 100 mg twice daily and be increased over days up to 4 to 5 tablets during the waking hours. Amantadine may occasionally provoke psychosis and is not advised in patients already experiencing hallucinations or delusions. Patients who have been taking amantadine for years often require a very slow taper to discontinue the drug.

CARE OF PATIENTS WITH PD IN HOSPITALS AND NURSING FACILITIES

Most problems in the care of patients with PD who are hospitalized or reside in nursing facilities relate to carbidopa-levodopa dosage. Ten problems/issues that may compromise care in these settings are summarized in [Table 2](#).

Carbidopa-Levodopa Confusion

Carbidopa-levodopa comes in different pill sizes with amounts specified by 2 numbers (eg, 25/100, 10/100, 25/250). The first number denotes the amount of carbidopa in each pill, and this dosage need not be adjusted unless the patient experiences nausea. The second number relates to levodopa, which indicates the potency.

Carbidopa-levodopa comes in 2 formulations: the regular (immediate-release) formulation and a sustained-release product (also termed *CR* or *controlled-release*). The most commonly prescribed carbidopa-levodopa tablet is the immediate-release 25/100-mg formulation, and this is preferred for routine use. Health care professionals can recognize this formulation by its yellow color (one generic formulation comes in blue but is uncommonly available).

The controlled-release formulation is only partially able to enter the circulation (ie, reduced bioavailability); hence, there is *not* a milligram-to-milligram correspondence with

the regular (immediate-release) formulation. Restated, these formulations are *not* interchangeable. About 30% to 50% more levodopa is needed with the sustained-release formulation to equate to the immediate-release product.¹¹ Occasionally, even pharmacists will mix up these 2 formulations. Note that controlled-release carbidopa-levodopa does not come in yellow pills.

As noted previously, carbidopa-levodopa may be formulated with entacapone, provided as the brand name Stalevo. For practical purposes, Stalevo may be considered nearly identical to regular (immediate-release) carbidopa-levodopa; it is slightly more potent and has slightly longer duration in the circulation. Stalevo pills are red-brown. The Stalevo pill size is given as a single number corresponding to the levodopa amount, eg, Stalevo-100 contains 100 mg of levodopa.

Timing of Carbidopa-Levodopa Administration in Regard to Meals and Surgery

Carbidopa-levodopa must be taken on an empty stomach in order to cross the blood-brain barrier. The levodopa transporter at the blood-brain barrier selectively transports certain amino acids (levodopa is an amino acid), and the transporter binding sites are easily saturated by dietary amino acids. To be fully effective, carbidopa-levodopa must be taken *at least an hour before meals and at least 2 hours after the end of a meal*. This rule is routinely violated in hospitals, and patients with short-duration responses may lose their levodopa effect until the next dose taken on an empty stomach. Be aware that proteins are contained in not only solid foods but also milk products and nutritional supplements. Patients receiving tube feedings must also have the carbidopa-levodopa administered separately, 1 hour before and 2 hours after feeding.

Carbidopa-levodopa should not be withheld beyond several hours postoperatively. Prolonged delays in restarting the medication may result in loss of the long-duration levodopa response described previously, which may require days to recapture. Ideally, carbidopa-levodopa should be administered the morning of surgery and be restarted that day after the operation is completed.

TABLE 2. Ten Issues That May Sabotage Parkinson Disease Care in Hospitalized/Nursing Home Patients

1. Carbidopa-levodopa confusion
2. Timing of carbidopa-levodopa in regard to meals and surgery
3. Carbidopa-levodopa dosing intervals
4. Insomnia
5. Orthostatic hypotension
6. Nausea
7. Hallucinations and delusions
8. Pain and levodopa
9. Dyskinesias
10. Anxiety and panic

Carbidopa-Levodopa Dosing Intervals

Patients or family will often be able to inform the staff about short-duration responses and the need for a specific carbidopa-levodopa dosing interval. The staff must then reconcile this need with mealtimes (ie, 1 hour before and 2 hours after the end of a meal). Note that there can be a dramatic decline when the levodopa effect has worn off. This may translate into a major gait change (eg, shuffling, freezing of gait) as well as a variety of nonmotor symptoms, such as anxiety or even panic, inner restlessness (akathisia), extreme apathy, or depression. If it becomes apparent that there are major gaps in coverage with the current dosing scheme (so-called wearing-off), the responsible clinician may reschedule the dosing intervals so that they match the response duration. Although more doses will then be administered, the same individual dose should be used, ie, the dose that works the best. There is no cumulative toxicity from adding doses (as long as the effects do not overlap).

Insomnia

Insomnia is especially common among people with PD, and this problem is often magnified when they are admitted to the hospital or a nursing facility. The need for carbidopa-levodopa coverage to allow sleep is underrecognized. Underdosed patients cannot get comfortable in bed (akathisia, stiffness, cannot turn over), preventing sleep. For those with a long-duration levodopa response, simply increasing the daytime doses to capture the full benefit is often helpful (typically up to 600-800 mg daily in divided doses^{1,2}). By definition, the long-duration levodopa response should last around the clock. For those with a short-duration levodopa response, adding a full carbidopa-levodopa dose an hour before bedtime often allows sleep. For those who awaken hours later and are unable to return to sleep, another full dose may be administered. The dose that produces the best response during the waking hours should also be used at night (ie, a full dose). Insomnia, like certain other PD symptoms, responds in an all-or-none fashion; a partial dose may be subtherapeutic and not allow sleep. There may be other reasons for insomnia, and use of a sleep aid medication is acceptable; however,

in the absence of adequate levodopa coverage, even a potent sleep aid may prove insufficient.

Orthostatic Hypotension

Patients with PD may experience orthostatic hypotension (OH) (a sudden drop in BP on changing position from sitting or lying to upright), putting them at risk for fainting and falls. It will be missed if the BP is checked only in the sitting or lying position. There are several possible reasons for OH in this setting: (1) PD-related dysautonomia, (2) hypovolemia from surgical blood loss, vomiting, diarrhea, or poor fluid intake, (3) prolonged bed rest, (4) medications such as antihypertensives, diuretics, or α -blockers for prostatism, and (5) carbidopa-levodopa use.

Carbidopa-levodopa use is a major OH risk factor and typically is overlooked. In susceptible patients with PD, it lowers the standing BP beginning about an hour after a dose and persisting for 3 to 4 hours. This problem will be missed if the BP is checked many hours after the last carbidopa-levodopa dose. Detection before syncope occurs is crucial. When the patient is ambulatory, BP checks should include standing values obtained 1 to 3 hours after a dose of carbidopa-levodopa. As a rule of thumb, as long as the standing systolic BP is consistently over 90 mm Hg, cerebral perfusion should be adequate. When ambulating a patient in the hospital for the first time (eg, with nursing assistance), the standing BP should be assessed at the outset.

There are various treatments for OH,^{1,2} but the first step should be reviewing the medication list and considering withholding offending drugs, such as antihypertensives and diuretics. Increased salt and fluid intake is another simple short-term strategy. For susceptible patients, a bedside commode or handheld urinal may prevent syncope en route to the bathroom. Short-acting medications to elevate the BP, such as midodrine, may be administered with each dose of carbidopa-levodopa if necessary.^{1,2,12} Parenthetically, knee-high compressive hose are insufficient, whereas thigh- or waist-high compressive hose are helpful for PD-related OH.

Supine hypertension may complicate treatment of OH. Elevation of the head of the bed by 6 inches will reduce this tendency. It may

be necessary to accept intermittent mild to moderate BP elevations.

Nausea

Nausea is common among hospitalized patients. Antiemetic drugs that block dopamine should not be administered to patients with PD because they may cause parkinsonism and block the effect of carbidopa-levodopa. Thus, use of metoclopramide (Reglan) and prochlorperazine (Compazine) is precluded. Acceptable drugs include ondansetron (Zofran) and trimethobenzamide (Tigan). Outside the United States, domperidone may be available; however, it has potential for prolongation of the QT interval. Narcotics commonly induce nausea, which should not be overlooked in the hospital.

Hallucinations and Delusions

Patients with PD are at risk for hallucinations or delusions when in an unfamiliar environment, especially if they are receiving centrally acting drugs such as pain medications.¹² Major surgery may provoke several days of postoperative delirium among those with PD. Simple infections (eg, a simple urinary tract infection) may also provoke psychosis.

Drugs for treatment of PD may contribute to hallucinatory/delusional potential. Often unappreciated is that carbidopa-levodopa is the least likely to be responsible. If PD drugs must be decreased to treat psychosis, a 50% reduction of the dopamine agonists (pramipexole, ropinirole, rotigotine) may be considered; they are much more likely to provoke psychosis than carbidopa-levodopa.⁷⁻⁹ Certain other PD drugs can be withheld without any major consequences, including rasagiline and selegiline, which have long half-lives, and entacapone, which is only mildly efficacious.

Even in the absence of psychoactive drugs, hospitalization may provoke delirium among those with PD, especially postoperatively. Staff should be aware of this potential and employ delirium-prevention precautions, such as minimizing sleep disruption, maintaining a stable hospital room environment, and frequent orientation by staff.

Nearly all of the available psychiatric drugs for psychosis block dopamine and should not be used in patients with PD. The exception is quetiapine, which can be started in a single dose of 25 mg at bedtime with slow

increments guided by the response. The efficacious dosing range is between 25 and 100 mg as a single bedtime dose, but higher doses are needed occasionally. Clozapine is the only other antipsychotic without potential for worsening parkinsonism, but it is rarely used because of adverse effects.

Finally, staff should be aware that patients with PD often act out their dreams (rapid eye movement sleep behavior), which should not be confused with nocturnal hallucinations or confusion. Dream enactment behavior occurs during deep sleep and is not dangerous provided it is not so vigorous as to cause the patient to fall out of bed.

Pain and Levodopa

Problems leading to hospitalization often include painful conditions. Two important observations about pain often go unrecognized. First, pain is sometimes the direct consequence of PD (eg, painful leg cramps, toe curling, or a dystonic limb), which is highly responsive to carbidopa-levodopa. If pain comes and goes, consider the relationship to the levodopa state (ie, does it recur when the levodopa effect has worn off?). Pain in this pattern may reflect inadequate levodopa coverage. Second, pain from other sources is exacerbated during levodopa off-states or with underdosing of carbidopa-levodopa. Pain thresholds are reduced and pain is enhanced if patients are undertreated.^{13,14} If elective surgery is imminent, it might be wise to optimize carbidopa-levodopa before hospital admission.

Dyskinesias

Dyskinesias are involuntary movements that might jeopardize the integrity of orthopedic or other surgical sites. The choreiform movements seen in patients with PD (dyskinesias) reflect an excessive effect from each dose of carbidopa-levodopa. Levodopa dyskinesias have the appearance of flowing, dancing movements of the trunk or limbs (occasionally the face). They start about an hour after each carbidopa-levodopa dose, last a few hours, and then abate. They must be distinguished from dystonias, which manifest as sustained postures (eg, toe curling or fixed foot inversion). Dystonia reflects the opposite dopamine state, ie, PD-associated dystonia usually indicates loss or absence of the levodopa effect. Note also that the subjective

feeling of inner restlessness (akathisia) represents a levodopa underdose state.

Levodopa dyskinesias (chorea) can always be abolished by reduction of the individual carbidopa-levodopa doses. However, if the dose reduction is too great, parkinsonism may result. In occasional patients, the therapeutic window between parkinsonism control and dyskinesias is very narrow. Levodopa dyskinesias relate to the most recent carbidopa-levodopa dose and are largely independent of the total daily levodopa dose. To reduce dyskinesias, lower each levodopa dose by a small amount (eg, 50 mg of levodopa, such as one-half of a 25/100-mg tablet). If the next dose still causes dyskinesias, then subsequent doses can be further reduced by small increments until control is achieved. As noted previously, amantadine may be added if the levodopa reduction necessary to control dyskinesias causes recurrent parkinsonism. However, it may induce hallucinations or delusions in susceptible patients, especially in higher doses (eg, 300-500 mg daily).

Anxiety and Panic

Anxiety is one of the most common nonmotor symptoms of PD. If anxiety comes and goes, it may reflect a short-duration effect of carbidopa-levodopa, recurring during wearing-off states. If relatively constant anxiety is experienced, the doses of carbidopa-levodopa may be insufficient or are being administered with meals. Note that anxiety responds in an all-or-none fashion to levodopa. If this is problematic throughout the day, the immediate-release 25/100-mg carbidopa-levodopa doses can slowly be increased by half-tablet increments of all doses, up to 3 tablets per dose. An alternative strategy of benzodiazepine administration is often used but at the expense of gait instability, drowsiness, or confusion.

CONCLUSION

Patients with PD have unique problems and special medication needs that can be challenging when they are hospitalized or admitted to a nursing facility. These patients deserve

seamless care. The potential for good care can be reduced to a few basic principles, which especially includes knowledge about carbidopa-levodopa.

Abbreviations and Acronyms: BP = blood pressure; OH = orthostatic hypotension; PD = Parkinson disease

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