Letter to the Editors

Authors' response to Marras and Oakes, 'piecing together the puzzle of progression and mortality in Parkinson's disease'

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Marras and Oakes [1] have suggested that our conclusions that selegiline is associated with increased mortality may be an artifact of our modelling assumptions [2]. The crux of their argument is that an observed Unified Parkinson's Disease Rating Scale (UPDRS) score measured while taking selegiline does not reflect the disease severity because of 'symptomatic' effects that improve the UPDRS but do not change the underlying risk of death. They conclude, therefore, that an increase in hazard of death associated with selegiline is an artifact due to inclusion of the symptomatic benefit when adjusting the hazard for disease severity based on UPDRS.

This supposition is a straw man. Marras and Oakes provide no evidence that UPDRS scores in the presence of selegiline do not reflect disease severity. In contrast, we have confirmed [3] the original observation reported by Oakes and his colleagues that selegiline slows the rate of progression of Parkinson's disease measured with UPDRS [4]. This slowing of progression of UPDRS has been shown to reduce the hazard of death, disability, dementia and depression [3].

One can consider an even larger straw man. Levodopa has a much larger symptomatic effect than selegiline, e.g. 12 UPDRS units for levodopa at 300 mg day⁻¹ and 1.2 units for selegiline at 10 mg day⁻¹ [5]. According to Marras and Oakes, this would mean that levodopa should be associated with an even larger increase in the hazard of mortality because the symptomatic benefit of levodopa lowers the UPDRS but does not change the risk of death. If the estimate of levodopa-associated hazard of death was conditional on the UPDRS score, there would be an excess of deaths predicted in the levodopa group at any given observed UPDRS. In fact, there is no evidence that levodopa increases the risk of death. Our own analysis of the risk of death, using the same model that we used for selegiline, showed no increase in hazard with levodopa after

adjusting for the UPDRS. This provides strong evidence against the symptomatic straw man conjecture.

Marras [6] previously reported that selegiline was not associated with increased risk of mortality. That analysis was based on an intention-to-treat analysis that ignored the treatment with selegiline, which was stopped and restarted several times in the various add-on trials in the DATATOP cohort. We found that selegiline use without adjusting for UPDRS was associated with a nonsignificant decrease in hazard ratio (0.71, with 95% confidence interval 0.48–1.07). A decrease in hazard is not unexpected, because the beneficial effects on hazard reflected in UPDRS are not taken into account. In contrast, adjusting for UPDRS revealed an increased hazard ratio for death (2.54, with 95% confidence interval 1.51–4.25).

Our finding that selegiline is associated with increased mortality is in agreement with the only prospective large controlled trial comparing treatment with and without selegiline [7]. In conclusion, we thank Marras and Oakes for identifying a possible criticism of our work, which has led us to understand even better that both the symptomatic and the disease-modifying changes in UPDRS caused by selegiline and levodopa contribute to understanding disease severity and its association with increased hazard of death.

This story is not finished because of the increasing use of rasagiline, the pharmacological brother of selegiline. It is hoped that those involved with evaluating the safety of rasagiline will look carefully for a similar increased hazard of death.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf

(available on request from the corresponding author) and declare: N.H., T.V. and J.N. had support from the Michael J. Fox Foundation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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RECEIVED

1 June 2012

ACCEPTED

15 July 2012

ACCEPTED ARTICLE PUBLISHED ONLINE

18 September 2012

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