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CRD summary
This review evaluated neuroprotective and non-standard therapies for patients with Parkinson disease. The authors concluded that disease progression does not appear to be increased by levadopa and no strategy provided neuroprotection. Although the authors' conclusions appear to be supported by the review, inadequate reporting of review methods and study details make it difficult to confirm the reliability of the conclusions.

Authors' objectives
To evaluate neuroprotective and non-standard therapies for patients with Parkinson's disease and to answer the following questions:

Can any therapies slow disease progression for patients with Parkinson's disease?

Can any non-standard pharmacological or non-pharmacological therapies improve motor function in patients with Parkinson's disease?

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Database of Systematic Reviews were searched from 1997 to 2002 for English language reports; the search terms were reported. The MEDLINE search was extended to cover 1996 to August 2004. In addition, bibliographies of identified studies were screened and the views of experts in the review panel were sought (up to January 2005).

Study selection
Study designs of evaluations included in the review
Studies that evaluated neuroprotective agents had to have at least 6 months’ follow-up. Studies that evaluated non-standard pharmacologic or non-pharmacologic therapies had to have at least 10 participants.

Specific interventions included in the review
Studies that evaluated potential neuroprotective agents were eligible for inclusion. Studies that evaluated non-standard pharmacological or non-pharmacologic therapies had to be of at least 1 week in duration. The included studies of neuroprotection evaluated: amantadine, coenzyme Q10, levadopa, pramipexole, rasagiline, ropinirole, thalamotomy, vitamin C and vitamin E. The included studies of non-standard pharmacologic or non-pharmacologic therapies evaluated: exercise therapy, naturopathic treatments, physiotherapy, speech therapy, vitamin therapy, chiropractic, acupunture, Alexander technique, music therapy and osteopathic manipulation.

Participants included in the review
Studies of patients with Parkinson's disease were eligible for inclusion.

Outcomes assessed in the review
Studies of neuroprotective agents that assessed the rate of disease progression were eligible for inclusion. Studies that only assessed the symptomatic benefit of neuroprotective agents were excluded. The included studies evaluated the time to require levadopa, Unified Parkinson's disease Rating Scale (UPDRS), UPDRS activities of daily living (UPDRS-ADL), single-photon enhanced computed tomography (SPECT) beta-CIT uptake, putaminal uptake of levadopa on fluorodopa positron emission tomography, self-validated disability scale, measures of psychological functioning, various specified measures of function, and various measures of speech volume and quality.

How were decisions on the relevance of primary studies made?
Panel members assessed the relevance of the identified studies and any disagreements were resolved through consensus.
Assessment of study quality
The authors did not state how the validity assessment was performed. Studies were graded using a hierarchy of study design from class I to class IV. Class I represented blinded randomised controlled trials (RCTs) with a clearly defined primary outcome, clearly reported inclusion and exclusion criteria, adequate accounting for drop-outs, and baseline comparability of treatment groups or statistical adjustment. Class IV represented uncontrolled trials, case series, case reports or expert opinion. The grading system is presented in an appendix on the Neurology website, but a subscription may be required for access. For some studies, the review also reported blinding, completeness of follow-up and the adequacy of the sample size.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were grouped by intervention and combined in a narrative. The level of evidence for each intervention was graded using a hierarchy: level A indicated effective, ineffective or harmful evidence from at least 2 consistent blinded RCTs; level B indicated probably effective, ineffective or harmful evidence from at least 1 RCT or at least 2 consistent matched-group cohort studies; level C indicated possibly effective, ineffective or harmful evidence from at least 1 matched-group cohort study or 2 consistent non-randomised and non-matched studies; and level U indicated inadequate or conflicting evidence where there were inadequate data. The grading system is presented in an appendix on the Neurology website, but a subscription may be required for access.

How were differences between studies investigated?
Differences with respect to study design, interventions and outcome measures were discussed in the text.

Results of the review
Eleven studies evaluated neuroprotective agents. There were 7 class I studies, 1 class II study and 3 class IV studies.

The authors stated that 22 studies evaluated non-standard pharmacologic and non-pharmacologic therapies. There were 2 class I studies, 11 class II studies, 2 class III studies and 3 class IV studies (total 18 studies; the design of the other studies was not reported).

The number of participants was not reported for all studies.

Neuroprotective agents.

One class I study, a blinded RCT (n=800), reported no significant difference in the time to require levadopa between vitamin E (2,000 IU/day) and placebo with or without selegiline (hazard ratio 0.91, 95% confidence interval: 0.74, 1.12).

One class I study, a double-blind RCT (n=361), showed that patients on levadopa had significantly improved UPDRS scores compared with patients on placebo at 40 weeks. The change in UPDRS scores was 7.8 on placebo versus 1.9, 1.9 and -1.4, respectively, on three different levadopa doses; the latter showing the greatest improvements associated with the highest dose (600 mg/day). There was no significant difference between treatment groups in SPECT beta-CIT uptake (based on 116 patients) and dyskinesias were more common in patients on 300 mg levadopa.

One class I study, a double-blind RCT (n=404), reported that patients treated with 2 mg rasagiline for 1 year had a smaller increase in UPDRS and UPDRS-ADL scores than patients treated with 2 mg rasagiline for only the previous 6 months (difference 2.29 in UPDRS and -0.96 in UPDRS-ADL, p=0.005).

There was no evidence of a neuroprotective effect for riluzole, coenzyme Q or pramipexole, but studies of riluzole and pramipexole were underpowered (based on 1 class I study for each agent).

There was insufficient evidence to assess the effects of thalamotomy and amantadine (based on 1 class IV study for...
each treatment).

Non-standard pharmacologic and non-pharmacologic therapies.

Eight class II studies, all blinded RCTs, reported small improvements in various specified functional measures in patients allocated to various exercise interventions; the data were not reported. Studies of speech therapy had sample sizes ranging from 12 to 45; drop-out rates, where reported, ranged from 15 to 27%. Two class II studies showed that individual speech therapy was possibly effective in improving speech volume (one focused on pitch and volume and also used visual feedback; the other was aimed at optimising phonatory effort). There was insufficient information to compare different types of speech therapy.

There was insufficient information to support or refute any of the other therapies evaluated.

**Authors' conclusions**
None of the treatments were shown to be neuroprotective. The rate of disease progression does not appear to be increased by levodopa. Exercise may improve motor function and speech therapy may improve speech volume. Vitamins and food additives are not associated with improvements in motor function.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention and outcomes; the criteria for the study design were broad. Several relevant sources were searched, but there were no attempts to reduce language bias and no reported attempts to minimise publication bias. The studies were classified according to a hierarchy of study design and other aspects of validity were reported for some studies. Methods were used to minimise reviewer error and bias in the selection of studies, but it was not clear whether similar steps were taken in the assessment of validity and extraction of data.

In view of the diversity of the studies, a narrative synthesis that highlighted the higher quality evidence identified was appropriate. Some details of the included studies were presented, although results of all the individual studies would have been helpful in interpreting the reported treatment effects. Although the authors' conclusions appear to be supported by the review, incomplete reporting of review methods and study details mean it is difficult to confirm their reliability.

**Implications of the review for practice and research**
Practice: The authors made the following recommendations. Levadopa may be considered as an initial treatment for Parkinson's disease (level B evidence) but there is no long-term evidence. Vitamin E should not be used as a neuroprotective agent (level B evidence) or for symptomatic treatment (level B evidence). Exercise therapy may be considered to improve function (level C evidence), while speech therapy may be considered for improving speech volume in patients with Parkinson's disease and dysarthria (level C evidence).

Research: The authors stated that there is a need for good-quality studies to evaluate alternative therapies for patients with Parkinson's disease. There is also a need to develop reliable and validated surrogate end points that can be used to evaluate nigrostriatal dopaminergic neurone loss, a need to develop methods for accurate early diagnosis in presymptomatic patients and a need for increased information about disease progression.

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**Bibliographic details**

**PubMedID**
16606908
Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Accidental Falls; Complementary Therapies /standards; Humans; Levodopa /therapeutic use; Neurology /standards; Parkinson Disease /drug therapy /physiopathology /therapy; Quality Assurance, Health Care; United States

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.