Review: Selegiline improves symptoms and levodopa is better than pramipexole for motor function in untreated Parkinson disease

Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. **Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review. Report of the Quality Standards Subcommittee of the American Academy of Neurology.** Neurology. 2002 Jan 8;58:11-7.

QUESTIONS

In previously untreated patients with Parkinson disease (PD), does selegiline have a neuroprotective effect? Are dopamine agonists more effective than levodopa (Sinemet) for symptomatic therapy? Is sustained-release or immediate-release levodopa more effective?

DATA SOURCES

Studies were identified by searching MEDLINE, EMBASE/Excerpta Medica, and the Cochrane Library (to 2000).

STUDY SELECTION

English-language studies were selected if they evaluated the neuroprotective effects or safety of selegiline or if they compared dopamine agonists with levodopa or sustained-release levodopa with immediate-release levodopa in previously untreated patients with PD.

DATA EXTRACTION

Studies were rated for quality (class I [high-quality randomized controlled trials with blinded outcome assessment] to class IV [uncontrolled studies, case series, case reports, or expert opinion]).

MAIN RESULTS

Selegiline: 2 class-II studies on the neuroprotective effects of selegiline were included. Selegiline improved symptoms, but the evidence was insufficient for showing a neuroprotective effect. 1 meta-analysis and 1 study showed that selegiline, alone or combined with levodopa, did not increase mortality. *Initiating dopaminergic treatment*: 1 class-I study and 2 class-II studies compared dopamine agonists with levodopa. The class-I study showed that after 23.5 months of treatment levodopa was better than pramipexole on the motor (mean score 7.3 vs 3.4, $P < 0.001$) and activities-of-daily-living (ADLs) (mean score 2.2 vs 1.1, $P = 0.001$) components of the Unified Parkinson Disease Rating Scale. Pramipexole led to fewer motor complications {hazard ratio 0.45, 95% CI 0.30 to 0.66}* but more somnolence ({32% vs 17%}*, $P = 0.003$), hallucinations ($P = 0.03$), and generalized ($P = 0.01$) and peripheral ($P = 0.002$) edema than did levodopa. In the class-II studies, follow-up was < 80% in 1 study, and the groups were not statistically compared in the other study. *Sustained-release levodopa compared with immediate-release levodopa:* One 5-year class-II study showed that the only difference was a greater improvement in ADLs for sustained-release levodopa than for immediate-release levodopa (mean score change –0.8 vs 0.2, $P = 0.031$).

CONCLUSIONS

In patients with Parkinson disease, selegiline improves symptoms and does not increase mortality; the evidence is insufficient to show a neuroprotective effect. Levodopa is better than pramipexole for motor function; pramipexole leads to more adverse effects but not more motor complications than does levodopa. Sustained-release and immediate-release levodopa do not differ for most outcomes.

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*Parkinson Study Group. JAMA. 2000;284:1931-8.

COMMENTARY

Miyasaki and colleagues review the evidence for suggested treatments for previously untreated patients with PD. Selegiline is a safe drug with modest efficacy for managing mild symptoms in patients who do not have limitations in ADLs. This drug has some properties that could diminish disease progression, but so far evidence that it delays progression or development of complications is scanty. Nevertheless, in patients who have had PD detected in an early stage, this drug can delay the need for levodopa (1). Amantadine and anticholinergics can also be considered for treating mild disease, but the incidence of side effects is high in older patients.

Levodopa improves motor functions and increases the expected life span of patients (2), but severe complications can ensue from long-term treatment. Sustained-release levodopa has some modest advantages, and laboratory studies suggest that more continuous stimulation of receptors is preferable. However, the results summarized here show that the present formulation with twice-daily dosing is not enough to prevent the complications of levodopa therapy. Hence, the choice between immediate and sustained-release levodopa is moot.

The authors review the evidence showing that 3 new dopamine agonists improve motor function similarly but not quite equally to levodopa. The reduction in the time to onset of dyskinesia with these new agonists is important, considering that 45% of patients develop the condition within 5 years of beginning levodopa therapy and that it is disabling in 23% of patients (3). This fact alone is enough to merit consideration of these drugs as first-line treatment when limitations in ADLs occur. This consideration must be balanced against the increased incidence of sedation with the nonergot agonists (15% more in the pramipexole study) and the rare occurrence of sleep attacks. Although the latter phenomenon appears to be a class effect (4), it occurs with ropinirole and pramipexole and makes driving safety a particular concern with these otherwise-promising drugs.

Deep-brain stimulation is useful in selected patients, and stem-cell and fetal implants hold promise for the future, but for now, drugs are the mainstay of therapy for most patients.

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