Review: Several drugs are efficacious for symptomatic treatment of Parkinson disease

Rascol O, Goetz C, Koller W, Poewe W, Sampaio C. **Treatment interventions for Parkinson's disease: an evidence based assessment.** Lancet. 2002;359:1589-98.

QUESTION

In patients with Parkinson disease (PD), what are the optimal treatments for preventing disease progression, controlling motor symptoms, managing and preventing motor complications, and treating nonmotor symptoms?

DATA SOURCES

Studies were identified by searching electronic databases and by checking the references of review articles and relevant studies.

STUDY SELECTION

English-language studies were selected if they were published full reports of randomized controlled trials (RCTs) that enrolled ≥ 20 patients with PD, used objective scales for outcome measurement, and had ≥ 4-week follow-up.

DATA EXTRACTION

Data were extracted on study quality, and studies were assessed for efficacy, clinical usefulness, and safety. To be considered efficacious, the intervention had to show a positive effect on outcomes based on data from ≥ 1 high-quality RCT and have no conflicting data from other RCTs.

MAIN RESULTS

The therapeutic interventions evaluated were drugs, surgery, and rehabilitation procedures. Interventions were evaluated with respect to prevention of disease progression, treatments of signs and symptoms, symptomatic treatment and prevention of motor complications, and symptomatic treatment of nonmotor features. The Table shows efficacious interventions. No interventions were shown to be efficacious for neuroprotection in PD. In patients with nonmotor features of PD, 1 drug was shown to be efficacious for drug-induced psychosis; no drugs were efficacious for such other nonmotor features as dementia, depression, or orthostatic hypotension. No strong RCT evidence supports the efficacy of surgery or rehabilitation.

CONCLUSIONS

In patients with Parkinson disease, several drugs are efficacious for controlling motor symptoms and motor complications and preventing motor complications. Recent surgical interventions have not been adequately assessed in RCTs. Insufficient evidence exists for prevention of disease progression and control of most nonmotor features and to support rehabilitation.

Sources of funding: 8 funding agencies.

For correspondence: Professor O. Rascol, Toulouse University Hospital, Toulouse, Cedex, France. E-mail rascol@cict.fr.

Interventions for Parkinson disease (PD) shown to be efficacious in randomized controlled trials (RCTs)*

PD indicators	Drug
Signs and symptoms in patients with early PD not receiving levodopa	Standard levodopa, controlled-release levodopa, dihydroergocryptine, pergolide, pramipexole, ropinirole, selegiline
Signs and symptoms in patients with advanced PD already receiving levodopa	Controlled-release levodopa, bromocriptine, cabergoline, pergolide, pramipexole, entacapone, tolcapone
Motor fluctuations and dyskinesias	Pergolide, pramipexole, ropinirole, entacapone, tolcapone, amantadine
Psychosis	Clozapine
Prevention of motor complications in levodopa-naive patients	Cabergoline, pramipexole, ropinirole

*Efficacious interventions showed a positive effect on studied outcomes based on data from ≥ 1 high-quality RCT and had no conflicting data from other RCTs.

COMMENTARY

The review by Rascol and colleagues covers a wide range of procedures. The questions at hand are whether the rigid methodology of this systematic review applies equally to the heterogeneous set of interventions analyzed and whether the distinction between motor efficacy as monotherapy or as adjunctive treatment is clinically relevant (and pathophysiologically appropriate).

The methodological faults of most drug trials for PD (1) also apply to the studies selected for this review. Most RCTs meeting the inclusion criteria were designed as regulatory trials to prove the efficacy of a defined drug, compared with placebo, in a specific disease stage, rather than to address fundamental aspects of treating PD. The separation of symptomatic interventions that are efficacious as monotherapy from those for which the treatment is an adjunct to levodopa is a distinctive end point of regulatory trials, not a crucial clinical issue.

The review states that controlled-release levodopa is a useful adjunct to standard levodopa, but provides no answer to the essential clinical question of whether adding controlled-release levodopa is better than simply increasing the standard levodopa dose.

Some surgical interventions are considered to be likely efficacious as adjunct treatments, but lack sufficient evidence to be recommended as monotherapy, mainly because ethical concerns suggest that surgery should be postponed until drug treatments have failed.

The most solid evidence in this review is the labeling of interventions as nonefficacious. Controlled-release levodopa does not prevent motor complications, which further supports the complementary observation that dopamine agonists delay the onset of such complications.

The analysis does not deal with dopamine agonists as a group but evaluates individual studies of each drug. The clinical use of dopamine agonists spans more than 30 years, but most of the older studies were not RCTs. Thus, insufficient evidence exists for the use of apomorphine (the only dopamine agonist with a potency similar to that of levodopa [2]) as monotherapy, although the same drug is considered a likely efficacious adjunct to levodopa.

Finally, off-period motor fluctuations and on-period dyskinesias were considered together as "motor complications," although they have different pathophysiology (3) and require different clinical interventions.

Alberto Albanese, MD
Istituto Nazionale Neurologico Carlo Besta
Milano, Italy

References

1. **Wheatley K, Stowe RL, Clarke CE, et al.** BMJ. 2002;321:1508-11.
2. **Lees AJ.** Fundam Clin Pharmacol. 1993;7:121-8.
3. **Chase TN.** Drugs. 1998;55(Suppl 1):1-9.