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Inferring the long duration response to levodopa in Parkinson's disease

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ABSTRACT

Introduction: The long duration response to levodopa in Parkinson's disease outlasts drug elimination by days to weeks. Though a substantive part of anti-parkinsonian motor benefit, it cannot easily be observed.
Objectives: To infer the magnitude of the long duration response during the first decade of Parkinson's disease and identify factors that influence it.
Methods: Serial practically defined *off* scores of 24 patients from a longitudinal study of levodopa short duration response were used to establish their rate of motor progression. A line of notional untreated disability (as if drug treatment had never been given) with the same progression gradient was the basis for calculation of the long duration response. Predictors of mean long duration response amplitude were identified using a multiple linear regression model.
Results: Over a mean treatment period of 16.6 ± 4.4 years, annual increase in motor disability was 2.3% of the maximum score. The long duration response composed 49% of total levodopa response during the first decade of treatment, and this proportion was significantly higher soon after commencing levodopa ($p = 0.001$). Higher pre-treatment motor score ($r = 0.60$) and lower MMSE ($r = 0.60$) were the main predictors of a larger long duration response. There was little correlation between long and short duration responses.
Conclusions: Long duration responses contribute almost half of the total levodopa benefit during the first decade of treatment. An appreciation of both long and short duration components of drug symptomatic effects is important in clinical trial design to investigate possible neuroprotective treatments.

1. Introduction

The long duration response (LDR) to levodopa is a motor benefit in a patient with Parkinson's disease (PD) that outlasts the elimination of the drug by days to weeks. Right at the beginning of the era of dopaminergic therapy, George Cotzias and his colleagues were aware of it. They noted that after prolonged use of D,L-dopa, it took 4–14 days for motor state to return to baseline when the drug was ceased [1]. Two previous levodopa withdrawal studies have estimated the LDR at about one third of the total levodopa response [2,3]. In the first year of treatment, the majority of motor benefit comes from the LDR [4]. Drugs other than levodopa, dopamine receptor agonists for instance, have LDRs as well [5,6].

The magnitude of the initial levodopa LDR can be estimated by comparing motor disability immediately before treatment with when the drug is withheld overnight after weeks to months of treatment [7]. Thereafter, it is only possible to measure it by prolonged drug withholding, impractical because of the difficulties in managing the loss of motor benefit and the delay in restoring it. There is uncertainty about the duration of withdrawal needed to reveal fully a LDR. LDRs are the 'dark matter' of anti-parkinsonian motor benefit, substantive but not directly observable.

Using serial measurements of practically defined *off* states in a cohort of PD patients studied longitudinally, we devised a method to estimate the LDR. By determining the gradient of progression of *off* scores, it is possible to infer the level of disability if drug treatment had never been commenced and to quantify the motor benefit that is not captured by *on* and *off* phase assessments. In presenting another way of evaluating the LDR, we aimed to remind clinicians and researchers of the scale of this often under-appreciated component of symptomatic drug treatment for PD.

2. Methods

Thirty-four patients with PD were recruited to a longitudinal study of the levodopa motor response that began almost 30 years ago.

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Detailed methodology including entry criteria are described in earlier publications [8,9]. A modified Webster scale (12 areas of motor function scored from 0 to 3 to give a maximum disability score of 36) [10] was the chief motor assessment. A motor score was recorded before levodopa was started and at optimum treatment response during the next 6 months, with the initial drug response being the difference. At 3-year intervals, a researcher conducted practically defined *off* state levodopa test-dose assessments on surviving subjects. Levodopa was administered while fasting and after withholding of other medication, with the *on* state defined as the maximum improvement over the subsequent 30–90 min. Amplitude of the short duration response (SDR) was calculated as *off* minus *on* score. The Folstein Mini Mental State Examination (MMSE) [11] was performed at each assessment. Patients were classified for the presence of early motor fluctuations (during the first 5 years of levodopa treatment) [9], and for motor subtype from their modified Webster scale scoring [12]. Two patients had been lost to follow up prior to their first test-dose assessment; thereafter, all patients were followed to death or the end of the study period. Levodopa equivalent daily doses (LEDD) were calculated using standard conversion factors [13]. This study has institutional research ethics approval.

2.1. Notional untreated disability and LDR calculation

In patients with at least two test-dose assessments, individual gradients of *off* state motor progression were calculated using linear least squares regression. A second line with an identical gradient was drawn from each subject's pre-treatment motor score to represent their notional untreated disability (hypothetical progression as if anti-parkinsonian treatment had never been commenced). Fig. 1 shows these parallel lines on a graph of mean results from all participants.

The LDR amplitude was calculated by subtracting the *off* score from the notional untreated disability score. This was done only for the 3 test-dose assessments performed within the first 10 years of treatment because of uncertainty about extrapolation beyond this point. The test dose for these assessments was levodopa 200mg/carbidopa 50 mg. Total levodopa response was defined as the sum of the SDR and LDR.

2.2. Statistical methods

A linear regression model of individual mean LDRs was employed to identify clinical variables that predict LDR amplitude. Age of disease onset, pre-treatment motor score, MMSE, LEDD, mean SDR, disease phenotype and presence of early motor fluctuations were the factors of interest. We used the backward elimination method and ANOVA to compare model fit and we tested for interactions using product terms.

We also examined disease progression with a linear mixed-effects regression model of *off* state scores, using treatment duration as a fixed effect. We estimated random effects for subjects to account for repeated measures and differing durations of follow-up.

Descriptive statistics are reported as mean ± standard deviation. Continuous non-parametric variables were compared using the Wilcoxon signed rank test. Data analysis was performed using R statistical software [14] and the packages nlme [15] and ggplot2 [16].

3. Results

Twenty-four patients had two or more test-dose assessments, which allowed estimation of their gradient of *off* state progression. Their mean age at PD diagnosis was 61.1 ± 11.6 years; time from diagnosis to treatment initiation was 0.6 ± 2.1 years. The mean follow-up duration for these patients was 16.6 ± 4.4 years. Nine had a tremor-dominant phenotype; 14 had developed early motor fluctuations. Only 5 patients were still alive at the end of the study period. Mean treatment duration for those who had died was 15.2 ± 5.0 years (range 5.2–20.3). At the final assessment performed during the first treatment decade, the mean MMSE score was 26 ± 5.4 and the mean LEDD was 628 ± 305 mg. Although all patients began with levodopa monotherapy, by the end of this 10-year period other drugs had also been used: bromocriptine (2), pergolide (2), deprenyl (4), benztropine (1).

3.1. Motor progression & LDR amplitude

Fig. 1 shows the pooled initial and test-dose motor scores for all 34 patients originally enrolled in the study, with numbers of survivors at each assessment. Fig. 2 shows the 24 individual lines of best fit for progression of motor disability. According to the linear mixed effects regression model, annual progression in disability for this group was 2.3% of maximal motor disability.

Using individual notional untreated disease trajectories, we calculated mean LDR amplitude at the first defined *off* state assessment as

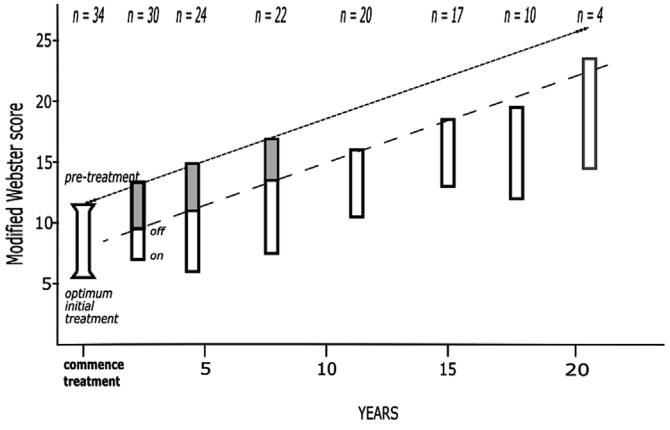

Fig. 1. Pooled motor scores for all original 34 subjects. This figure is presented to show the survival profile of the original cohort and the geometry used to derive the LDR. The actual LDR calculations use the individual off progression lines shown in Fig. 2. Trapezium-ended box: upper pole, pre-treatment motor score; lower pole, optimum initial treatment response. White rectangular boxes: mean levodopa SDR amplitudes. Long-dashed line of best fit for mean *off* phase scores. Short-dashed line for notional untreated disease trajectory; gray shaded boxes show how the LDR is inferred.

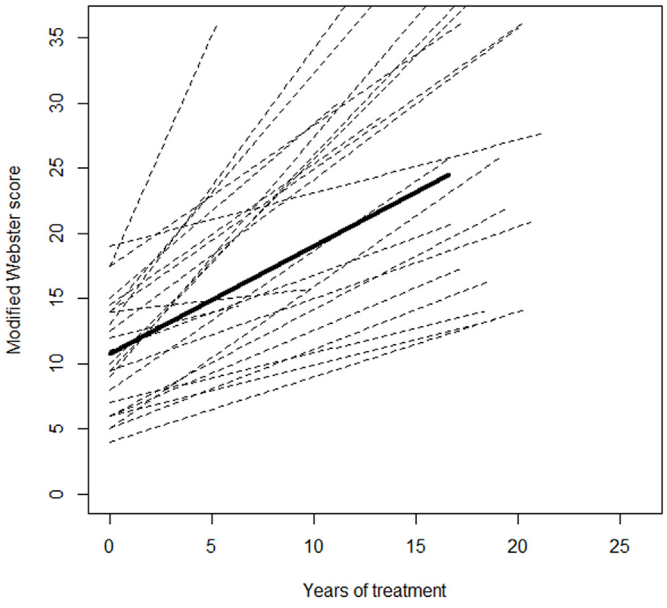

Fig. 2. *Off* motor score gradients. Dashed lines of best fit from each subject's *off* motor scores. Solid line with gradient of 2.3% p.a. obtained from the linear mixed effects regression model of all *off* scores. The lengths of lines are proportional to treatment durations.

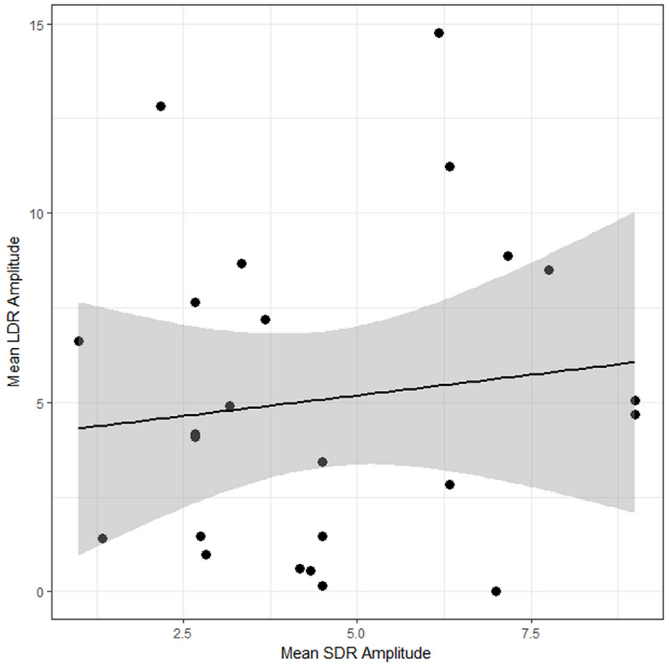

Fig. 3. Mean short and long duration response amplitudes. Each data point represents mean SDR and LDR for each subject's first decade of treatment. There is little correlation ($r = 0.12$, $p = 0.58$). 95% confidence interval shaded in gray.

4.8 ± 3.6, which is equivalent to 62% of the total motor response. The mean of all LDR amplitudes calculated for the first decade of treatment was 5.1 ± 4.2 or 49% of the total motor response. There was a significant reduction in the contribution of the LDR to total motor response between the first and the last of these estimations (p = 0.002, r = −0.44). There was no significant change in the absolute magnitude of the LDR. The SDR amplitude demonstrated a significant increase over the same time interval (2.7 to 6.1, p < 0.05).

3.2. Predictors of LDR amplitude

Only higher pre-treatment motor score ($r = 0.60$, $p = 0.001$) and lower MMSE ($r = 0.60$, $p = 0.001$) correlated with LDR amplitude. In a two-factor regression model, pre-treatment disability and MMSE predicted 65% of the variance in mean LDR. Although mean SDR (Fig. 3) and motor fluctuations did not correlate with mean LDR, their addition as factors improved the regression model of mean LDR (four-factor model adjusted $R^2 = 0.74$, $F(21,19) = 4.50$, $p = 0.03$), and were thus included in the final model (Table 1). LEDD, age at diagnosis and disease phenotype were not significant predictors and there were no interactions.

4. Discussion

Overall, the LDR composed about half of the total levodopa motor response during the first treatment decade, comparable to the size of the SDR and somewhat larger than previous estimates. The percentage was significantly higher early in the disease course, starting at 62% for the first test-dose measurement and falling to 42% by the final reckoning. As shown by the multiple regression analysis and Fig. 3, there is surprisingly little correlation between the sizes of LDRs and SDRs. The strongest predictors of a large LDR were pre-treatment disability and reduced MMSE score, each of these accounting for about 35% of the variation of the mean LDR. Greater initial motor deficit and early cognitive decline both imply a heavier burden of Lewy pathology in the brain, yet these patients appear to have a greater early LDR. Age at diagnosis had no significant effect. The reduction in the LDR over time has been suggested to correlate clinically with the emergence of motor fluctuations, which are thought to be driven by the SDR [7]. The trend towards lower LDRs and higher SDRs that we found over the first treatment decade is broadly consistent with this.

Our method for calculating the LDR takes advantage of longitudinal defined *off* state measures of the SDR. It relies on several important assumptions. That disease progression is linear during the first part of the disease course and that the rate of decline is 2–3%. Three other longitudinal studies, though not employing rigorous levodopa test-dose methods, estimated annual deterioration at between 1.4% and 3.1% [17–19]. Serial motor scores over 8 years in each of these studies support the assumption of linear progression in the first decade. We presuppose that commonly used symptomatic treatments do not modify the underlying disease process. On this depends the validity of a notional untreated disability line that runs from the pre-treatment motor score in parallel to the trajectory of the defined *off* phase scores. The best interpretation of available evidence is that levodopa, the dominant anti-parkinsonian drug in this study, has a powerful but purely symptomatic effect on PD with no influence on the underlying rate of progression.

There are other methodological uncertainties in our approach to the LDR. The SDR measures that form the basis for the ascertainment of LDR have their own margin of uncertainty. Defined *off* states at the start of the day may incorporate a sleep benefit element. A minority of patients were taking dopamine receptor agonists or monoamine oxidase inhibitors with longer durations of action than levodopa. The first calculation after commencement of drug treatment, which returned the largest LDR result, is evidence that the use of polypharmacy did not cause the LDR to be significantly over-estimated. At this point, 22 of 24 subjects were on levodopa monotherapy. The size of the cohort of patients is modest, though the strengths of this study are its prospective character and its timespan. Progression rates were established by multiple measurements over many years in some subjects, with correspondingly robust determinations of their LDRs. Age of onset and duration of PD were comparable to other surveys of the entire disease course [20,21].

Large clinical trials of possible neuroprotective agents have struggled to discern symptomatic motor benefit from an effect on the natural disease course [22–24]. Several LDR considerations are relevant. Trial designs have incorporated questionable assumptions about wash-in and wash-out times for symptomatic effects [23,24]. Wash-in is an estimate of the time taken for both SDR and LDR to fully develop. Wash-out, on the other hand, is mainly an estimate of time taken for a LDR to decay, since SDRs of most drugs can be predicted to follow their pharmacokinetic elimination curve after discontinuation. Another impediment to neuroprotective drug trials is the difference in magnitude between symptomatic and disease modifying effects. 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 1 year. A drug that retarded progression by 20% would cause the line to deviate by only 0.4%–0.6% p.a. But the symptomatic effect of dopaminergic therapy runs at around 22% of the maximum disability score for the combined SDR and LDR. In a clinical trial of several years, even modest variability of symptomatic effects may obscure a disease modifying one. Such variability could come from standard therapy or from an inherent

Table 1
Multiple regression factors that predict mean LDR amplitude.

Disease factors	*b* coefficient	95% confidence interval	*p* value
Pre-treatment motor score	0.67	0.43: 0.91	< .001
MMSE	−0.44	−0.62: −0.27	< .001
Motor fluctuations	2.86	0.42: 5.30	.024
Mean SDR amplitude	−0.80	−1.38: −0.22	.009

The adjusted R^2 of this model was 0.74.

symptomatic effect of a putative neuroprotective agent. At least the SDR can be measured by a defined *off* phase test dose method. There is no practical way of directly measuring variations of a LDR over time. Until a better biomarker for pathological progression in PD is found, proof of neuroprotective effect must depend on measurement of the rate of deterioration of motor disability scores. Simple, placebo-controlled study designs of long (5–10 years) duration may be the best approach. Standardisation of anti-parkinsonian drug therapy and avoidance of delayed drug start or withdrawal protocols should reduce the risk of confounding LDR effects.

The origin of the LDR is not well understood, and hypotheses involving 'storage' of administered levodopa or dopamine receptor sensitization are problematic [25]. An explanation involving dopamine-induced plasticity in the striatum and its cortical connections has been proposed, with effects on motor learning and reward weighting, resulting in enhanced motor 'vigour' [25,26]. This evokes a LDR that is qualitatively different from the SDR, perhaps capable of modifying a patient's perception of their disability and day-to-day life. The longevity of the LDR would be consistent with such a 'downstream' post-synaptic mechanism.

On balance though, we prefer a simpler explanation of a dopaminergic response in the absence of dopaminergic drugs—that dopamine release from the surviving nigral neurons is responsible for the LDR. A residual population of nigral cells is important, probably essential, to the dopaminergic drug response. Roughly 50% can be lost and the dopaminergic nigrostriatal system has sufficient functional reserve to forestall motor deficit [27]. Thereafter, signs of parkinsonism appear and progress up to the point that drug treatment is commenced. But once an LDR is established, Fig. 1 shows that more than 5 years will pass before the level of pre-treatment disability is reached again. Concomitant dopaminergic pharmacological treatment may somehow restore the capacity of these neurons to synthesise and release dopamine when short duration effects wane or drugs are briefly withheld. Perhaps an alternative source of dopamine receptor stimulation, either from levodopa or from a dopamine receptor agonist, allows nigral cells temporarily to reduce their energy expenditure because of lowered demand on their metabolic or firing states. That the LDR is not immediately re-established by levodopa after a short drug holiday implies a compensatory mechanism that takes time to recover [28]. Levodopa withdrawal studies suggest a relationship between the LDR and the number of surviving nigral neurons. There is a LDR in advanced PD but it decays more rapidly than in less severely affected patients [29]. The LDR of levodopa can be sustained by the dopamine receptor agonist apomorphine [30].

Rightly has the main focus of research into PD moved away from established pharmacological treatments on to molecular pathophysiology, its patterns of involvement beyond the motor system, and the keys that this might hold to modifying disease progression. Yet that singular feature of PD, its dopaminergic motor response, remains a mysterious thing. We have tried here to show how an appreciation of both long and short duration components of the levodopa symptomatic effect is essential to clinical trial design to identify neuroprotective drugs.

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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: writing of first draft, review and critique.

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Alty J. Stock Ownership in medically-related fields: Clearsky Medical Diagnostics Ltd and Dr Carsten Grimm Medical Consultancy Ltd.

Advisory Boards: Merz Employment: Leeds Teaching Hospitals NHS Trust (LTHT).

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