Seniors with Parkinson's Disease: Initial Medical Treatment

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Parkinson's disease most often presents after age 60, and patients in this age group are best managed with levodopa therapy as the primary treatment modality. Unlike young-onset parkinsonism (onset < age 40), this older age group is much less prone to subsequent development of levodopa responsive instability (dyskinesias, fluctuations). When these problems do occur in seniors, they usually can be managed by medication adjustments. The treatment goal is to keep patients active and engaged; levodopa dosage should be guided by the patients' responses and not arbitrarily limited to low doses, which may compromise patients' lives.

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Introduction

This manuscript focuses on the medical treatment of Parkinson's disease (PD) patients over age 60. This senior age-group is much less susceptible to the delayed motor complications of levodopa therapy (fluctuations, dyskinesias), compared to young PD patients. This age-cohort is highly relevant to practicing clinicians since PD develops after age 60 years in more than 80% of cases.[1]

PD is a treatable disorder and drug therapy can be very gratifying for both the patient and clinician. PD, however, is progressive; after years, the benefits become less complete and eventually additional problems surface that are poorly or incompletely treatable. Thus, clinicians typically are cognizant of both the immediate needs of the patient, as well as the progressive course of PD that will likely evolve into more disability. Obviously, there are two therapeutic issues that confront clinicians treating new PD patients: 1) medical strategies for slowing the course of PD; 2) symptomatic treatment.

Medical Strategies for Slowing the Course of PD

Although the published focus is often on the dopaminergic problems of PD, these often are overshadowed by a myriad of non-dopaminergic conditions that evolve after years of PD. This includes cognitive impairment, dysautonomia and levodopa-unresponsive motor disability.

Cognitive impairment

Mild cognitive impairment is already apparent in 19-29% of early PD cases.[2-4] Dementia or mild cognitive impairment was documented in 85% of the Sydney, Australian PD cohort after 15 years of follow-up;[5] in Norway, 60% were demented after 12 years.[6] Age factors into this, and in a USA cohort, 65% were demented by age 85 years.[7] The substrate for the dementia is proliferation of the Lewy neurodegenerative process.[8-12] In later stage PD, dementia often becomes the most disabling problem. Unfortunately, it is poorly responsive to medical treatment, although acetylcholinesterase inhibitors may provide mild benefit.

Dysautonomia

Autonomic problems may precede the motor symptoms of PD,[13,14] but are usually mild or minimal during the early years. However, advancing PD is often associated with orthostatic hypotension causing presyncope/syncope, neurogenic bladder with urinary incontinence and severe constipation. These may be difficult to treat. The substrate for these is Lewy (alpha-synuclein) neurodegeneration.[15-18]

Levodopa-refractory motor symptoms

During the early years of PD, the parkinsonian motor symptoms typically respond dramatically to aggressive dopamine replenishment. Unfortunately, after a decade or longer, extrapyramidal symptoms surface that fail levodopa and related drugs. This is apparent when perusing published data from PD clinical trials; drug treatment of early PD cases results in near-normal mean

Unified Parkinson's Disease Rating Scale (UPDRS). However clinical drug trials of more advanced PD cases reveals much higher UPDRS scores despite maximal medical treatment, consistent with incomplete responses. The substrate for this is, again, proliferation of the Lewy neurodegenerative process.[9] In advanced PD, severe gait instability with falls and levodopa-unresponsive gait freezing may render patients wheelchair-bound.

Levodopa motor complications

Instability of the levodopa response, with dyskinesias and motor fluctuations, also reflects the natural history of PD. Thus, levodopa dyskinesias and fluctuating responses are rare during the first years of PD, but with about a 40% risk by five levodopa-treatment years.[19] In contrast, when levodopa was first introduced for general use about 40 years ago, dyskinesias commonly developed within the first few months, likely relating to much longer durations of PD before treatment.[19]

The substrate for these unstable levodopa responses presumably includes the increasing loss of nigrostriatal dopaminergic terminals with PD progression. These presynaptic terminals normally modulate synaptic concentrations of dopamine; when the loss is nearly complete in certain striatal areas, synaptic dopamine is no longer controlled, and levels may widely fluctuate. A secondary consequence of this occurs postsynaptically, where downstream responses may amplify these problems.[20] These levodopa motor complications, however, differ from the cognitive, autonomic and levodopa-refractory motor responses discussed above in that they are much more treatable.

Medication adjustments often stabilization fluctuations and reduce dyskinesias; when these are unsatisfactory, deep brain stimulation is available. Although the medical literature often focuses on levodopa dyskinesias and fluctuations, these ultimately contribute much less of declining quality of life (QoL) compared to the levodopa-refractory motor symptoms, dementia and dysautonomia.[5]

Medications for slowing the progression of PD

Over the past 20 years, several drugs proposed to slow PD progression were tested in large multi-center trials. Unfortunately, these trials were ultimately negative or sufficiently confounded to obscure interpretation. This included selegiline (deprenyl),[21-24] pramipexole,[25,26] ropinirole[25,27] and two independent apoptosis inhibitors.[28,29] Thus, the American Academy of Neurology (AAN) consensus panel that reviewed these and other more limited trials concluded in 2006 that "No treatment has been shown to be neuroprotective".[30]

Following the above pronouncement by the AAN, a multi-center trial assessing rasagiline for a "disease modifying" effect has captured much attention; this is the so-called ADAGIO tri-

al.[31] This study, however, employed a complex design, with certain counter-intuitive findings (i.e., positive results with only the lower of two doses). Careful scrutiny of this data reveals substantial potential for confounding, and the implications seem uninterpretable.[32]

More recently, the US National Institute for Neurological Disorders and Stroke has funded an ongoing program of drug screening using futility trial design.[33] Although several drugs have been evaluated (creatine, minocycline, coenzyme Q10 and the neuroimmunophilin, GPI-1485), no drug has advanced beyond very preliminary trials.

Conclusion: drugs to slow PD progression

Unfortunately, despite much focus on drugs to slow the course of PD, no medications have yet surfaced with proof of true disease-modifying effects. Thus, the AAN conclusion from 2006 still holds true: we have no drugs with proof of a neuroprotective effect.

Levodopa and longevity

What should not be overlooked, however, is the rather dramatic effect levodopa therapy had on longevity when it was first introduced about four decades ago. Every trial that assessed mortality rates among PD cohorts concluded that the advent of the levodopa era was tightly time-locked to a substantial increase in longevity.[34-41] Thus, in the current era, mean longevity among PD patients is only a few years less than those without PD.[42] Likely, this increase in longevity simply relates to mobilizing PD patients, who without symptomatic treatment, would have eventually been relegated to a wheelchair-nursing home existence.

Symptomatic Treatment of PD Patients Over Age 60: Background

The goals of symptomatic treatment

When considering any medication for any disorder, clinicians need appropriate goals to guide treatment. Who needs treatment and how aggressively? Since we have no proof that any medication truly affects the pathogenic PD substrate, the treatment target is based on symptoms. There are two sensible goals:

1) Maintain PD patients in the mainstreams of their lives and keep them active; a sedentary lifestyle has it's own inherent health risks.

2) Optimize QoL.

There is no compelling reason to start any therapy if patients remain active, engaged and satisfied. However, declining activity or QoL due to PD indicates that symptomatic treatment is appropriate. Once patients develop sedentary lifestyles due to PD, it is difficult to reverse bad habits and deconditioning. Thus, efficacious medications should be used when PD symptoms become compromising.

Which drug is best for symptomatic therapy?

The primary drugs for initial symptomatic treatment are levodopa and the dopamine agonists. Although certain minor PD drugs may be used for symptomatic treatment, these should be reserved for patients with minimal problems. This includes such drugs as selegiline and rasagiline, which have mild symptomatic PD benefits. Amantadine also falls into this class, although it may have a clear indication later in the course to attenuate dyskinesias. Anti-cholinergic drugs no longer can be recommended for routine use, given their side effects: memory impairment, constipation, dry mouth and eyes, blurred vision.

For the past four decades, the foundation of symptomatic treatment of PD has been levodopa. This remains the most efficacious medication for PD. Clinicians treating PD must have a clear understanding of how and when to use levodopa; all other treatment revolves around that. Unfortunately, much of the medical literature provides varied and conflicting guidelines about levodopa treatment. When to start, and how aggressive to dose has been extensively debated. Conservative use of levodopa has been urged because of concerns regarding later-developing motor complications: fluctuations and dyskinesias. Moreover, certain early authors raised concerns that levodopa might be toxic. Hence, several issues relating to levodopa therapy deserve clarification.

Is levodopa toxic?

Early investigators questioning the cause of PD focused exclusively on the dopaminergic substantia nigra. The nigra is obviously a lynchpin in basal ganglia motor control systems and the degeneration of this small nucleus translates into dramatic (and medically reversible) symptoms. Of course, this overlooks the fact that Lewy neurodegeneration extends widely beyond the substantia nigra; this accounts for the problems of advancing PD with levodopa-refractory motor symptoms, dementia and dysautonomia. We now recognize that the PD neurodegenerative process probably starts in non-dopaminergic nuclei, later affecting the nigra and eventually non-dopaminergic neo- and limbic cortex.[43,44]

However, the early focus on the substantia nigra led some investigators to propose that the nigral neurotransmitter, dopamine, was inherently cytotoxic, and by extrapolation, levodopa therapy should accelerate PD progression.[45,46] Although initial *in vitro* studies reported dopamine toxicity, this was later shown to be an artifact of the cell culture medium.[47] Both animal and human studies have failed to identify evidence of levodopa toxicity[48,49] and this includes the large multicenter clinical trial specifically designed to asses such toxicity.[50] Notable, also is the fact that some dopaminergic nuclei are largely spared in PD.[51] Thus, concerns about levodopa toxicity have largely been put to rest.

Should the dose of levodopa be restricted?

Some authors advise conservative dosing with levodopa; perhaps this might translate into better responses years later. In clinical practice, however, it is apparent that many PD symptoms tend to respond in an all-or-none manner, as if there is a dose threshold.[52] Thus, restricting the dose may translate into inadequate benefit, contrary to our above goals of maximizing activity and QoL. Only a single clinical trial has assessed this, comparing "low dose" carbidopa/levodopa to optimal dosing ("high dose").[53] After six years, parkinsonism in the low dose group was poorly controlled and moreover, there were not dramatic differences in the frequencies of levodopa fluctuations or dyskinesias. The authors concluded that dose restriction was not beneficial, early or later.

In clinical practice, optimal individual levodopa doses vary among patients. However, it seems rational to identify the dose that works the best in any given patient and utilize that. Unlike narcotics, where the doses must be continuously increased to maintain an effect, the optimal individual dose of levodopa tends to remain fairly constant in any given patient over years.[52] Obviously, more frequent doses may eventually be required to counter levodopa wearing-off effects, but not progressively higher individual doses.

There is a levodopa dosing range (discussed below) that captures the best possible response in all PD patients. There is a ceiling dose, beyond which, there is no further benefit. With this knowledge, clinicians can escalate the dose to capture the most benefit for any given patient.

Should levodopa be delayed?

Levodopa therapy works best during the first decade of PD. Some authors argue that you can "save" these best responses for later by deferring treatment. However, the likely reason that the earlier levodopa responses are more gratifying relates to the natural progression of PD. Thus, the Lewy neurodegenerative process is relentless, not only causing further nigral neuron loss, but also extending into widespread non-dopaminergic brain regions.[43,44] Trying to "save" the best responses may simply translate into missed opportunities and needless early disability. Moreover, patients initially rendered house-confined due to undertreatment may be difficult to subsequently return to an active lifestyle.

Start a dopamine agonist first?

Despite the unequivocal superiority of levodopa, initial dopamine agonist treatment is often advocated.[54,55] This primarily relates to concerns for later-developing unstable levodopa responses, with dyskinesias and motor fluctuations. Note however, that this is an age-related phenomenon. These are indeed a considerable problem in the very young; among patients with PD on-

set before age 40, both the dyskinesia-risk, and fluctuation-risk is over 95% after five years on levodopa.[56,57] However, more than 80% of PD patients present after age 60,[1] and in this age group, dyskinesia and fluctuation risks are markedly less. For those between ages 60-70, the dyskinesia risk after 5 years of levodopa is 26%; it drops to 16% after age 70.[58]

It should also be noted that the published data on dyskinesia and fluctuation risks are incident data; these are frequencies regardless of severity, persistence, or whether they were easily treated. In fact, these problems are quite treatable,[52] and sometimes are mild and do not require treatment. Thus, in one community-based study, the risk of dyskinesias that could not be adequately controlled with medication adjustments was only 12% after ten years of levodopa therapy.[59]

Several multi-center, controlled drug trials comparing initial dopamine agonist to levodopa therapy have shown less dyskinesias and fluctuations with the agonists.[27,60-64] However, an overlooked, consistent finding in all of these trials was significantly less agonist efficacy in treating PD symptoms, despite allowing ad libitum levodopa added to agonist therapy. What also was clear from these studies was that monotherapy with an agonist was typically insufficient after 2-4 years, requiring added levodopa.

Note that when dopamine agonists were first introduced many years ago, the strategy at that time was to add the agonist after levodopa fluctuations became problematic, with concurrent reduction of levodopa.[65-67] Overlooked is that the outcomes in these older trials appear very similar to those in the recent trials cited above, where the agonist was started first, before levodopa. If fluctuations can be reduced by either starting the agonist first or deferring until they actually occur, why not wait? The agonists are expensive and have unique side effects (see below); hence, it seems wise to defer them until they seem appropriate, later in the course.

Why not start with a dopamine agonist in this age group over 60 years?

Conservative use of the dopamine agonists seems wise, based on their potential for adverse events. The agonists now in common use around the world are pramipexole and ropinirole. In clinical trials, these each were approximately three times more likely than levodopa to cause hallucinations.[27,61-63] These two drugs also may induce somnolence or sleep attacks, which can be especially problematic among PD patients still driving.[68] In these clinical trials somnolence was documented in 27% to 38% of agonist-treated patients,[27,61-63] although other factors likely contributed. Also surfacing in clinical trials was leg edema, which occasionally can be massive and difficult to treat without stopping the drug.

Overlooked in the above published trials, was the remark-able potential for pramipexole and ropinirole' to provoke pathological behaviors, including gambling,[69,70] hypersexuality,[71] compulsive eating,[70-72] and excessive and compulsive shopping/spending money.[70,71,73,74] Among PD patients treated with therapeutic doses of ropinirole or pramipexole in one community, the frequency of pathological gambling or hypersexuality was 13%.[75] These side effects, in the aggregate, suggest that they should be deferred until clearly needed by PD patients over age 60 years.

Should levodopa be started with a COMT inhibitor?

Some advocate starting levodopa combined with the Catechol-O-methyl transferase (COMT) inhibitor, entacapone, arguing that this longer-duration effect may provide less pulsatile and more physiologic stimulation of dopamine receptors.[76,77] The presumption is that this prolonged levodopa response will ultimately translate into a lower subsequent risk of dyskinesias and fluctuations. Note, however, that entacapone prolongs the levodopa response by no more than 60 minutes.[78] This is actually a little less than the prolongation when levodopa is formulated as a controlled-release drug. When sustained-release levodopa was compared to immediate-release levodopa in 5 years clinical trials, dyskinesia and motor fluctuation frequencies were similar.[79,80] Hence, there is no reason to expect that early use of entacapone would generate a different result.

Conclusion

Levodopa therapy is the most appropriate choice for initial treatment of PD patients over age 60 years. The dose should be adjusted to provide the best symptomatic benefit, allowing patients to remain active and engaged.

Initiating Levodopa Therapy

Which formulation: sustained-release versus regular (immediate-release)?

When the sustained-release formulations of levodopa were first introduced, they were advocated for initial therapy, arguing that the longer levodopa duration was more physiologic; presumably, this would result in a lower subsequent risk of fluctuations and dyskinesias. As cited above, this was investigated in two large, multi-center trials, with negative results;[79,80] after five years, patients randomized to sustained-release levodopa had essentially the same frequencies of motor fluctuations and dyskinesias as did those taking immediate-release levodopa. Since the prolongation of the response is modest (60-90 minutes),[81,82] this is not surprising.

There are some disadvantages to the sustained-release formulation of levodopa. First, it is only about 70% bioavailable.[82]

Although this can be compensated by using higher doses, there is concern when patients experience suboptimal responses that this may be due to poor absorption.

Second, the sustained-release formulations have complex interactions with meals. They are impeded from entering the circulation when the stomach is empty.[82] However, circulating levodopa is notoriously prevented from crossing the blood-brain barrier when taken with or after meals (via competition for transport by protein-derived amino acids).[83] With immediate-release levodopa, meal influences can be eliminated by simply having patients take their doses an hour or more before meals, or two or more hours after meals.[52] How best to dose the sustained-release formulation to produce the most consistent clinical response has never been studied. Finally, in circumstances where patients must pay for their drugs, the added expense of sustained-release compounds influences prescribing habits.

Inhibition of dopa decarboxylase: carbidopa, benserazide

When levodopa was first introduced in the late 1960's, large doses were necessary to overcome the rapid degradation by dopa decarboxylase (aromatic L-amino acid decarboxylase). Moreover, dopamine generated in the circulation by peripheral dopa decarboxylase, crossed into the brainstem chemoreceptive trigger zone, provoking nausea and vomiting. The addition of the dopa decarboxylase inhibitors in the early 1970's was a huge advance in the treatment of PD and they have become the standard of treatment. The two available decarboxylase inhibitors, carbidopa and benserazide are largely interchangeable with no apparent advantages of one over the other. A conventional dosage of each is 25 mg, formulated with 100 mg of levodopa.

Carbidopa/levodopa and benserazide/levodopa are similar

Dosing guidelines for the remainder of this manuscript will focus just on carbidopa/levodopa. This is to avoid redundancy since benserazide/levodopa is dosed identically.

Initiating carbidopa/levodopa

Immediate-release carbidopa/levodopa is usually started using the 25/100 formulation. To avoid inhibition by dietary protein (amino acids), it is best taken an hour or more before meals. By convention, it is started three times daily. Although some clinicians favor starting with just a half of the 25/100 tablets three times daily, most patients tolerate a full tablet 3-times per day as the starting dose. Patients may be informed that this starting dose is often too low to provide noticeable benefit; otherwise, they may abandon the drug if not initially helpful.

There is a long-duration effect from levodopa that requires about a week to fully manifest.[52,84] Hence, doses should be main-

tained for a week (or longer if desired) before escalating. The full benefit from carbidopa/levodopa taken on an empty stomach is achieved by 2 ½ to 3 tablets of the 25/100 immediate-release formulation, each dose.[52] Doses higher than 3 tablets at a time provide no incremental benefit. Restated, the therapeutic range for carbidopa/levodopa is between 1-3 tablets each dose. With these premises in mind, a reasonable dose escalation schedule is shown in the Table 1. Ultimately, the patient should maintain the most beneficial dose; however, if several doses are equally beneficial, they should then settle on the lowest of those equipotent doses. As discussed above, there is no compelling evidence to suggest that arbitrarily low doses are preferable; patients should be dosed with whatever works best for them.

Levodopa Side Effects

Nausea

Despite carbidopa or benserazide, nausea occasionally occurs. This is transient among most patients. Taking the pills with dry bread, crackers of some other non-protein food may prove helpful. Centrally-acting dopamine blocking drugs, such as metoclopramide or prochlorperazine, must be avoided. Domperidone blocks dopamine receptors but does not cross the blood-brain barrier; it is tolerated and a very effective anti-emetic.

Plain carbidopa in 25 mg tablets is available to boost dopa decarboxylase inhibition, which may attenuate nausea; one to two of these tablets may be administered with or just before each carbidopa/levodopa dose. Carbidopa by itself appears to have no side effects or detrimental properties, so overdosage is not a concern in this setting.

Orthostatic hypotension

PD patients often have dysautonomia as a component of their condition. As a consequence, they may be prone to orthostatic hypotension. Hence, it is wise to measure the standing blood pressure (BP) before starting levodopa. Levodopa tends to lower the standing BP in susceptible patients for a few hours after each dose. Systolic BP's below 100 mmHg before starting levodopa raise concerns. Sometimes other drugs can be reduced or eliminated in that setting (e.g., diuretics, anti-hypertensives,

Table 1. Initiation of therapy carbidopa/levodopa 25/100 immediate-release tablets

Week	Tablets, each dose (taken 3 times daily*)
1	One
2	One & a half
3	Two
4	Two & a half
Option, week 5	Three

*Conventionally administered at least one hour before each meal; if a meal is skipped, it may be taken at any time.

alpha-1 adrenergic blockers for prostatism). Once levodopa is started, symptoms (presyncope) should not occur if the systolic BP remains consistently above 90 mmHg.

Hallucinations, delusions

Occasional PD patients experience hallucinations from levodopa, but this is extremely rare if dementia is not present and if carbidopa/levodopa (or benserazide/levodopa) is the only psychoactive drug. If the initial doses of carbidopa/levodopa provoke hallucinations, it is wise to scrutinize the medication list and eliminate other PD drugs or psychoactive medications.

Non-Motor Symptoms to Consider When Starting Levodopa

Titration of the levodopa dose to achieve optimum responses should target non-motor as well as the usual PD motor symptoms. Insomnia, anxiety, cramps are common and consistently levodopa responsive. Sometimes pain, paresthesia or depression also improves with levodopa.[52] Among occasional patients, dyspnea is a levodopa-responsive symptom,[52] although cardiopulmonary causes should first be considered.

Insomnia

Insomnia beginning after PD onset is usually responsive to levodopa.[52] Among new PD patients, the long-duration effect[84] from daytime levodopa doses may carry-over through the night to allow sleep. If not, an additional dose of levodopa may be added an hour or so before bedtime. Patients adding a bedtime dose to counter insomnia should be advised to use the same full dose that they have identified as optimal for their waking-day symptoms; this tends to be an all-or-none response and lower doses may prove ineffective.[52]

Insomnia is easily explained by known PD symptoms: akathisia (inner restlessness), stiffness (rigidity), difficulty turning in bed, as well as tremor. These are all levodopa-responsive.

Anxiety

Anxiety is a common non-motor symptom of PD and may even predate it by 20 years or more.[85] Occasionally, this is the most prominent complaint. It is responsive to levodopa in most cases.[52] Patients also describe variations of this symptom that likewise are levodopa-responsive, including restlessness (akathisia), inability to get comfortable, inner tension or inner tremor.

Cramps

Cramps are common in all adults, but among PD patients, complaints of "cramps" usually represent dystonia. Most common are toe "cramps", with tonic deviation of the toes up or down. Dystonic foot inversion or calf cramps are also frequent com-

plaints, especially at night. Adequate levodopa coverage works better for these problems in PD than the usual medications for routine cramp syndromes such as quinine. As with insomnia, if the three daytime doses fail to control nocturnal "cramps", a fourth full dose at bedtime may be added.

Conclusions

In this modern era with many new drugs for PD, levodopa therapy often is relegated to an afterthought in discussions about treatment. It remains the most efficacious drug for dopamine deficiency symptoms, by far. With proper dose adjustments it may maintain PD patients in the mainstreams of their lives for many years.

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