whole, P values at interim analyses would have to be considerably less than 0.01 to achieve significance with any of the common group sequential designs.³ Similarly, confidence intervals reported should be greater than 95%. Thus it is not clear that reports of significance are valid.

Finally, levodopa was given to all patients at a daily dose of 375 mg rather than adjusted according to clinical need. Microdialysis studies show that selegiline significantly increases brain dopamine concentrations in rodents after administration of levodopa.⁴ In our study, patients treated with selegiline required significantly less levodopa than patients taking levodopa alone. During the British study the median dose of levodopa was increased to 625 mg in the levodopa group but did not have to be changed in the patients taking levodopa plus selegiline despite their having comparable clinical benefits and increased dopaminergic side effects. Thus patients taking selegiline may have received much more levodopa than necessary, a factor that was related to increased mortality in the Prado study.⁵

We take the British report seriously and will continue to monitor mortality in our patients. Because of the reassuring findings of our study and the increasing evidence of possible neuroprotective benefits related to selegiline, however, we do not recommend that patients should stop taking selegiline on the basis of the results of the British study alone.

C WARREN OLANOW*

Professor, department of neurology

JAMES H GODBOLD*

Research associate professor, department of community medicine

Mount Sinai Medical Center,
Box 1137,
New York, NY 10029,
USA

WILLIAM KOLLER*

Professor

Department of Neurology,
University of Kansas,
Kansas City, KS 66160,
USA

*C Warren Olanow and William Koller have worked as consultants to, and have performed research sponsored by, Somerset Pharmaceuticals, which distributes selegiline in the United States. In addition, C Warren Olanow has lectured at conferences sponsored by Orion, which distributes selegiline in Europe. James H Godbold has no conflict of interest.

1 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. (16 December.)

2 Olanow CW, Hauser RA, Gauger L, Malapira T, Koller W, Hubble J, et al. A longitudinal double blind controlled study of the effect of deprenyl and levodopa on the progression of the signs and symptoms of Parkinson's disease. *Ann Neurol* 1995;38:771-7.

3 Fleming TR, Harrington DP, O'Brien PC. Designs for group sequential trials. *Control Clin Trials* 1984;5:348-61.

4 Brannan T, Prikhojan A, Martinez-Tica J, Yahr MD. In vivo comparison of the effects of inhibition of MAO-A versus MAO-B on striatal L-dopa and dopamine metabolism. *J Neural Transm* (in press).

5 Przuntek H, Welzel D, Blumner E, Danielczyk W, Letzel H, Kaiser HJ, et al. Bromocriptine lessens the incidence of mortality in L-dopa-treated parkinsonian patients: Prado study discontinued. *Eur J Clin Pharmacol* 1992;43:357-63.

Selegiline is effective and safe in early stages

EDITOR,—The safety of selegiline is being questioned in view of the unexpected findings of the Parkinson's Disease Research Group,¹ which contrast with previous reports of the drug's safety and efficacy.^{2,3} Treatment with selegiline alone in the early stage of Parkinson's disease was not an option in this trial, and the findings cannot be extrapolated to this indication. The effect of early selegiline on symptoms is well proved, though it was originally misinterpreted as neuroprotection. The drug's safety in the early period is confirmed by the fact that the survival curves overlap in the first two years in the research group's trial.

Later in the disease selegiline is used to diminish fluctuations in symptoms, particularly those due to end of dose fading. We note the trend towards lower disability scores in the study patients given selegiline. This supports the anecdotal impression of reduced disability and improved quality of life in patients given the drug, which may be more subtle than the rating scales used could show.

Anecdotally, many older patients have reduced the dose or stopped taking selegiline because of side effects (commonly psychological). Some find lower doses effective and better tolerated: a recent audit of our patients showed that a quarter took less than the 10 mg stated in the datasheet. One octogenarian has found by personal experimentation that a daily dose of 1.25 mg (half a 5 mg tablet on alternate days) is sufficient to maintain control. If he omits the drug his control deteriorates after several days, to be re-established within days of his resuming the drug.

We are unable to find sufficient pharmacokinetic, pharmacodynamic, or safety data on long term treatment in aging patients, but one of us has suggested that further attention should be focused on these aspects since we may be using too high a dose for too long.⁴ Possible explanations of the findings of the Parkinson's Disease Research Group include the loss of monoamine oxidase B selectivity, the effects of selegiline's amphetamine metabolites, and interactions with other drugs.⁵

Until further analysis of these mortality data is available it would be wrong to deny patients the benefit of this drug, though perhaps it should be used more carefully than hitherto. Its continued use, especially in older patients, merits further study (including an assessment of its effect on quality of life), as does the investigation of lower doses.

D G MACMAHON*

Consultant physician

Corwall Healthcare Trust,
Barncoose Hospital,
Redruth,
Corwall TR15 3ER

R BLAND*

Consultant physician

*D G MacMahon is chairman of the Parkinson's disease special interest group of the British Geriatrics Society and has been paid for advice by Roche Products, DuPont Pharma, SmithKline Beecham, Britannia Pharmaceuticals, and Scherer DDS. Both authors have received support and educational grants to attend meetings from several pharmaceutical companies and have participated in research trials with some of the above companies. Both authors participated in the Parkinson's Disease Research Group's trial.

1 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. (16 December.)

2 Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl Med J* 1989;321:1364-71.

3 Parkinson Study Group. Effect of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl Med J* 1993;328:176-83.

4 MacMahon DG. The use of selegiline in elderly patients: current indications and future potential. *Reviews in Contemporary Pharmacotherapy* 1992;3:77-85.

5 Johnson FN, Sandler M. The pharmacology of selegiline. *Reviews in Contemporary Pharmacotherapy* 1992;3:51-65.

Parkinson's disease is rarely a primary cause of death

EDITOR,—As many patients with Parkinson's disease in Britain currently receive selegiline, any conclusions drawn from the Parkinson's Disease Research Group's study will have important implications.¹ The decision to close arm 2 of the trial (levodopa plus selegiline) may precipitate a change in prescribing practice. While the research group does not draw any firm conclusions about the causal relation between treatment with selegiline and excess mortality, many readers will nevertheless infer such a connection.

Several points are relevant. Most of the excess

deaths in arm 2 were directly attributed to Parkinson's disease itself, this information being obtained from death certificates. We were surprised to find that Parkinson's disease featured as a primary cause of death, as most patients with the disease die of its complications. Accurate determination of the cause of death can be revealing in attempts to determine a causal relation between treatment and outcome. The authors speculate that excess adverse events in the selegiline group (arm 2) may have resulted from deleterious effects on the cardiovascular and cerebrovascular systems. The data in their table 3, however, do not support this, with total deaths attributable to vascular disease overall being 20 in arm 1 (levodopa alone) and 21 in arm 2, with a relative death rate per 1000 patient years of 14.6 to 14.0 respectively.

It is well recognised that in a minority of patients initially treated for Parkinson's disease the diagnosis is subsequently revised.² We also recognise that data should be analysed on an intention to treat basis. With such a high proportion of patients being withdrawn from the study (52% in arm 1 and 45% in arm 2), interpretation of results with regard to causality becomes more hazardous. As groups were analysed on an intention to treat basis, roughly half of the patients could have been taking a non-trial drug and yet still figure in the analysis.

We believe that the assertions in Donald B Calne's editorial are premature.³ A considerable body of evidence shows oxidative stress and damage, in conjunction with mitochondrial dysfunction, in substantia nigra from patients with Parkinson's disease. Any case made against the use of selegiline in Parkinson's disease does not reflect the role that these biochemical abnormalities may have in the pathogenesis of dopaminergic cell death. We agree with the research group that data from further studies should be available for scrutiny before a radical change in prescribing practice is recommended.

MARK T SILVA

MRC research fellow

PAUL M WATTS

MRC research fellow

PETER JENNER

Director

Neurodegenerative Diseases Research Centre,
Pharmacology Group,
King's College London,
London SW3 6LX

1 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. (16 December.)

2 Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181-4.

3 Calne DB. Selegiline in Parkinson's disease. *BMJ* 1995;311:1583-4. (16 December.)

Selegiline may be toxic in presence of increased dopamine concentrations

EDITOR,—In the trial carried out by the Parkinson's Disease Research Group of the United Kingdom levodopa plus selegiline seemed to offer no clinical benefit over levodopa alone, although less levodopa was required for the combined treatment.¹ Mortality was significantly higher with the combined treatment. These findings contradict several earlier reports that selegiline, either alone or in combination, confers a beneficial effect in Parkinson's disease.

During the course of Parkinson's disease a progressive degeneration of nigrostriatal dopaminergic neurones occurs, with the remaining neurones becoming further stressed because of increased dopamine turnover (that is, the ratio of homovanillic acid to dopamine is increased). This increases oxidative stress. Reactive oxygen species can be generated from dopamine by both