FPIN's Clinical Inquiries

Treatment of Early Parkinson's Disease

Clinical Question

What is the best medical therapy for early Parkinson's disease?

Evidence-Based Answer

Treatment of early Parkinson's disease with either selegiline (Eldepryl), a dopamine agonist (pramipexole [Mirapex], ropinirole [Requip], or bromocriptine [Parlodel]), or the combination of levodopa and carbidopa (Sinemet) or levodopa and cabidopa with entacapone (Stalevo) improves symptoms and quality of life, but all medication regimens are associated with significant side effects (Table 1). There is no compelling evidence favoring a medication option, so treatment should be individualized. [Strength of recommendation: A, based on systematic reviews of randomized controlled trials (RCTs)]

TABLE 1

| Medications Commonly Used for Parkinson's Disease |
|----------------------------------|----------------------------------|-----------------|------------------|
| Generic name | Brand name | Initial dosage | Target dosage range* | Common adverse effects |
| Levodopa plus carbidopa | Sinemet | 10 mg carbidopa with 100 mg levodopa; 25 mg carbidopa with 100 mg levodopa; 25 mg carbidopa with 250 mg levodopa (medication three times per day)† | Increase by one tablet every day or every other day to a maximum of eight tablets per day | Dyskinesia, dystonia, hallucinations, hyperkinesia, dizziness, fatigue, abdominal pain, constipation, diarrhea, nausea, vomiting, urine discoloration, cardiac abnormalities, orthostatic hypotension |

Cost for brand name drug (cost for generic): $84 ($72 to $85) per month
<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Dosage</strong></th>
<th><strong>Increase to</strong></th>
<th><strong>Price</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sinemet CR</strong></td>
<td>50 mg carbidopa with 200 mg levodopa two times per day</td>
<td>Increase one tablet every three days to a maximum of eight tablets per day</td>
<td>$121 per month</td>
</tr>
<tr>
<td><strong>Levodopa plus Stalevo</strong></td>
<td>12.5 mg carbidopa with 50 mg levodopa and 200 mg entacapone two times per day</td>
<td>Increase slowly to a maximum of eight tablets per day</td>
<td>$198 per month</td>
</tr>
<tr>
<td><strong>Dopamine agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bromocriptine Parlodel</strong></td>
<td>1.25 mg two times per day</td>
<td>Adjust every two weeks up to 5 to 20 mg two times per day</td>
<td>$106 ($66 to $70) per month</td>
</tr>
<tr>
<td><strong>Pramipexole</strong></td>
<td>Mirapex 0.125 mg three times per day</td>
<td>Adjust every week up to 1.5 mg three times per day</td>
<td>$107 per month</td>
</tr>
<tr>
<td><strong>Ropinirole</strong></td>
<td>Requip 0.25 mg three times per day</td>
<td>Adjust every week up to 1 mg three times per day</td>
<td>$135 per month</td>
</tr>
<tr>
<td><strong>MAOI-B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Selegiline</strong></td>
<td>Eldepryl 5 mg at breakfast and lunch</td>
<td>No dosage titration required</td>
<td>$81 per month</td>
</tr>
</tbody>
</table>

MAOI-B = monoamine oxidase inhibitor type B.

* After initiation of therapy, dose should be adjusted to achieve the desired therapeutic response rather than to achieve the maximum dosage.

† Studies show that patients receiving less than 70 to 100 mg per day of carbidopa may experience nausea and vomiting. Usual tablet strength used is 25 mg of carbidopa with 100 mg of levodopa. Based on severity of symptoms, some physicians choose an initial dosage of four times per day.

Information from references 19 and 21.
Evidence Summary

Parkinson's disease affects more than 1 percent of persons 65 years of age or older. Parkinson's disease is associated with resting tremor, cogwheel rigidity, and bradykinesia. Early Parkinson's disease is defined as a disease duration of fewer than five years or a patient with Parkinson's disease who has not developed motor complications from levodopa. The Unified Parkinson Disease Rating Scale (UPDRS) measures the longitudinal course of Parkinson's disease on a scale of zero (no disability) to 199 (total disability). Treatment should be initiated when symptoms begin to cause impairment, disability, or affect quality of life.

A systematic review was performed for the Agency for Healthcare Research and Quality based on 49 RCTs of pharmacologic treatment involving 9,968 patients with Parkinson's disease. Limitations of the evidence include heterogeneity in the definition of early disease and motor fluctuations, variation in the measurement of UPDRS scores (during the "off" and "on" periods), and use of levodopa as needed in the dopamine agonist arms of the RCT. The focus of this systematic review was comparing levodopa plus a dopamine agonist (such as bromocriptine) with levodopa alone, for which there was no statistically significant difference (effect size: 0.16; 95% confidence interval: -0.05 to 0.35). The authors of the systematic review concluded that the use of levodopa monotherapy is limited by the development of motor fluctuations and drug-induced dyskinesias. Another significant finding of the systematic review was that treatment that mandated levodopa as an adjunct to a dopamine agonist controlled symptoms better than treatment that allowed levodopa on an as-needed basis. An earlier Cochrane review also stated that there was no convincing evidence to support or refute the widespread use of levodopa plus a dopamine agonist versus levodopa alone for early disease.

One large RCT directly compared bromocriptine with levodopa in a 10-year treatment of early Parkinson's disease. At three years, patients receiving bromocriptine had lower disability scores than those in the levodopa arm of the trial; however, the difference was not significant at nine years, and there was no overall difference in mortality between the groups.

In two Cochrane systematic reviews, patients receiving levodopa for three years were more likely to develop dyskinesias (number needed to treat to harm [NNH]: 4) and dystonias (NNH: 5) than patients receiving bromocriptine, but there were more dropouts in the bromocriptine group because of intolerable side effects (NNH: 4). More recent RCTs compared the newer dopamine agonists pramipexole and ropinirole with levodopa and found that levodopa was associated with more dyskinesia and motor fluctuation (NNH: 3 to 4). By 48 months, however, the occurrence of disabling dyskinesias was uncommon and did not differ between pramipexole- and levodopa-treated patients. Pramipexole was more likely to cause somnolence (NNH: 7) than levodopa. Levodopa was more effective in improving the total UPDRS score (9.2 versus 4.5 points at two years; \( P < .001 \)) but was no better than ropinirole at improving scores on activities of daily living scales. A meta-analysis reported that pramipexole and ropinirole were twice as likely to be associated with hallucinations, somnolence, and edema than levodopa. Another dopamine agonist, pergolide (Permax), should be avoided because of its recent association with restrictive valvular heart disease.
RCTs have found that selegiline improves symptoms of Parkinson's disease and delays the need for levodopa therapy for up to nine to 12 months.\textsuperscript{2,5,13} However, one open-label trial found that selegiline compared with placebo significantly increased mortality after 5.6 years of monitoring (NNH: 10).\textsuperscript{14} This finding was not replicated in other RCTs and may have been the result of the open study design leading to bias in physicians' decisions about treatment withdrawal.\textsuperscript{14} A recent meta-analysis found no increase in mortality in patients with Parkinson's disease taking selegiline.\textsuperscript{15}

Anticholinergic agents (e.g., benztropine [Cogentin] and trihexyphenidyl [Artane]) should be avoided because of neuropsychiatric and cognitive adverse effects.\textsuperscript{16} Based on Cochrane reviews,\textsuperscript{17,18} there also is a lack of evidence to support the use of beta-blockers or amantadine (Symmetrel) for Parkinson's disease symptoms. The combination of levodopa and carbidopa, with entacapone ([Comtan] a selective and reversible catechol O-methyltransferase inhibitor) is suggested for patients currently receiving levodopa who experience end-of-dose depreciation. Switching to this combination may allow for a dosage reduction in levodopa but has not been shown to improve the UPDRS score. It is not recommended as an initial agent because of its higher cost and lack of proven benefit in patients with early Parkinson's disease.\textsuperscript{19} This answer updates previous answers from the Family Physicians Inquiries Network that reviewed aspects of this topic.\textsuperscript{2,13}

Recommendations from Others

The American Association of Neurology (AAN) recommends levodopa or a dopamine agonist for initial therapy of Parkinson's disease, depending on the need to improve motor disability (better with levodopa) or lessen motor complications (fewer with a dopamine agonist). The AAN also comments that sustained-release levodopa offers no benefit for motor complications when compared with the immediate-release products.\textsuperscript{20} Selegiline was mentioned as an alternative for the initial symptomatic treatment of Parkinson's disease, and was thought to have no convincing evidence for increased mortality.\textsuperscript{20}

Clinical Commentary

The trigger for initiating treatment of Parkinson's disease is interference with activities of daily living or symptoms significantly affecting quality of life. These changes are highly subjective, relating to the patient's ability to tolerate deviations from their normal state. Physicians commonly try a dopamine agonist first because levodopa may have a limited effective duration of use. Selegiline also is acceptable as first-line therapy. Each drug should be started at a low dosage and be titrated slowly.

LORI M. DICKERSON, Pharm D.

Associate Professor
Department of Family Medicine
Medical University of South Carolina
Charleston, South Carolina
REFERENCES


Clinical Inquiries provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (http://www.cebm.net/levels_of_evidence.asp).

This series of Clinical Inquiries is coordinated for American Family Physician by John Epling, M.D., State University of New York Upstate Medical University, Syracuse, N.Y. The complete database of evidence-based questions and answers is copyrighted by FPIN. If you are interested in submitting questions to be answered or writing answers for this series, go to http://www.fpin.org or contact CL2Editor@fpin.org.

Author disclosure: Nothing to disclose.

Address correspondence by e-mail to Lori M. Dickerson, Pharm. D., macfarll@musc.edu. Reprints are not available from the authors.

Copyright© Family Physicians Inquiries Network. Used with permission.