# Initiating Therapy In Early Parkinson's Disease

VHA Pharmacy Benefits Management Strategic Healthcare Group
and the Medical Advisory Panel with the PADRECC Directors

*The following recommendations are dynamic and will be revised, as new clinical data become available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing cost effective, consistent, high quality care.*

Parkinson's Disease (PD) is a degenerative, progressive disorder that affects approximately 500,000 to 1 million people in the United States. Approximately 50,000 new cases are diagnosed each year. The Department of Veterans Affairs' Parkinson's Disease Research Education and Clinical Centers (PADRECC) estimates that 40,000 veterans are treated annually for the disorder.

Since it is a progressive disorder, significant disability and morbidity accompany the disease. Medication, caregiver as well as societal costs infer a significant financial burden to this disease. The underlying etiology of Parkinson's disease involves the progressive loss of dopamine producing cells in the substantia nigra, which results in a decrease in dopamine in the corpus striatum. Drug therapy is initially aimed at preventing long-term therapeutic complications and possibly slowing disease progression while later in the course of the disease symptomatic relief dictates therapy. Patients should be evaluated for rehabilitation services as part of an initial workup.

Agents commonly employed in the treatment of early PD include, anticholinergics, amantadine, dopamine agonists, and levodopa. The selection of which agent to use is patient dependent and should take into account such features as life expectancy, predominant symptoms, physiologic age, comorbidity and cognitive/functional status.

- There is insufficient evidence* to support the neuroprotective abilities of amantadine, selegiline or dopamine agonists.
- There is insufficient evidence to support the delay of disease progression with anticholinergic therapy.
- Anticholinergic therapy is useful in the symptomatic treatment of PD both as monotherapy and as adjunctive therapy. (Level I evidence).
- Dopamine agonist is useful in the symptomatic treatment of PD both as monotherapy and as adjunctive therapy. (Level I evidence).
- There is insufficient evidence to conclude one dopamine agonist is more efficacious than the other agents in the class, with the one exception of marginal superiority of ropinirole over bromocriptine. Decisions regarding therapy should be made in light of side effects, tolerability and ease of administration. **Table 1** illustrates the dosing of dopamine agonist agents and levodopa/carbidopa preparations.
- There is insufficient evidence to document that the controlled release form of levodopa/carbidopa, or the combination of levodopa/carbidopa and entacapone, is more efficacious than the immediate release preparation of carbidopa/levodopa in preventing disease progression or development of dyskinesias/motor complications in de novo PD patients
- The major adverse effects limiting anticholinergic therapy include urinary retention, disorientation, dry mouth, constipation, orthostasis, blurred vision and hallucinations.
- The major adverse effects limiting levodopa therapy are drowsiness, dyskinesias, nausea, hallucinations, orthostasis and psychosis.
- The major adverse effects of the dopamine agonists are somnolence, constipation, peripheral edema, hallucinations, orthostasis and nausea.

- Therapy with the dopamine agonists is based on development of adverse effects or efficacy.
- Pergolide, pramipexole and ropinirole are all efficacious in the treatment of de novo PD. Long term data is available for pergolide. (Level I evidence)
- Pramipexole and ropinirole have been proven efficacious in the prevention of motor complications. (Level I evidence). Levodopa may exhibit better control of motor symptoms.
- Sudden onset of sleep has been reported with the dopamine agonists. These attacks may happen with levodopa monotherapy as well. The etiology of these attacks has not been fully elucidated. Patients receiving these therapies should be counseled about their occurrence and appropriate measures taken to lessen the likelihood of adverse events from these episodes.
- The use of alternate agents in the class of dopamine agonists or anticholinergics is suggested if adverse events develop to another agent in the class.
- Functional disability (as measured by ADL or Unified Parkinson Disease Rating Score) is important in therapy selection, as levodopa has been shown to be more efficacious than dopamine agonists in symptomatic control and improvement in functional scales.
- Physiologic age is important in considering levodopa initiation because of the development of motor complications. Levodopa therapy is associated with motor complications in 20-50% after 2-5 years of use. In patients requiring long-term therapy, initial treatment with a dopamine agonist may offset development of this complication. Additionally, consensus agrees that patients with a physiologic age greater than 75 years are more likely to develop confusion, disorientation and other neurologic adverse effects of dopamine agonist therapy.

***Quality of Evidence**

**I:** Evidence obtained from at least one properly randomized controlled trial. US Preventative Task Force scale Am J Prev Med 2002; 20(3S): 21-35.

**References**


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***Quality of Evidence [QE]***

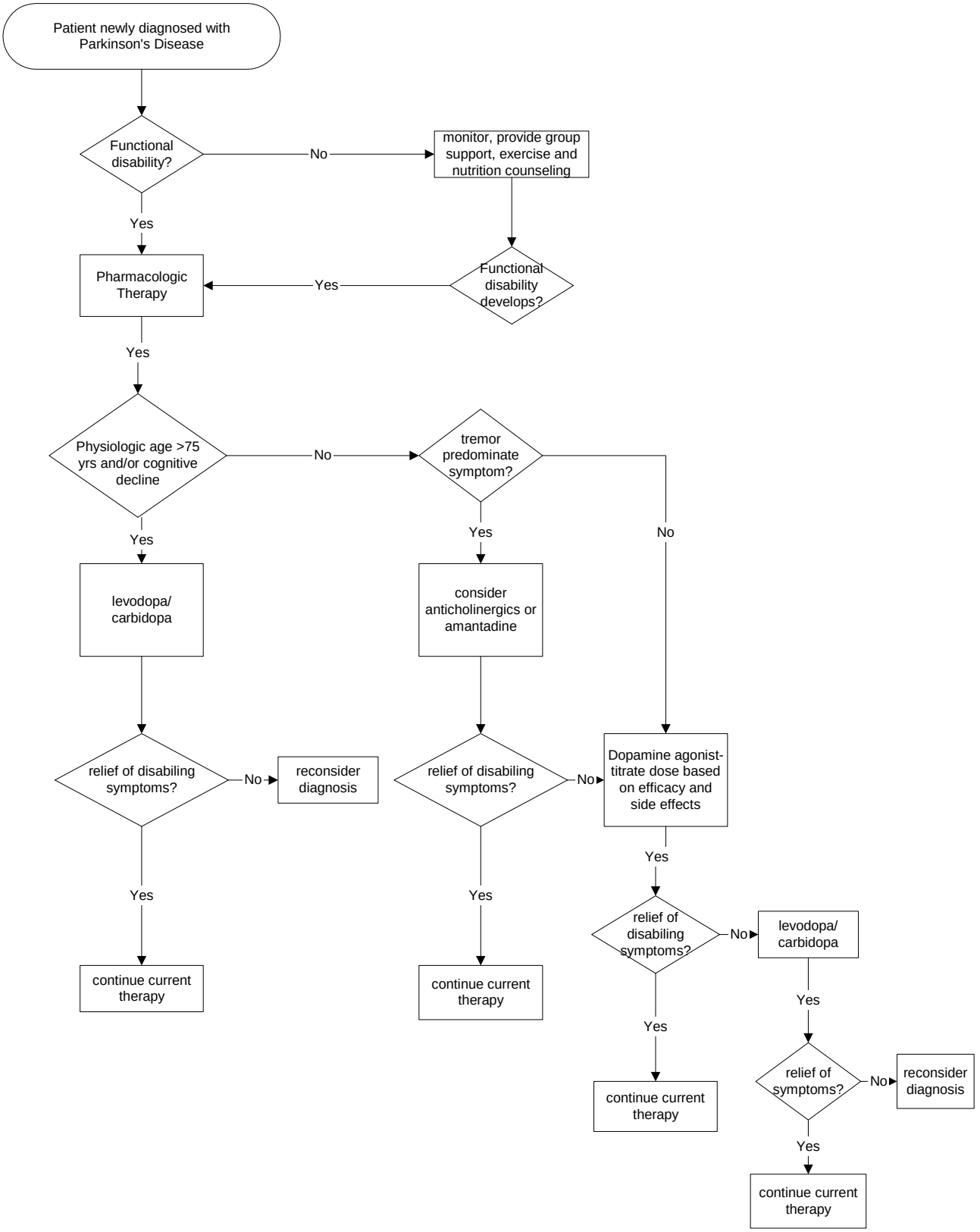
| | |
|---|---|
| **I** | At least one properly done RCT |
| **II-1** | Well designed controlled trial without randomization |
| **II-2** | Well designed cohort or case-control analytic study |
| **II-3** | Multiple time series, dramatic results of uncontrolled experiment |
| **III** | Opinion of respected authorities, case reports, expert committees. |

US Preventative Task Force scale Am J Prev Med 2002;20(3S):21-35.

**Table 1: Dosing and administration**

| | | Anticholinergic | | Dopamine Agonist | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Amantadine** | **Benztropine** | **Trihexyphenidyl** | **Bromocriptine (*rarely used*)** | **Pergolide** | **Pramipexole** | **Ropinirole*** | **Carbidopa/Levodopa** |
| **Initial Dose** | 100 mg QD | 0.5 mg BID | 0.5 mg BID | 1.25 mg BID with meals | 0.05 mg QD for 1st two days | 0.125 mg TID x 1 week | 0.25 mg TID x 1 week | 25/100 BID |
| **Titration** | After one to several weeks at 100 mg once/day, increase to 100 mg twice/day, if necessary<br><br>Patients whose responses are not optimal at 200 mg/day may occasionally benefit from an increase up to 400 mg/day in divided doses; supervise closely | Increase to effective dose or 2 mg BID | Increase to 1 mg BID, can further increase to 2 mg TID | Assess at 2-week intervals, may increase by 2.5mg/day every 14-28 days<br><br>Common doses to see clinical benefit are 20-40 mg/day | Gradually increase by 0.1 or 0.15 mg q 3rd day for next twelve days of therapy. Then increase by 0.25 mg/day every 3rd day until therapeutic dosage achieved.<br><br>Most trials used doses between 1.5-3.5 mg/day with TID regimen | Week 2 – 0.25 mg TID<br>Week 3 – 0.5 mg TID<br>Re-evaluate and if necessary continue titration as follows<br>Week 4 – 0.75 mg TID<br>Week 5 – 1.0 mg TID<br>Week 6 – 1.25 mg TID<br>Week 7 – 1.5 mg TID | Week 2 – 0.5 mg TID<br>Week 3 – 0.75 mg TID<br>Week 4 – 1.0 mg TID<br><br>After week 4, Re-evaluate and if necessary increase by 1.5 mg/day each week up to 9 mg/day, then by 3 mg/day weekly up to a total daily dose of 24 mg/day | Dosage may be increased by 1 tablet every day or every other day, as necessary. Preferred dosing with the IR formulation is TID or QID.<br><br>Provide at least 70 to 100 mg carbidopa per day. When more carbidopa is required, substitute one 25/100 tablet for each 10/100 tablet. |
| **Food Effects** | | Give before or after meals, as determined by patient's reaction. | If the mouth dries excessively, take before meals, unless it causes nausea. If taken after meals, mint candies, chewing gum, or water can allay thirst. | Recommended to be taken with food | May be taken without regard to food | Does not affect the extent of absorption, however Tmax is increased by 1 hour when given with a meal | Does not affect the extent of absorption, however Tmax is increased by 2.5 hour when given with a meal. May be taken without regard to food | Administer on an empty stomach or at least 20-30 min before meals to decrease competition with dietary proteins and to facilitate absorption |
| **Dose adjustment** | Renal insufficiency<br>CrCl (ml/min/1.73m$^2$)<br>30-50 200 mg load then 100mg QD<br>15-29 200 mg load then 100 mg QOD<br><15 200 mg every 7 days | N/A | N/A | N/A | N/A | Renal insufficiency<br>Mild: start 0.125 mg TID, max 1.5 mg TID.<br>Moderate: start 0.125 mg BID, max 1.5mg BID<br>Severe: start 0.125 mg QD, max 1.5 mg QD | Titrate with caution in patients with hepatic impairment | N/A |

* not currently on VA National Formulary


Patient newly diagnosed with Parkinson's Disease
Functional disability?
No
monitor, provide group support, exercise and nutrition counseling
Yes
Pharmacologic Therapy
Yes
Functional disability develops?
Yes
Physiologic age >75 yrs and/or cognitive decline
No
tremor predominate symptom?
Yes
No
levodopa/ carbidopa
consider anticholinergics or amantadine
relief of disabiling symptoms?
No
reconsider diagnosis
relief of disabiling symptoms?
No
Dopamine agonist- titrate dose based on efficacy and side effects
Yes
Yes
continue current therapy
continue current therapy
Yes
relief of disabiling symptoms?
No
levodopa/ carbidopa
Yes
Yes
continue current therapy
relief of symptoms?
No
reconsider diagnosis
Yes
continue current therapy