

10 THINGS TO KNOW TO MANAGE PD WELL

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1. No intervention has been proven to change the natural history of Parkinson's disease.

- Medications used to treat Parkinson's disease are purely symptomatic, and do not do anything under the surface that patients cannot appreciate
- No drug, supplement, surgery or physical activity has been proven to slow down or accelerate the progression of Parkinson's disease
- This is a fundamental concept with wide-ranging implications. Clinicians can draw on this principle to formulate the following management guidelines, and use these statements in discussions with patients:
 - a) There is no obligation to take any medication at any time
 - b) If a medication is not helping in a tangible way, it is not helping
 - c) If a medication's side effects, costs and inconvenience outweigh its benefits, there is no point in continuing to take it
 - d) Whether one does or does not take medication now does not affect the future. A person's status with respect to their Parkinson's disease in 5 years will not be affected by what medication they have taken during that 5-year period, only by the medication they are taking at that time.

Frequent patient question: "I read that such-and-such drug slows down the progression of Parkinson's disease. Is that true?"

Answer: "There have been numerous studies over the years designed to show whether a variety of drugs can have that effect. So far, unfortunately, none of them have been proven to do so."

Frequent patient question: "I read that levodopa loses its effect after 5 years. Shouldn't I hold off taking it?"

Answer: "No. There is no proof that you will be better off taking it in 5 years if you do not take it now, while there is proof that you will be worse off now, if it is the most appropriate thing to help you and you do not take it."

2. It is helpful to have specific roles in mind for antiparkinsonian drugs, or drug classes, in your management scheme.

Medications for Parkinson's disease can be divided into 3 categories

| | |
|--------------------------|---------------------------------|
| Most effective drugs | Levodopa, Dopamine agonists |
| Modestly effective drugs | Amantadine, Anticholinergics |
| Levodopa boosters | MAO inhibitors, COMT inhibitors |

- Levodopa is the most potent reliever of symptoms of Parkinson's disease. Virtually everyone with Parkinson's disease will wind up taking it regularly.
- Dopamine agonists are very effective drugs as well. The choice between these drugs and levodopa is based mainly on their side-effect profiles (see discussion below) and cost.
- Anticholinergic medications such as trihexyphenidyl are effective for resting tremor, but have little or no benefit otherwise. Also, they have the most potent cognitive side effects, so their use is usually limited to younger patients.
- Amantadine is less effective for tremor than anticholinergic medications, but more useful for other symptoms
- MAO inhibitors (rasagiline, selegiline) and COMT inhibitors (tolcapone, entacapone) are mainly used to relieve dose-related fluctuations by prolonging the duration of effect of individual doses
- Rasagiline could also be classified with the modestly effective drugs, and does have FDA approval as monotherapy

3. Taking a dopamine agonist no more "delays" the onset of dyskinesias and dose-related fluctuations than taking levodopa "delays" the onset of psychosis, sedation and impulse-control disorders.

- Levodopa and dopamine agonists are similar, but not identical, drugs with similar, but not identical, side effect profiles. In this respect, they should be viewed like any other prescribed drugs.
- One of the keys to avoiding and managing side effects in Parkinson's disease is to know thoroughly the side-effect profiles of available alternatives
- Levodopa and dopamine agonists each tend to cause certain side effects more than the other

| <i>More likely with Levodopa</i> | <i>More likely with Dopamine Agonists</i> |
|----------------------------------|---|
| Nausea | Hallucinosi/s/Psychosis |
| Dose-related fluctuations | Sedation/Sleep attacks |
| Dyskinesias | Impulse-control disorders |
| | Edema |
| | Orthostatic hypotension |

- Dose-related fluctuations and dyskinesias are more likely to occur in younger patients, so age is a consideration in choice of medication
- Just as with the symptomatic benefits, side effects of these drugs should be managed according to the tangible effects they have on an individual patient

4. Nausea is the most common early side effect of levodopa, and the main reason for initial intolerance

When levodopa was first introduced as an oral treatment for Parkinson's disease, up to 50% of patients could not tolerate it due to nausea and other gastrointestinal side effects. The addition of the decarboxylase inhibitor carbidopa (and, in other countries, benserazide) in the 1970s allowed a much greater proportion of people with Parkinson's disease to tolerate and benefit from levodopa. Still, nausea remains a common early side effect and a major obstacle to the ability of many patients to enjoy the benefits of levodopa. Since virtually everyone with Parkinson's disease winds up taking levodopa, this obstacle must be confronted sooner or later.

Fortunately, nausea is a habituating phenomenon. Nausea gradually dissipates with prolonged exposure to levodopa, and few people continue to experience nausea after taking levodopa for a year.

Mitigating strategies for levodopa-induced nausea include:

a) Take the medication on a full stomach

- We give contradictory advice to patients regarding the juxtaposition of levodopa and food, depending on the stage of the disease. When patients develop dose-related fluctuations (see below), we often instruct patients to avoid mingling levodopa intake with protein consumption. At the initiation of treatment, however, this is not a concern. Tell patients to start levodopa immediately after eating. Tell them to ignore any handout, vial sticker or any other communication from their pharmacist that states they should avoid taking the medication with food. If they are still having trouble tolerating levodopa, exploit the habituation phenomenon by starting patients on just one-half of a tablet after the biggest meal of the day. Warn the patient that this will have no effect on their Parkinson's symptoms, but it is an investment of their time to be able to eventually tolerate a higher dose that will be beneficial. The dose should be increased by one half-tablet at a time only after full tolerance of the previous dose is assured.

b) Increase the ratio of carbidopa to levodopa

- Modern formulations of carbidopa/levodopa are all based on a 1:4 ratio. However, the original carbidopa/levodopa formulations (10/100, 25/250) were based on a 1:10 ratio, and were less effective at controlling nausea. These products are still commercially available and occasionally prescribed by older physicians. Be certain that the patient is taking a 1:4 formulation

- You can increase the ratio of carbidopa to levodopa further by prescribing extra carbidopa to be taken along with the carbidopa/levodopa. Carbidopa is available as stand-alone 25-mg tablets. Some individuals require up to 225 mg of carbidopa daily to neutralize all of their peripheral decarboxylase. This means that a person taking carbidopa/levodopa 25/100 t.i.d. might benefit from up 50 mg of additional carbidopa t.i.d.

c) Help the patient obtain domperidone

- Domperidone is a dopamine receptor blocker that does not penetrate the blood-brain barrier. It is highly effective in eliminating nausea due to levodopa, without antagonizing any of its symptomatic benefit.

Domperidone has been available for this purpose for decades in most countries where Western-style medicine is practiced, but not in the U.S.A.

- Within the U.S.A., domperidone is readily available from online Canadian pharmacies via mail order at a reasonable cost. It is perfectly legal for individuals to import medications for their own personal use with a valid prescription. All you have to do is provide your patient with the prescription.

- Domperidone is manufactured as 10-mg tablets. Standard dosing is 10 or 20 mg taken one hour prior to taking carbidopa/levodopa. Expect a success rate better than 90%.

5. Drugs for Parkinson's disease rarely have interactions with other drugs, and are all compatible with each other

- This is a major convenience for patients, and for clinicians treating Parkinson's disease

- Rasagiline should not be prescribed in people taking other MAO inhibitors, meperidine, dextromethorphan, and sympathomimetic medications (e.g., ephedrine, pseudoephedrine). - Rasagiline plasma concentrations may be raised by concomitant consumption of ciprofloxacin and other CYP1A2 inhibitors.

6. Dose-related fluctuations have numerous potential solutions

Wearing off of benefit from an individual dose of levodopa, plus or minus other antiparkinsonian medications, prior to the next dose is one of the most common and problematic complications of Parkinson's disease and its treatment. Resuppression of symptoms by the next dose, followed by a repeat of the same waning and waxing benefit at each dose time, leads to a cyclic up-and-down daily course referred to as "fluctuations". Fortunately, these have multiple possible solutions. MAO and COMT inhibitors are specifically FDA-approved for this purpose. Alternative management choices include:

- alterations of oral levodopa dosage, scheduling and formulation

- redistribution of protein in the diet

- dopamine agonists

- occasionally, amantadine or anticholinergic medications may be helpful in this regard

- deep brain stimulation

- intrajenunal administration of carbidopa/levodopa enteral suspension

- The choice of intervention is dictated by the usual considerations: age, comorbidities, potential side effects, costs, etc.

- It is important to inform patients that there are a number of medication options available, and not to become discouraged if the first intervention fails. The corollary of this is that you must prepare patients for the possibility that it may take some time before arriving at a satisfactory solution.

- Fluctuations that cannot be managed by medication are the most common reason for resorting to surgical options for Parkinson's disease

7. Dyskinesias are much less important than fluctuations to most patients with Parkinson's disease

- Wearing off of benefit from antiparkinsonian medication, particularly levodopa, is almost always bothersome and frequently disabling; dyskinesias are rarely disabling and frequently not even noticed by the patient

- Try to resist the notion that dyskinesias necessarily represent too much medication. Some patients must put up with some degree of dyskinesias in order to avoid wearing off of benefit from their medication

- Try also to resist appeals from family members to "do something" about dyskinesias for cosmetic reasons. Only the patient's perspective should matter in determining whether dyskinesias require intervention or not.

- Amantadine has acquired a niche as a frequently effective agent to control levodopa-induced dyskinesias; it is the only antiparkinsonian drug with that capability

8. Non-motor complications are important components of the experience of having Parkinson's disease, and frequently more disabling than the motor features

- In quality-of-life studies of persons with Parkinson's disease, autonomic dysfunction, mood disorders, fatigue, sleep problems, psychosis, and impaired concentration or memory all correlate more strongly with overall status than UPDRS ratings.
- Many of these disorders are treatable as individual symptoms, requiring management separate from medications for motor manifestations. The key is to detect them in your patients.
- Despite all the efforts of regulatory obligations to force you to devote more time to them and less to the needs of your patients, try to incorporate screening measures for non-motor manifestations into your routine assessment of patients with Parkinson's disease; they can represent a major opportunity to improve your patient's quality of life

9. Impaired blood pressure regulation can be one of the most disabling features of Parkinson's disease

- People with Parkinson's disease, as a group, tend to show a gradual long-term trend toward progressively lower blood pressure
- Patients with a prior history of hypertension may no longer need treatment; this becomes an important consideration as they become more vulnerable to hypotension (see below)
- More problematic is the instability of blood pressure control
- Patients often develop orthostatic and/or postprandial hypotension; this is often aggravated by medications treating motor manifestations of Parkinson's disease, particularly dopamine agonists, but also levodopa and amantadine
- Think of possible presyncope or syncope in patients complaining of leg weakness or falls
- 24-hour ambulatory blood pressure monitoring shows wide swings in people with Parkinson's disease during the course of a day, with systolic pressures often spiking over 200 mm Hg, and fluctuations greater than 100 mm Hg observed in a majority of patients
- Thus random BP measurements can easily document hypertension
- Patients may also show a loss of normal blood pressure "dipping" at night, or even nocturnal hypertension
- Combined with mandates issued to primary care physicians to impose stricter control of blood pressure, more patients are experiencing bouts of hypotension, orthostatic or otherwise
- Prepare to have to educate your primary care colleagues about the need to refrain from aggressive treatment of blood pressure in people with Parkinson's disease
- Nonpharmacologic management of orthostatic hypotension includes increasing water and salt intake, elevating the head of the bed, fragmenting meals and exercise, water exercise, tilting exercises, avoiding heat, prolonged inactivity, coughing or straining, and wearing thigh-high compression stockings.
- Pharmacologic management includes enhancing fluid retention with fludrocortisone or vasoconstriction with midodrine or droxidopa.

10. Few complications of Parkinson's disease are as disturbing to patients and families as psychosis

- Hallucinations are more bothersome to patients, who may be frustrated by the fact that no one else sees what is plainly obvious to them
- But delusions, though less common than hallucinations, are typically more alarming
- They are usually paranoid in nature, involving thoughts of intruders in the house, spousal infidelity, misidentification or reduplication of family members or living quarters, etc.
- Delusional patients usually feel frightened or threatened, and may contact police, or family members living elsewhere
- There is only one FDA-approved treatment for psychosis in Parkinson's disease, and that is pimavanserin
- Unfortunately, it is costly and can only be obtained through a central pharmacy
- The clinical studies used to gain FDA approval mandated a single dosage for all active participants, two 17-mg tablets daily; there are no published results of any lower or higher dose
- Pharmacologic alternatives are limited
- Acetylcholinesterase inhibitors have modest ability to prevent hallucinations and may be useful for mild psychosis
- Quetiapine has often been used as the antipsychotic of choice in Parkinson's disease because, unlike other antipsychotics, it does not worsen motor symptoms; however, it has not been shown to be more effective than placebo
- Clozapine is an antipsychotic with demonstrated efficacy in psychosis in people with Parkinson's disease; however, its tendency to suppress bone marrow requires frequent (initially weekly) laboratory surveillance, which makes it cumbersome to use, especially in a population with limited mobility