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Q / Which drugs work best for early Parkinson's disease?

EVIDENCE-BASED ANSWER

A / LEVODOPA/CARBIDOPA is the most effective medical therapy for Parkinson's disease, but it's associated with dyskinesia (strength of recommendation [SOR]: A, Cochrane reviews and random-

ized controlled trials [RCTs]). Treating early Parkinson's disease with dopamine agonists such as bromocriptine can improve symptoms (SOR: B, Cochrane reviews, RCTs with heterogeneity).

Evidence summary

Levodopa/carbidopa is the most commonly prescribed medication for Parkinson's disease. Although its efficacy is established, it can cause dyskinesia and dystonia.¹ Recent studies (TABLE) have evaluated the use of other medications early in the course of Parkinson's disease in hopes of delaying the waning effectiveness of levodopa over time.

Dopamine agonists:

Dyskinesia reduction, but at a price

A Cochrane review of 29 trials with 5247 patients compared dopamine agonists with levodopa.² Levodopa controlled symptoms better than dopamine agonists, but inconsistent data reporting prevented quantifying this result.

Compared with the group taking levodopa, patients taking dopamine agonists demonstrated a significant reduction in dyskinesia (odds ratio [OR]=0.45; 95% CI, 0.37-0.54), dystonia (OR=0.64; 95% CI, 0.51-0.81), and motor fluctuations (OR= 0.71; 95% CI, 0.58-0.87).

However, patients taking dopamine agonists with or without levodopa experienced significantly more adverse effects than patients taking levodopa alone. Side effects included increased edema (OR=3.68; 95% CI, 2.62-5.18), somnolence (OR=1.49; 95% CI, 1.12-2.00), constipation (OR=1.59; 95% CI, 1.11-2.28), dizziness (OR=1.45; 95% CI, 1.09-1.92), hallucinations (OR=1.69;

95% CI, 1.13-2.52), and nausea (OR=1.32; 95% CI, 1.05-1.66). Patients treated with dopamine agonists were also significantly more likely to discontinue treatment because of adverse events (OR=2.49; 95% CI, 2.08-2.98; $P<.00001$).

Bromocriptine studies hampered by poor quality

Two Cochrane reviews specifically evaluated the dopamine agonist bromocriptine.^{3,4} The first focused on 6 head-to-head trials with levodopa that enrolled 850 patients.³ The studies were of poor quality, marred by methodological flaws and clinical heterogeneity. Problems included inadequate power, high variability in study duration (23 weeks to 5 years), differences in reporting, and lack of description of the randomization method in 3 of the 6 trials. Although bromocriptine showed a trend toward lower incidence of motor complications, many patients dropped out of the studies because of increased non-motor adverse effects and inadequate response to treatment.

The second review, of 7 trials with a total of 1100 patients, compared bromocriptine plus levodopa with levodopa alone.⁴ The studies were of poor quality for reasons similar to the studies in the first review. Researchers found no statistically significant or consistent evidence to determine whether bromocriptine plus levodopa prevents or delays motor complications.

TABLE

Medications commonly used to treat Parkinson's disease

Medication class brand (generic) ⁹	Advantages	Disadvantages	Approximate monthly cost at usual dosage (in US \$) for generic (brand name prices cited if no generic available) ¹⁰
Carbidopa/levodopa Sinemet (carbidopa/ levodopa)	First-line therapy; most effective at improving motor disability ¹	Dyskinesia, dystonia, hallucinations	\$34.99-\$101.98
Sinemet CR (carbidopa/ levodopa controlled- release)		No documented benefit of long-acting form ^{1,8}	\$80.99-\$295.97 (Highly variable due to dose range)
COMT inhibitor Comtan (entacapone)	Augments levodopa, may improve activities of daily living ⁶	Same side effects as above plus possible increased nausea, vomiting, diarrhea ⁶	\$310.97-\$414.62
Stalevo (carbidopa/ levodopa/entacapone)		Possible increased cardiovascular risk and prostate cancer	\$318.00-\$1043.97
Dopamine agonist Mirapex (pramipexole)	Reduced dyskinesias, dystonia, and motor complications ²	Nausea, dizziness, constipation, somnolence, hallucinations, edema ²	\$239.99
Requip (ropinirole)			\$71.99-\$143.98
Parlodel (bromocriptine)			\$385.97-\$1133.92
MAO-B inhibitor Eldepryl (selegiline)	Mild improved motor symptoms of disease, decreased motor fluctuations of treatment, possible "levosparing effect" ⁵	Limited efficacy and multiple adverse effects leading to high dropout rate; not recommended by Cochrane review ⁵	\$101.99
Anticholinergic Cogentin (benztropine mesylate)	Improved symptoms, mostly tremor ⁷	Confusion, memory loss, hallucinations, restlessness; contraindicated in dementia ⁷	\$13.99-\$22.99
Other Symmetrel (amantadine)		No good updated studies, unproven long-term benefit, nausea, dizziness, insomnia, can cause psychosis ⁹	\$43.17

COMT, catechol-O-methyltransferase; MAO-B, monoamine oxidase type B.

MAO-B inhibitors: Minimally effective with troubling side effects

A Cochrane review of monoamine oxidase type B (MAO-B) inhibitors included 10 trials with 2422 participants.⁵ The review found statistically, but not clinically, significant improvements in scores on 2 sections of the United Parkinson Disease Rating Scale (UPDRS), a standardized assessment tool that facilitates accurate documentation of disease

progression and treatment response.

Compared with the control groups (either placebo or levodopa at study onset), the MAO-B group (either alone or with levodopa) showed significant improvement on the motor section (weighted mean difference [WMD]=−3.81 on a 108-point scale; 95% CI, −5.36 to −2.27) and activities of daily living section (WMD=−1.50 on a 52-point scale; 95% CI, −2.53 to −0.48). Fewer motor complications occurred in the MAO-B

➤ **Dopamine agonists can reduce dyskinesia, but have significant adverse effects.**

group (OR=0.75; 95% CI, 0.59-0.94) than the control group. Lower doses and shorter treatment with levodopa were necessary to control symptoms in the MAO-B group.

The clinical impact of MAO-B inhibitors on Parkinson's symptoms was small, and almost all patients required the addition of levodopa to the treatment regimen after 3 or 4 years. Withdrawals because of medication side effects were significantly higher in the MAO-B inhibitor group than controls (OR=2.36; 95% CI, 1.32-4.20). Side effects included nausea, confusion, hallucinations, and postural hypotension. Concerns about cardiovascular adverse effects raised in previous studies, especially with selegiline, weren't found to be significant (OR=1.15; 95% CI, 0.92-1.44). Because of their minimal effectiveness and worrisome adverse effects, MAO-B inhibitors aren't recommended for routine use in early Parkinson's disease.

COMT inhibitors may boost levodopa/carbidopa's effects

A randomized double-blinded trial followed 423 patients for 39 weeks to compare the combination of the catechol-O-methyltransferase (COMT) inhibitor entacapone and levodopa/carbidopa (LCE) with levodopa/carbidopa alone (LC).⁶ The researchers found statistically significant improvements with LCE in UPDRS scores for activities of daily living (mean change from baseline=3.0 for LCE vs 2.3 for LC on a 52-point scale;

$P=.025$) but not mentation or motor symptoms.

Dyskinesia and wearing-off symptoms (motor fluctuations) didn't differ significantly between the 2 groups. LCE was associated with a higher incidence of adverse effects than LC, and involved mostly nausea (26.6% vs 13.5%) and diarrhea (8.7% vs 2.8%).

Anticholinergics may help, but cause adverse mental effects

Another Cochrane review compared anticholinergic agents with placebo or no treatment in 9 studies that included 221 patients.⁷ Meta-analysis wasn't possible because of heterogeneity in patient populations, outcomes, and measurements and incomplete reporting. Compared with placebo, anticholinergic agents may improve Parkinson's-related motor symptoms but have significant mental adverse effects, including confusion, memory problems, restlessness, and hallucinations.

Recommendations

The most recent guidelines (2002) from the American Academy of Neurology recommend levodopa and dopamine agonists as first-line therapies.⁸ Levodopa is more effective at improving the motor symptoms of Parkinson's disease but is associated with a higher risk of dyskinesia than dopamine agonists. No compelling evidence suggests a difference in efficacy between long- and short-acting levodopa. **JFP**

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