

Title: **Study of Levodopa Response in Parkinson's Disease: Observations on Rates of Motor Progression.**

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ABSTRACT

Background: It is important to understand how the rate of motor progression in Parkinson's disease relates to dopaminergic treatment.

Methods: Prospective defined *off* state measurements of the levodopa response at 3-year intervals over a mean 13.3 year period in 34 patients enrolled prior to treatment initiation.

Results: Despite worsening of *on* and *off* scores, the magnitude of the levodopa short duration response is maintained as the disease progresses. A linear mixed effects regression analysis of *off* phase motor scores showed a yearly deterioration of 2.3% of the maximum disability score. Greater motor disability at the commencement of treatment was an independent predictor of faster progression. Demented patients had worse motor function than those without dementia ($P = 0.02$), and motor deficit appeared to accelerate towards the end of the disease course in patients who had died.

Conclusions: These observations should inform clinical trial design for drugs with possible neuroprotective properties.

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INTRODUCTION

Distinguishing Parkinson's disease (PD) from virtually all other degenerative disorders of the nervous system is a prolonged moderation of its chief clinical deficit by pharmacological means. This therapeutic advantage does, however, make it more difficult to measure the progression of the underlying disease. It also creates problems in the search for drugs which possess an even greater power—that of retarding the degeneration of neurons. All previous clinical trials have been hampered by an inability to discern disease modification from the symptomatic benefit, since the distinction largely relies on interpreting differences in objective motor scores.

This longitudinal observational study has now been in progress for more than 20 years. It was conceived to address the need to understand disease progression in terms of the effects of dopaminergic therapy. With a starting point before the initiation of treatment, serial defined *off* state levodopa test-doses have shown how drug treatment influences motor function at various points on the disease trajectory. This report concentrates on the rate of deterioration of motor scores and the factors that govern the temporal pattern of the disease.

METHODS

Detailed methodology including entry criteria are described in earlier publications of this study.^{1,2} A modified Webster scale (12 areas of motor function scored from 0 to 3 to give a maximum possible motor disability score of 36)³ was the chief motor assessment. A motor score was recorded before levodopa was started and at optimum treatment benefit during the next 6 months, with the initial drug response defined as the difference. At 3-year intervals, a researcher conducted defined *off* state levodopa test-dose studies on surviving subjects. Patients' usual morning levodopa tablets served as the test-dose (the mean levodopa dose for the latest tests was 178 ± 78 mg). Amplitude of the short duration motor response was *off* minus *on* score. The Folstein Mini Mental State Examination (MMSE)⁴ was performed with each assessment. Levodopa equivalent daily doses were calculated using standard conversion factors.⁵ This study has institutional research ethics approval.

Statistical methods

Group comparisons were made using the two-tailed *t*-test or Mann Whitney *U* test. The rate of progression of motor disability was calculated by linear mixed effects regression (LMER) analysis of *off* motor scores for each patient against their disease duration using the statistical package nlme in R.^{6,7} To identify clinical factors that predict progression, we tested age and motor disability at the commencement of treatment, motor subtype and initial drug response for significance as fixed effects in univariable regression. Dementia was included as a fixed effect to evaluate for group differences. We examined for interactions (product terms) between disease duration and each factor. All significant factors and interactions were placed in a multivariable model of motor disability to test for independence. R^2 was calculated using lmmfit.⁸

RESULTS

The serial motor scores of all 34 patients are displayed in Figure 1A. It reflects both progressive recruitment to the study and drop out after death. The mean age at treatment initiation was 64.2 ± 11.3 years. Clinical ascertainment has been complete for the last 18 years. A mean disease duration of 13.3 ± 6.9 years has been studied; the mean levodopa treatment duration for the 5 surviving patients was 19.9 ± 1.4 years. Mean levodopa equivalent daily dose for survivors was 797 ± 424 mg.

The mean initial drug response, expressed as percentage reduction of the pre-treatment modified Webster score, was 46%. Comparing first and last test-doses for patients completing two or more measurements ($n = 24$), both *off* ($P < 0.0001$) and *on* ($P < 0.0001$) scores progressed but the mean response amplitude did not change significantly. The mean of the levodopa test-dose responses shown in Figure 1A was 37% of the *off* score, or 16% of the maximum disability score.

Rate of progression of motor disability

A line of best fit for pooled *off* phase scores for the entire cohort shown in Figure 1A gives an annual rate of worsening of 2.0% of maximum disability score. Figure 1B shows the gradient from the regression model of motor progression in patients who had at least two levodopa test-doses. The annual rate of progression of *off* motor disability by this method equates to 2.3%.

Greater motor disability at commencement of treatment independently predicted faster progression of the *off* score. Both age at commencement of treatment and dementia had statistically interdependent interactions with disease duration on progression. Table 1 summarises the results of the multivariable model. Motor subtype at diagnosis and initial levodopa response had no significant effect on the progression of motor disability.

Cognitive decline and motor disability

Of 14 patients who registered a MMSE score of less than 24, 12 have died. There was no significant difference between demented and non-demented patients for age at diagnosis, pre-treatment motor score or initial levodopa response. Regression analysis showed that the patients who developed dementia had faster *off* motor progression than those without dementia. Comparing the final modified Webster scores in subjects who had been followed for more than 12 years since levodopa commencement, both *off* and *on* scores were significantly worse for those with dementia ($P = 0.02$). The development of dementia did not affect the mean levodopa response amplitude.

Serial motor scores in patients who have died

Twenty-seven patients have died. The mean interval from diagnosis to death was 12.2 ± 6.9 years.

Figure 2 contains information on 24 patients who had at least one levodopa test-dose assessment.

The results are aligned at time of death to reveal the pattern of levodopa response late in the disease course. A curve of best fit for *off* phase motor scores suggests accelerating motor disability in the final segment of the disease course. But the final motor assessments, performed on average 2 years before death, show that the levodopa response amplitude is maintained in the advanced disease state.

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DISCUSSION

As shown in Figure 1A, the defined *off* state measurements give the best indication of progression, whereas scoring of prevailing motor function without regard to medication response would reduce accuracy. The gradient of deterioration of *off* phase scores in this figure is 2.0% of the maximum disability score per annum (p.a.). The line of best fit is subject to some distortion because the composite values derived from later data are dominated by a subset of survivors with more benign disease patterns. The rate of 2.3% p.a. obtained from the LMER (Figure 1B) accounts for individual variation in repeated measures and for different durations of follow up. We believe this to be the more reliable estimate of the rate of progression. The motor disability at commencement of treatment was its only independent predictor. Younger age at commencement of treatment predicts slower progression, statistically interdependent with disease duration.

Previous estimates of the rate of motor deterioration, though spanning shorter time intervals and without rigorous levodopa test-dose methods, have arrived at roughly similar figures. Yearly motor deterioration of between 1.4 – 3.1% has been reported from longitudinal studies over 3 – 5 years.⁹⁻¹² A recently published study of 129 patients for 5 years found that the annual rate of decline was 2.3%.¹³

Our findings on the rate of motor progression show the impediment faced by clinical studies that are attempting to detect drug neuroprotective effects over a one- or two-year trial period. An agent that is capable of completely arresting the disease would cause a 2 – 3% deviation from the trajectory of a placebo control group over one year. A drug that retarded progression by 10%, undeniably a major therapeutic breakthrough, would cause the line to deviate by only 0.2 – 0.3% p.a. But the symptomatic effect of dopaminergic therapy consistently runs at around 16% of the maximum disability score for the short duration levodopa response alone, meaning that a modest symptomatic effect of such an agent would be likely to obscure a disease modifying one in a clinical trial of less than a decade. Or to express the problem differently—a trial with the research aims and time-frame of the ADAGIO study¹⁴ would, whatever research tactics were employed, be attempting to detect a neural protection effect of less than the smallest unit of objective measurement (a single point on the UPDRS motor scale), whereas symptomatic dopaminergic properties of rasagiline might change the score by a number of points.

Inferences about the correlation between the rate of motor deterioration and loss of dopaminergic neurons in the substantia nigra can be drawn. Four pathological studies have employed cell counting techniques to produce plots of residual cell count against disease duration.¹⁵⁻¹⁸ The derived gradient of cell loss ranged between 1.2% and 1.9% of control cell count per year. These calculations rely on assumptions that there was a common rate of progression and that patients who died earlier had not reached the natural end of their disease course, both questionable propositions. The studies are in broad agreement that patients who died soon after diagnosis had nigral counts roughly 50% of those of controls, and that the disease end-stage corresponded to a nigral population that had fallen to around 20%. Over an average disease course of 12-15 years, an annual rate of nigral cell loss of between 2% and 3%, in line with our estimate of motor deterioration, seems likely. While nigral degeneration probably sets a roughly linear rate of clinical progression for most of the disease course, Figure 2 suggests that rostral accumulation of Lewy pathology¹⁹ may contribute to a late acceleration of disability.

Some limitations of the study are clear to see—the modest size of the sample and the use of an outmoded motor scoring system because of a decision taken 25 years ago. It is possible that the levodopa challenges are not a consistent measure of dopaminergic therapy because of changes that have occurred over time in peripheral levodopa pharmacokinetics, the ratio of short- to long-duration response, or the placebo effect. The study's main strengths are its duration and the high rate of retention of subjects. The power of dopaminergic therapy is still its most important message. Motor deficits increase and non-motor features of the advanced disease stage, such as hallucinations and cognitive impairment, eventually develop. But the magnitude of the levodopa motor response does not really wane. Almost 50 years after George Cotzias showed the way to practical levodopa therapy for PD,^{20,21} it is still a miracle that the drug works so well for so long.

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DOCUMENTATION OF AUTHOR ROLES

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Research project: organization and execution

Statistical analysis: execution, review and critique

Manuscript: writing of first draft, review and critique

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Manuscript: review and critique

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Statistical analysis: review and critique

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Manuscript: review and critique

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Expert Testimony: none

Employment: Monash Health

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Other: none

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Partnerships: none
Honoraria: none
Grants: none
Intellectual Property Rights: none
Expert Testimony: none
Employment: Monash Health, private neurological consulting practice.
Contracts: none
Royalties: none
Other: none

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TABLE AND FIGURE LEGENDS

Table 1:

Summary of the multivariable regression factors that determine the progression of motor disability.

The R^2 of this model was 0.74.

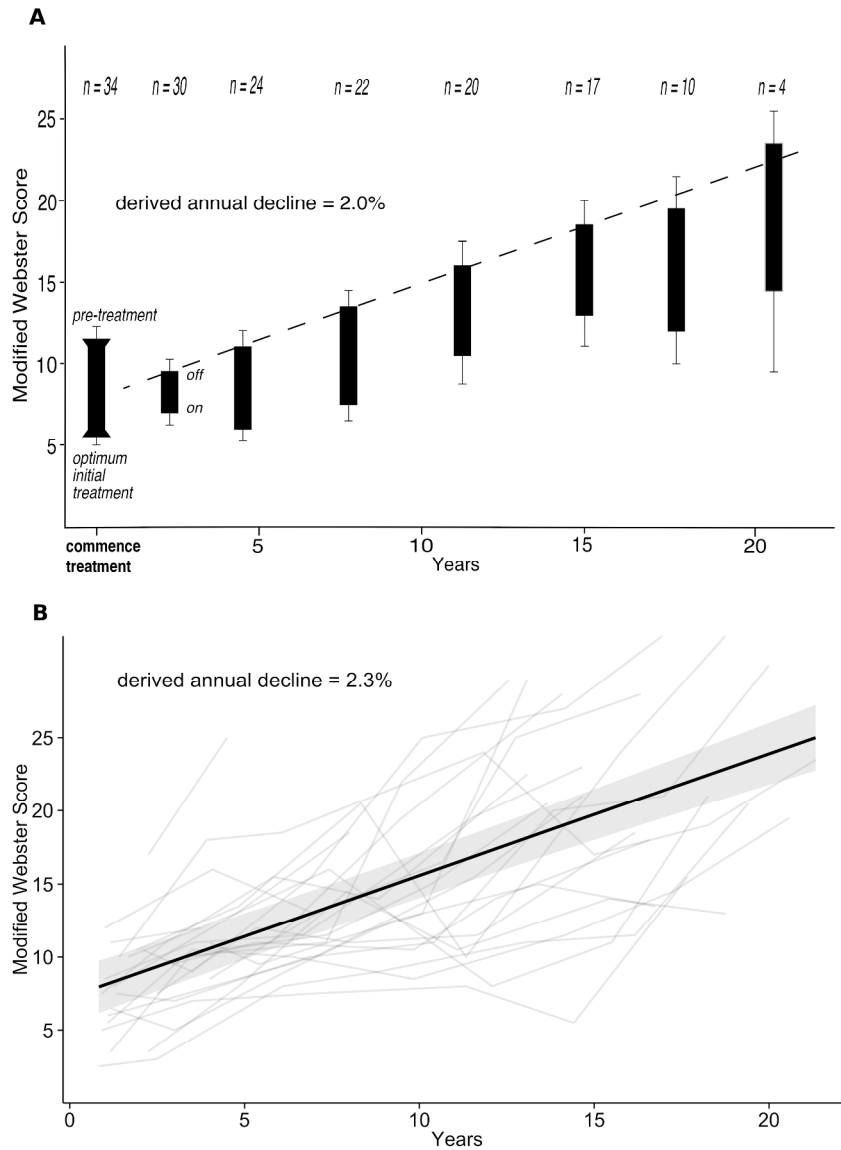
Figure 1: Rate of motor progression.

(A). Trapezium-ended boxes: initial drug response. Rectangular boxes: levodopa test-dose measurements. Line of best fit for mean *off* scores.

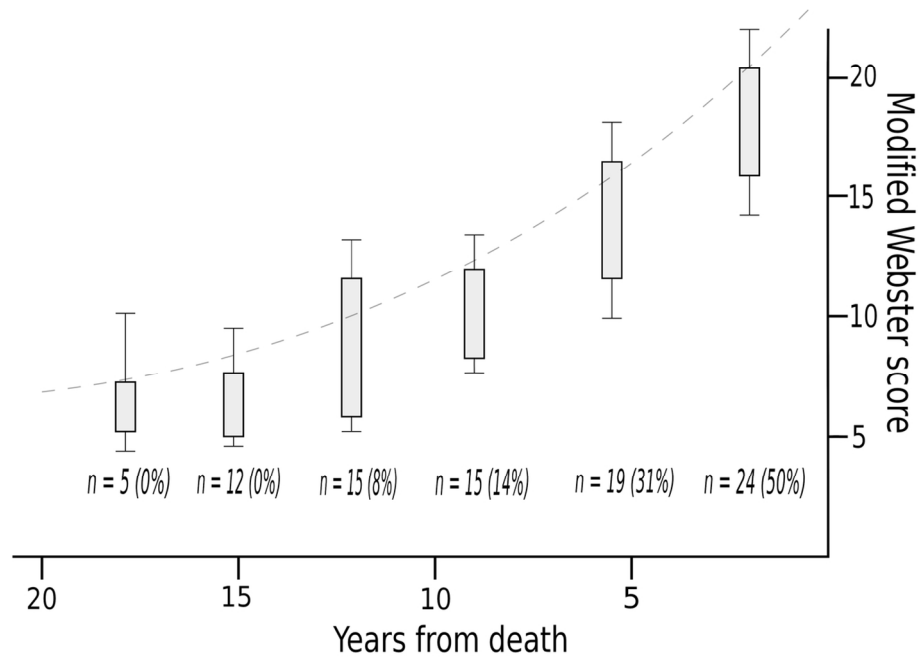
(B). The LMER model (solid line) of individual *off* scores (faint lines). Shading of 95% confidence interval.

Figure 2:

Serial mean levodopa test-dose responses aligned from time of death. Number of patients (percentage demented) shown for each stage. Hypothetical curve for mean *off* scores.



Rate of motor progression.
 (A). Trapezium-ended boxes: initial drug response. Rectangular boxes: levodopa test-dose measurements. Line of best fit for mean off scores.
 (B). The LMER model (solid line) of individual off scores (faint lines). Shading of 95% confidence interval.
 247x337mm (300 x 300 DPI)



Serial mean levodopa test-dose responses aligned from time of death. Number of patients (percentage demented) shown for each stage. Hypothetical curve for mean off scores.
123x88mm (300 x 300 DPI)

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TABLE

Table 1:

Factors	β coefficient	95% Confidence Interval	P value
Initial Severity	0.64	0.43 – 0.85	<0.01
Disease duration & age at commencement of treatment	0.01	0.001 – 0.02	0.03
Disease duration & Demented	0.58	0.35 – 0.81	<0.01

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The mean initial drug response, expressed as percentage reduction of the pre-treatment **disability modified Webster** score, was 46%. Comparing first and last test-doses for patients completing two or more measurements ($n = 24$), both *off* ($P < 0.0001$) and *on* ($P < 0.0001$) scores progressed but the mean response amplitude did not change significantly. The mean of the levodopa test-dose responses shown in Figure 1A was 37% of the *off* score, or 16% of the maximum **disability possible** score.

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commencement, both *off* and *on* scores were significantly worse for those with dementia ($P = 0.02$).

The development of dementia did not affect the mean levodopa response amplitude.

Serial motor scores in patients who have died

Twenty-seven patients have died. The mean interval from diagnosis to death was 12.2 ± 6.9 years.

Figure 2 contains information on 24 patients who had at least one levodopa test-dose assessment.

The results are aligned at time of death to reveal the pattern of levodopa response late in the disease course. A curve of best fit for *off* phase motor scores suggests accelerating motor disability in the final segment of the disease course. But the final motor assessments, performed on average 2 years before death, show that the levodopa response amplitude is maintained in the advanced disease state.

Accepted Article

DISCUSSION

As shown in Figure 1A, the defined *off* state measurements give the best indication of progression, whereas scoring of prevailing motor function without regard to medication response would reduce accuracy. The gradient of deterioration of *off* phase scores in this figure is 2.0% of the maximum possible disability score per annum (p.a.). The line of best fit is subject to some distortion because the composite values derived from later data are dominated by a subset of survivors with more benign disease patterns. The rate of 2.3% p.a. obtained from the LMER (Figure 1B) accounts for individual variation in repeated measures and for different durations of follow up. We believe this to be the more reliable estimate of the rate of progression. The motor disability at commencement of treatment was its only independent predictor. Younger age at commencement of treatment predicts slower progression, statistically interdependent with disease duration.

Previous estimates of the rate of motor deterioration, though spanning shorter time intervals and without rigorous levodopa test-dose methods, have arrived at roughly similar figures. Yearly motor deterioration of between 1.4 – 3.1% has been reported from longitudinal studies over 3 – 5 years.⁹⁻¹² A recently published study of 129 patients for 5 years found that the annual rate of decline was 2.3%.¹³

Our findings on the rate of motor progression show the impediment faced by clinical studies that are attempting to detect drug neuroprotective effects over a one- or two-year trial period. An agent that is capable of completely arresting the disease would cause a 2 – 3% deviation from the trajectory of a placebo control group over one year. A drug that retarded progression by 10%, undeniably a major therapeutic breakthrough, would cause the line to deviate by only 0.2 – 0.3% p.a. But the symptomatic effect of dopaminergic therapy consistently runs at around 16% of the maximum disability score for the short duration levodopa response alone, meaning that a modest symptomatic effect of such an agent would be likely to obscure a disease modifying one in a clinical trial of less than a decade. Or to express the problem differently—a trial with the research aims and time-frame of the ADAGIO study¹⁴ would, whatever research tactics were employed, be attempting to detect a neural protection effect of less than the smallest unit of objective measurement (a single point on the UPDRS motor scale), whereas symptomatic dopaminergic properties of rasagiline might change the score by a number of points.

Inferences about the correlation between the rate of motor deterioration and loss of dopaminergic neurons in the substantia nigra can be drawn. Four pathological studies have employed cell counting techniques to produce plots of residual cell count against disease duration.¹⁵⁻¹⁸ The derived gradient of cell loss ranged between 1.2% and 1.9% of control cell count per year. These calculations rely on assumptions that there was a common rate of progression and that patients who died earlier had not reached the natural end of their disease course, both questionable propositions. The studies are in broad agreement that patients who died soon after diagnosis had nigral counts roughly 50% of those of controls, and that the disease end-stage corresponded to a nigral population that had fallen to around 20%. Over an average disease course of 12-15 years, an annual rate of nigral cell loss of between 2% and 3%, in line with our estimate of motor deterioration, seems likely. While nigral degeneration probably sets a roughly linear rate of clinical progression for most of the disease course, Figure 2 suggests that rostral accumulation of Lewy pathology¹⁹ may contribute to a late acceleration of disability.

Some limitations of the study are clear to see—the modest size of the sample and the use of an outmoded motor scoring system because of a decision taken 25 years ago. It is possible that the levodopa challenges are not a consistent measure of dopaminergic therapy because of changes that have occurred over time in peripheral levodopa pharmacokinetics, the ratio of short- to long-duration response, or the placebo effect. The study's main strengths are its duration and the high rate of retention of subjects. The power of dopaminergic therapy is still its most important message. Motor deficits increase and non-motor features of the advanced disease stage, such as hallucinations and cognitive impairment, eventually develop. But the magnitude of the levodopa motor response does not really wane. Almost 50 years after George Cotzias showed the way to practical levodopa therapy for PD,^{20,21} it is still a miracle that the drug works so well for so long.

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Statistical analysis: execution, review and critique

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TABLE AND FIGURE LEGENDS

Table 1:

Summary of the multivariable regression factors that determine the progression of motor disability.

The R^2 of this model was 0.74.

Figure 1: Rate of motor progression.

(A). Trapezium-ended boxes: initial drug response. Rectangular boxes: levodopa test-dose measurements. Line of best fit for mean *off* scores.

(B). The LMER model (solid line) of individual *off* scores (faint lines). Shading of 95% confidence interval.

Figure 2:

Serial mean levodopa test-dose responses aligned from time of death. Number of patients (percentage demented) shown for each stage. Hypothetical curve for mean *off* scores.



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