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Commentary

Piecing together the puzzle of progression and mortality in Parkinson's disease

Connie Marras[1] & David Oakes[2]

[1]Toronto Western Hospital Movement Disorders Centre, University of Toronto and the Edmond J. Safra Program in Parkinson's Research, Toronto, Ontario, Canada and [2]Department of Biostatistics and Computational Biology, University of Rochester, Rochester, NY, USA

Parkinson's disease is a chronic, progressive disease that affects motor, autonomic, cognitive and emotional function and reduces lifespan. The rate of progression and survival in patients with Parkinson's disease is highly variable. The reasons for this are unknown, although some associations have been established. Greater baseline motor impairment, early cognitive disturbance and older age are the most consistently reported adverse prognostic factors; however, most of the heterogeneity remains unexplained [1, 2]. Summarizing this literature is challenging due to the multifaceted nature of Parkinson's disease and the many possible ways to describe progression of the condition.

In this issue of *British Journal of Clinical Pharmacology*, Vu *et al*. have undertaken a detailed examination of predictors of outcome in Parkinson's disease using a clinical trial cohort with long-term follow-up. In the original trial, subjects were randomized to groups receiving the monoamine oxidase B inhibitor selegiline (deprenyl) alone, vitamin E alone, both interventions or placebo, with the aim of determining whether or not either of the experimental agents could slow the progression of Parkinson's disease. Their analysis incorporates data from an average of 5 years and a maximum of almost 8 years of observation [3, 4].

Their analysis has several novel features. First, the vast majority of studies of prognosis in Parkinson's disease have examined predictors measured at a specific point in time. Few have examined the evolution of the disease as a predictor of later prognosis. Vu *et al*. have examined change in Unified Parkinson's Disease Rating Scale (UPDRS) scores, which they coin 'time course of disease status', as a predictor of progression. This is a novel approach that may help explain more of the variability in progression than cross-sectional measurements of any single or combined clinical or demographic feature. Second, their study incorporates multiple outcomes in the same study (survival, motor disability, cognitive impairment and depression), confronting the multifaceted nature of Parkinson's disease. This is important because it is unclear whether or not the determinants of each outcome are the same or not, and this can best be clarified by examining multiple outcomes in the same data set, thus controlling the variability of methods that is inevitably introduced between studies. Third, they examine treatment with selegiline as a predictor of progression and mortality. Selegiline is still used for its beneficial effect on the symptoms of Parkinson's disease. The relationship between selegiline and mortality in Parkinson's disease has been debated and remains unresolved [5]. Selegiline undoubtedly provides some short-term benefit, but its long-term effect remains unclear. Debate was sparked in 1995 when the Parkinson's Disease Research Group (UK) reported higher mortality in the arm of their clinical trial allocated to receive selegiline and levodopa compared with levodopa alone [6]. Autonomic dysfunction and resulting postural hypotension was postulated as a mechanism [7]. Subsequent studies have produced conflicting results [8–10], but have generally not revealed a higher mortality in individuals receiving selegiline.

The authors have performed many analyses. Their study found that older age and UPDRS scores were associated with a shorter time to reaching most of the endpoints they studied, in keeping with prior studies. They note that using the change of UPDRS scores ('time course of disease status') in their modelling was an important determinant of their results and a better predictor of future clinical events than baseline characteristics. This has useful implications for future studies of predictors of progression in Parkinson's disease, namely that additional insight may be gained from the inclusion of time-varying covariates that incorporate longitudinal information about disease or treatment status that changes over time.

There are drawbacks to this approach, however, which need to be taken into account when interpreting the

analyses. Changes in therapy may themselves be indicative of changes in disease status; a fact clearly recognized in the original deprenyl and tocopherol antioxidant therapy of Parkinson disease (DATATOP) study, which used as primary outcome the reaching of a level of disability that, in the view of the enrolling investigator, merited symptomatic therapy. The modelling approach described by Vu *et al*. views treatments as exogenous variables, disregarding their possible informativeness as to disease status.

The results concerning selegiline and mortality are particularly important to examine. Selegiline treatment had no apparent influence on the hazard for death when tested alone; however, when considered in conjunction with the change in UPDRS scores, there was an increased risk of death associated with selegiline treatment that was apparent during approximately the first 1.5 years of the study. This result persisted after adjusting for many other potential explanatory variables. However, the analytical capabilities of their modelling approach may have led the authors astray in their interpretation of the apparent effect of selegiline on mortality. The issue here is unrelated to the specifics of the computational details presented in the paper. Let us suppose, which may be a reasonable hypothesis, that selegiline has no effect, beneficial or harmful, on underlying disease progression or mortality, but that it does have a beneficial effect on certain symptoms, which is reflected in a reduction in measures such as the UPDRS. Let us further assume that there is a 'true' biological level of disease severity, which cannot be measured directly but is a strong predictor of mortality and which is correlated with UPDRS scores. Consider a large, well-conducted clinical trial in which patients are randomized equally to selegiline or to placebo and followed for a number of years. The two treatment groups will be comparable at baseline due to the randomization and, we have assumed, will have similar mortality rates. An unadjusted analysis, or one that adjusts only for baseline characteristics, will reflect this similarity. However, the two groups will differ in postbaseline measures of disease severity. The selegiline group will have lower follow-up UPDRS scores than the placebo group. What happens if we adjust the comparison of the mortality between the two groups for this imbalance in the follow-up measures? It will appear that the selegiline group, being less impaired than the placebo group, should also have lower mortality. If the mortality of the two groups is, in fact, the same, the adjusted analysis will lead to the false conclusion that selegiline has an adverse effect on mortality. The correct conclusion would be that the beneficial effects of selegiline on symptoms are not reflected in a beneficial effect on mortality. To put the same point another way, the adjusted analysis compares the mortality rates of subjects with the same measured level of disease severity in the two groups. But subjects in the selegiline group and the placebo group with the same measured level of total UPDRS (say, 30 points) will not really be comparable. Owing to the assumed symptomatic effect of selegiline, the underlying true disease severity in the former subject might be better reflected in a UPDRS score of (say) 35 points. As subjects with UPDRS scores of 35 points have higher mortality than subjects with UPDRS of 30 points, the adjusted analysis will suggest that selegiline has an adverse effect.

Undoubtedly, the real situation in the DATATOP study and its many follow-on protocols is much more complex than the one we have described above. But the suspicion remains that some, if not all, the excess mortality due to selegiline that the authors claim to have detected is artifactual. It would be helpful to see more details of the analysis, which includes selegiline as a time-dependent variable but does not adjust for disease course. We are told that the selegiline effect is not significant (using the criterion $P > 0.01$) but are not given the point estimate or confidence interval.

In conclusion, the paper shows the power of modelling methods in elucidating the course of progression in Parkinson's disease, but the qualitative interpretation of the selegiline effect is unclear. Specifically, the analysis does not show that selegiline, independent of its beneficial effect on disease status, is associated with an increased risk of death.

Competing Interests

Connie Marras has received honoraria from EMD Serono for participating in educational programmes and from Merck Serono for her services as a clinical trial site investigator. Her research co-ordinator has also been paid by Merck Serono for clinical trial services. David Oakes was the chief biostatistician for the DATATOP study and its extension protocols. In the period 1992–1996 he received research support from Somerset Pharmaceuticals for some of this work.

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CORRESPONDENCE
Dr Connie Marras, Toronto Western Hospital Movement Disorders Centre, 399 Bathurst St., Toronto, Ontario, Canada M5T 2S8.
Tel.: +1 416 603 6422
Fax: +1 416 603 5004
E-mail: connie.marras@utoronto.ca