

Monoamine oxidase type B inhibitors in early Parkinson's disease: meta-analysis of 17 randomised trials involving 3525 patients

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Abstract

Objective To quantify more reliably the benefits and risks of monoamine oxidase type B inhibitors (MAOBIs) in early Parkinson's disease.

Data sources Searches of the Cochrane Library, Medline, Embase, PubMed, and Web of Science for years 1966-2003, plus major journals in the field, abstract books, and proceedings of meetings, for randomised trials comparing MAOBIs with placebo or levodopa.

Data extraction Available data on mortality, motor complications, side effects, treatment compliance, and clinician rated disability (for example, unified Parkinson's disease rating scale) were extracted from 17 trials and combined using standard meta-analytic methods.

Results No significant difference in mortality existed between patients on MAOBIs and control patients (odds ratio 1.13, 95% confidence interval 0.94 to 1.34; $P=0.2$). Patients randomised to MAOBIs had significantly better total scores, motor scores, and activities of daily living scores on the unified Parkinson's disease rating scale at three months compared with patients taking placebo; they were also less likely to need additional levodopa (0.57, 0.48 to 0.67; $P<0.00001$) or to develop motor fluctuations (0.75, 0.59 to 0.95; $P=0.02$). No difference existed between the two groups in the incidence of side effects or withdrawal of patients.

Conclusions MAOBIs reduce disability, the need for levodopa, and the incidence of motor fluctuations, without substantial side effects or increased mortality. However, because few trials have compared MAOBIs with other antiparkinsonian drugs, uncertainty remains about the relative benefits and risks of MAOBIs. Further large, long term comparative trials that include patient rated quality of life measures are needed.

Introduction

Monoamine oxidase type B inhibitors (MAOBIs) have been used either alone or in addition to levodopa in both early and later Parkinson's disease in the hope that they may slow disease progression. Clinical trials

in the 1980s, such as the DATATOP study,¹ suggested that the MAOBI selegiline might have a neuroprotective effect, but this remains controversial.² Further uncertainty arose in 1995, when a study by the Parkinson's Disease Research Group of the United Kingdom (UK-PDRG) found 57% higher mortality in patients receiving combined selegiline and levodopa treatment compared with patients on levodopa alone.³ Other randomised trials have, however, failed to show any increase in mortality.⁴⁻⁵ To clarify the role of MAOBIs, we did a meta-analysis of data from all published trials comparing any MAOBI with either levodopa or placebo in early Parkinson's disease.

Methods

Identification of trials

We systematically searched the literature from 1966 to December 2003 by using the Cochrane Library, Medline, Embase, PubMed, and Web of Science and by hand searching major journals in the field, abstract books, conference proceedings, and reference lists of retrieved publications.

Inclusion criteria

Eligible studies had to be randomised trials in early Parkinson's disease comparing an MAOBI (selegiline, lazabemide, or rasagiline), with or without levodopa, versus placebo, levodopa, or both, with all other aspects of treatment being the same in both arms. We defined early disease as patients with idiopathic Parkinson's disease who had no history of motor complications and were untreated or had received limited (generally less than 12 months) exposure to antiparkinsonian drugs.

Outcome measures

Two independent reviewers extracted outcome data, which were validated by a third reviewer, with any discrepancies resolved by consensus. Data extracted

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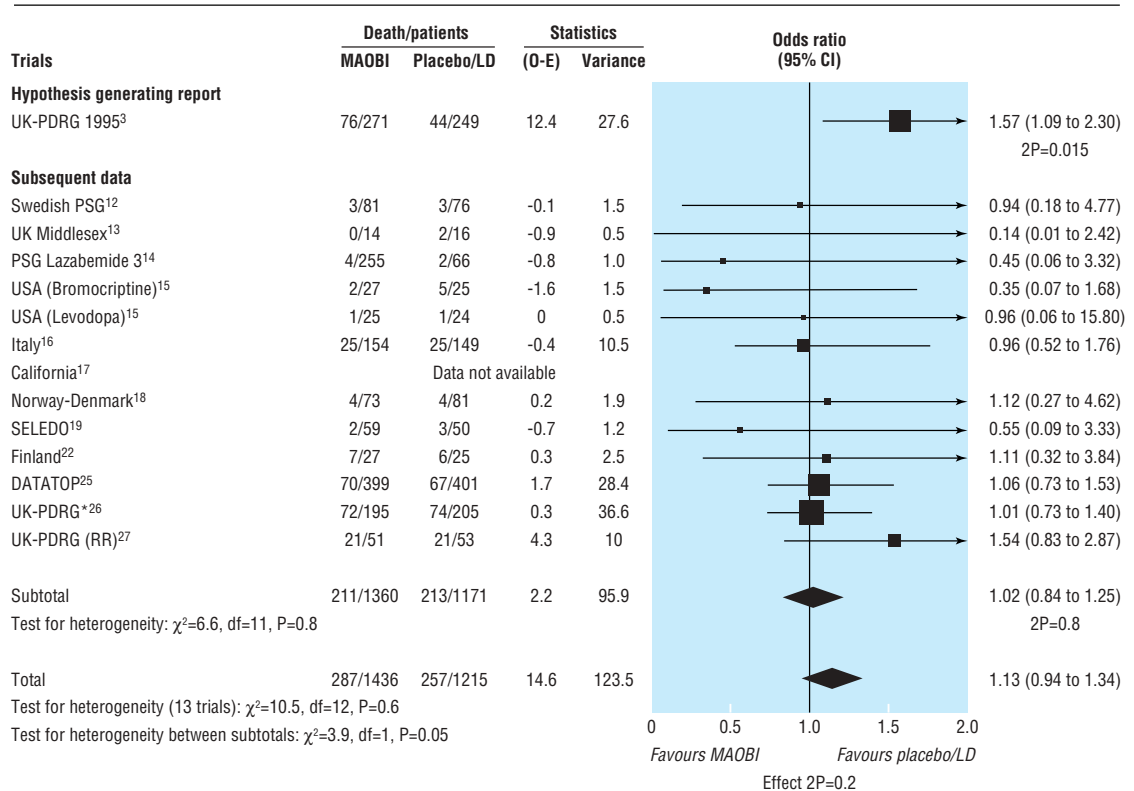


Fig 1 Mortality in trials of monoamine oxidase type B inhibitors. (LD=levodopa; MAOBI=monoamine oxidase type B inhibitor; O-E=observed minus expected; RR=re-randomisation data from UK-PDRG. *Data from subsequent follow up of UK-PDRG trial—patients counted only once in total denominator)

included mortality; clinician rated disability scales, such as the unified Parkinson's disease rating scale; need for levodopa; incidence of motor complications; side effects; and withdrawal of patients from the trial. We used outcome data at the longest available follow up, other than for unified Parkinson's disease rating scale data, which we analysed at three months after randomisation.

Statistical analysis

We combined the results of each trial to estimate an overall treatment effect for MAOBI versus non-MAOBI treated patients. We subclassified trials according to the randomised treatment comparison: MAOBI versus placebo; MAOBI+levodopa (LD) versus placebo+LD or MAOBI+LD versus LD (classified as MAOBI+LD versus LD); and MAOBI versus LD. We used tests of heterogeneity to assess for differences in treatment effects between trials and subgroups of trials.

For event data (such as mortality) we obtained estimates of the treatment effects for most trials from the number of events reported in each arm and then used the methods of Mantel and Haenszel to combine them. For continuous variables (such as clinician rated disability scales), we used weighted mean difference methods. See bmj.com for details of statistical methods.

Results

Trials and patients

We identified 18 randomised trials of MAOBI treatment in early Parkinson's disease. We excluded one crossover study, and therefore included 17 trials

involving 3525 patients in this meta-analysis (see bmj.com).^{3, 6-27} Thirteen trials were of selegiline, three were of lazabemide, and one was of rasagiline. Duration of treatment varied from six weeks to 10 years; shorter trials assessed symptomatic control and tolerability, and longer trials assessed disease progression and mortality. One trial contributed data to more than one comparison (MAOBI v placebo and MAOBI+LD v LD).¹⁵ In the UK-PDRG study, patients who had inadequate symptom control or were unable to tolerate their original allocation to the dopamine agonist bromocriptine were re-randomised to selegiline plus levodopa or levodopa alone.³

Ten trials described the method of randomisation used; only four trials clearly had an adequate concealment of allocation procedure. All trials provided information on blinding (15/17 trials were double blind), and all trials reported follow up data.

Mortality

Mortality data were available from nine trials of selegiline and one of lazabemide (fig 1). We considered the UK-PDRG study, which initially reported 76/271 (28%) deaths in the selegiline arm compared with 44/249 (18%) deaths in the levodopa arm (odds ratio 1.57, 95% confidence interval 1.09 to 2.30; P=0.015) to be hypothesis generating.³ In the other trials, which we treated as confirmatory studies, no excess of deaths occurred with MAOBI compared with the control arm. Taking all available data, no excess of deaths occurred in the MAOBI treated patients. We found no significant heterogeneity between trials, even including the UK-PDRG study.

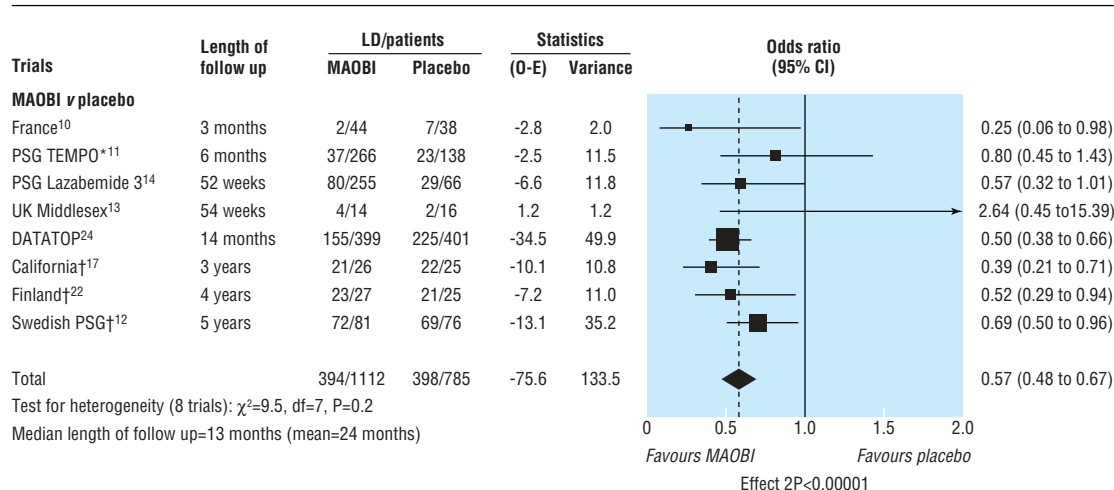


Fig 2 Need for levodopa treatment in trials comparing monoamine oxidase type B inhibitors and placebo. (O-E=observed minus expected; LD=levodopa; MAOBI=monoamine oxidase type B inhibitor. *Rasagiline. †O-E and variance based on published time to event analyses)

Clinical disability rating scales

Data from rating scales were available from only six trials of selegiline.^{6 10 15 17 18 23} Unified Parkinson's disease rating scale scores at three months were 2.7 (95% confidence interval 1.4 to 4.1; $P=0.00009$), 1.8 (0.8 to 2.7; $P=0.0004$), and 0.9 (0.5 to 1.4; $P=0.00007$) points better with selegiline than with control for total score, motor score, and activities of daily living score (see bmj.com). The large DATATOP study accounted for more than 65% of the patients analysed and more than 79% of patients in the MAOBI versus placebo comparison.²³ However, combined results from the other two studies of MAOBI versus placebo were consistent with those from DATATOP and independently significant ($P=0.004$).^{6 10}

Need for levodopa

For the 12 trials comparing an MAOBI with placebo, data on the need for levodopa were available from eight studies with a median follow up of 13 months (range 3 months to 5 years) (fig 2). A highly significant reduction in the need for levodopa occurred in patients randomised to an MAOBI compared with those on placebo (fig 2). For trials comparing selegiline and levodopa with levodopa alone, adequate data on dose of levodopa for meta-analysis were available from two trials.^{15 18} The dose of levodopa needed for adequate symptom control was 67 (14 to 119) mg lower in the selegiline arm ($P=0.01$).

Motor complications

Data on motor complications were available from five trials.^{16 18 19 21 26} A 25% reduction in motor fluctuations occurred in patients randomised to an MAOBI (odds ratio 0.75, 0.59 to 0.95; $P=0.02$). However, we found no difference in the incidence of dyskinesia between the MAOBI and non-MAOBI groups (odds ratio 0.97, 0.75 to 1.26; $P=0.8$). We found no evidence of heterogeneity.

Side effects and withdrawals

More side effects were reported in patients randomised to an MAOBI, which was of borderline significance (odds ratio 1.36, 1.02 to 1.80; $P=0.04$). More MAOBI patients than non-MAOBI patients withdrew owing to adverse events (odds ratio 2.16,

1.44 to 3.23; $P=0.0002$), with some evidence of heterogeneity between trials ($P=0.03$) but not between the three treatment comparisons ($P=0.09$). This heterogeneity was explained by the atypical results in the UK-PDRG study, which reported significantly more dropouts due to adverse events in the open label selegiline plus levodopa arm than with levodopa alone (14% v 3%). In contrast, significantly more patients were withdrawn from this trial in the levodopa arm owing to protocol violations (1% v 15%); 28/37 patients were withdrawn following the introduction of selegiline to their treatment regimen after publication of the DATATOP trial results. An analysis of these data excluding the UK-PDRG and Italy studies showed no difference between MAOBI and non-MAOBI patients (odds ratio 1.52, 0.87 to 2.68; $P=0.1$), with no evidence of heterogeneity between trials ($P=0.2$) or between the two treatment comparisons ($P=0.9$).

We found no difference between the two groups (MAOBI v non-MAOBI) in the overall numbers of patients withdrawing from the trials (18% v 19%; odds ratio 1.06, 0.87 to 1.28; $P=0.6$). However, patients withdrew from different trials for quite varied reasons, and this is reflected in the significant heterogeneity between trials ($P=0.007$).

Discussion

This is the first systematic review to assess MAOBIs as a drug class in early Parkinson's disease and the most comprehensive in the range of outcomes assessed. It provides evidence to refute the hypothesis that MAOBIs, and selegiline in particular, increase mortality in patients with Parkinson's disease, as suggested by the UK-PDRG trial.³ It therefore seems likely that the early excess of deaths in the selegiline arm of the UK-PDRG study compared with the levodopa arm was a chance finding, although the confidence interval reported in this review is compatible with a small increase, or indeed decrease, in mortality.

Our systematic review also shows that early use of selegiline delays the need for levodopa and that when selegiline is given concomitantly with levodopa lower

What is already known on this topic

Selegiline is used either alone or in addition to levodopa to try to slow the progression of Parkinson's disease

One trial reported increased mortality in patients treated with selegiline

What this study adds

Monoamine oxidase type B inhibitors reduce disability, the need for levodopa, and the incidence of motor fluctuations without substantial side effects or increased mortality

Further large, long term trials comparing selegiline with other available drugs, and assessing patient rated quality of life measures, are needed

doses of levodopa are needed. This may be due to symptomatic relief from selegiline: total scores, motor scores, and activities of daily living scores on the unified Parkinson's disease rating scale were significantly better with selegiline than with placebo in the first three months of treatment. (The lack of apparent benefit from selegiline when added to levodopa or bromocriptine is probably explained by adjustments in the dose of the concomitant drug.) However, whether the benefits seen are large enough to be clinically important is debatable. Avoiding exposure to levodopa should reduce the risk of developing motor complications, which are believed to be a consequence of long term use of levodopa. In the few studies that reported these data, fewer selegiline patients developed motor fluctuations. Interestingly, no reduction in dyskinesia was observed, although a benefit cannot be excluded given the wide confidence intervals. The reduction in motor fluctuations could be due to lower exposure to levodopa or to a neuroprotective effect of selegiline.

Our review suggests that selegiline could be one of the most clinically effective and cost effective treatments available for early Parkinson's disease. However, use of selegiline in the United Kingdom dropped substantially after the UK-PDRG report of increased mortality. The limited information available on lazabemide and rasagiline makes any conclusions on the role of MAOBIs as a class difficult.

The review also highlights the lack of data on the long term balance of benefits and risks of MAOBIs. Therefore, further large, well designed randomised trials that evaluate the long term balance of benefit and harm, comparing MAOBIs with other active agents, such as dopamine agonists and levodopa, are urgently needed—for example, the PD MED trial (www.pdmed.bham.ac.uk (accessed 22 Jun 2004)).

We recognise the work of all the original trial teams and the people who did the trials that contributed to this meta-analysis, and we thank the patients who agreed to help future patients by taking part in these trials.

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Ethical approval: Not needed.

- 1 Parkinson Study Group. DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. *Arch Neurol* 1989;46:1052-60.
- 2 Lang AE, Lees AJ. MAO-B inhibitors for the treatment of Parkinson's disease. *Mov Disord* 2002;17(suppl 4):S38-44.
- 3 Lees AJ on behalf of the Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995;311:1602-7.
- 4 Olanow CW, Myllyla VV, Sotaniemi KA, Larsen JP, Palhagen S, Przuntek H, et al. Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. *Neurology* 1998;51:825-30.
- 5 Counsell C. Effect of adding selegiline to levodopa in early, mild Parkinson's disease: formal systematic review of data on patients in all relevant trials is required. *BMJ* 1998;317:1586.
- 6 Mally J, Kovacs AB, Stone TW. Delayed development of symptomatic improvement by (-) deprenyl in Parkinson's disease. *J Neurol Sci* 1995;134:143-5.
- 7 Parkinson Study Group. A controlled trial of lazabemide (Ro19-6327) in untreated Parkinson's disease. *Ann Neurol* 1993;33:350-6.
- 8 Parkinson Study Group. A controlled trial of lazabemide (Ro 19-6327) in levodopa-treated Parkinson's disease. *Arch Neurol* 1994;51:342-7.
- 9 Nappi G, Martignoni E, Horowski R, Pacchetti C, Rainer E, Bruggi P, et al. Lisuride plus selegiline in the treatment of early Parkinson's disease. *Acta Neurol Scand* 1991;83:407-10.
- 10 Allain H, Pollak P, Neukirch HC. Symptomatic effect of selegiline in de novo Parkinsonian patients: the French selegiline multicenter trial. *Mov Disord* 1993;8(suppl 1):S36-40.
- 11 Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO study. *Arch Neurol* 2002;59:1937-43.
- 12 Palhagen S, Heinonen EH, Hagglund J, Kaugesaar T, Kontants H, Maki-Ikola O, et al. Selegiline delays the onset of disability in de novo Parkinsonian patients. *Neurology* 1998;51:520-5.
- 13 Kirolos C, Charlett A, Bowes SG, Purkiss AG, O'Neill CJA, Weller C, et al. Time course of physical and psychological responses to selegiline monotherapy in newly diagnosed, idiopathic parkinsonism. *Eur J Clin Pharmacol* 1996;50:7-18.
- 14 Parkinson Study Group. Effect of lazabemide on the progression of disability in early Parkinson's disease. *Ann Neurol* 1996;40:99-107.
- 15 Olanow CW, Hauser RA, Gauger L, Malapira T, Koller W, Hubble J, et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1995;38:771-7.
- 16 Caraceni T, Musico M. Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease: a randomized multicenter study. *Parkinsonism Relat Disord* 2001;7:107-14.
- 17 Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science* 1989;245:519-22.
- 18 Larsen JP, Boas J, Erdal JE for the Norwegian-Danish Study Group. Does selegiline modify the progression of early Parkinson's disease? Results from a five-year study. *Eur J Neurol* 1999;6:539-47.
- 19 Przuntek H, Conrad B, Dichgans J, Kraus PH, Krauseneck P, Pergande G, et al. SELEDO: a 5-year long-term trial on the effect of selegiline in early parkinsonian patients treated with levodopa. *Eur J Neurol* 1999;6:141-50.
- 20 Myllyla VV, Sotaniemi KA, Vuorinen JA, Heinonen EH. Selegiline as initial treatment in de novo parkinsonian patients. *Neurology* 1992;42:339-43.
- 21 Myllyla VV, Heinonen EH, Vuorinen JA, Kilkku OI, Sotaniemi KA. Early selegiline therapy reduces levodopa dose requirement in Parkinson's disease. *Acta Neurol Scand* 1995;91:177-82.
- 22 Myllyla VV, Sotaniemi KA, Hakulinen P, Maki-Ikola O, Heinonen EH. Selegiline as the primary treatment of Parkinson's disease: a long-term double-blind study. *Acta Neurol Scand* 1997;95:211-8.
- 23 Parkinson Study Group. Effects of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989;321:1364-71.
- 24 Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993;328:176-83.
- 25 Parkinson Study Group. Mortality in DATATOP: a multicenter trial in early Parkinson's disease. *Ann Neurol* 1998;43:318-25.
- 26 Lees AJ, Katzschlager R, Head J, Ben-Shlomo Y on behalf of the Parkinson's Disease Research Group of the United Kingdom. Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. *Neurology* 2001;57:1687-94.
- 27 Ben-Shlomo Y, Churchyard A, Head J, Hurwitz B, Overstall P, Ockelford J, et al. Investigation by Parkinson's Disease Research Group of United Kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: further results of randomised trial and confidential inquiry. *BMJ* 1998;316:1191-6.

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