

Slide 1

# Disease Progress

## Parkinson's Disease

### Interpretation of ELLDOPA

Nick Holford  
Dept Pharmacology and Clinical Pharmacology  
University of Auckland

Slide 2

$$\text{Clinical Pharmacology} = \text{Disease Progress} + \text{Drug Action}$$

©NHG Holford, 2017. All rights reserved.

Clinical pharmacology can be described as the science of understanding disease progress (clinical) and drug action (pharmacology). Disease progress implies that the disease changes with time. Drug action refers to the time course of drug effect and includes pharmacokinetics, pharmacodynamics and a link model to account for delays in effect in relation to drug concentration. Clinical pharmacology is not a static description of the use of a drug but includes the time course of disease, drug concentration and drug effect.

Slide 3

## Outline

1. What is disease progress?
2. Models for disease progress and drug action
3. Parkinson's disease and survival
4. Osteoporosis and fractures

©NHG Holford, 2017. All rights reserved.

Slide 4

## Disease Progress Model

### ● Quantitative model that accounts for the time course of disease **status**, $S(t)$ :

- » **“biomarkers”**
  - **Signs** - physiological or biological measurements of disease activity
  
- » **“clinical outcome”**
  - **Symptoms** - measure of how a patient feels or functions
  - **Survival** - Dead or alive (or had a stroke or not, etc.)

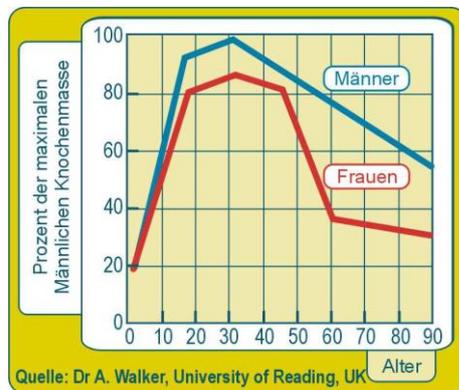
©NHG Holford, 2017, all rights reserved.

A symbol to describe disease progress is 'S' i.e. the disease status. Disease status is expected to vary with time,  $S(t)$ .

Disease status may be defined in terms of clinical outcomes such as survival and symptoms or in terms of a biomarker. Biomarkers are also known as clinical signs when used by clinicians as diagnostic or prognostic variables.

Slide 5

## Bone Mass in Humans



©NHG Holford, 2017, all rights reserved.

Slide 6

From: Ann Walker <a.f.walker@reading.ac.uk>  
Subject: Re: Bone mass in humans  
To: Nick Holford  
19/03/2009 11:01 p.m.

Dear Nick Holford

Thank you for drawing my attention to this. This is not my work and neither is it my research area. I have never had any contact with this food manufacturer.

Yours sincerely

Ann Walker

Dr Ann Walker PhD MNIMH RCPP  
Nutritionist/Medical Herbalist  
Tel: +44 (0) 118 966 6930  
"Discovering Herbal Medicine": [www.newvitality.org.uk](http://www.newvitality.org.uk)

On Mar 4 2009, Nick Holford wrote:

Dear Dr Walker,

I came across the figure shown below on the back of a Swiss muesli

©NHG Holford, 2017, all rights reserved.

Slide 7

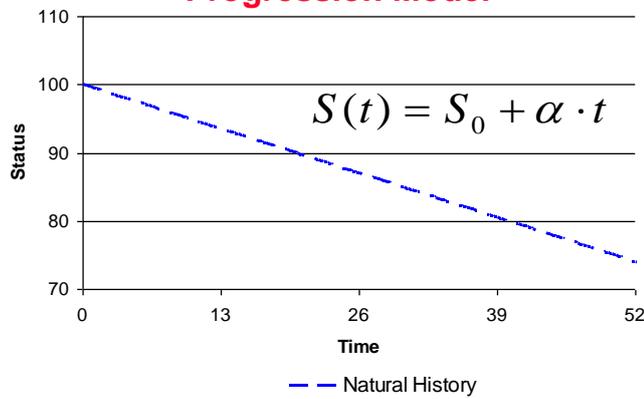
### The Link Between Biomarkers and Outcome Is Well Known



©NHG Hofstad, 2017, all rights reserved.

Slide 8

### Linear (Natural History) Disease Progression Model

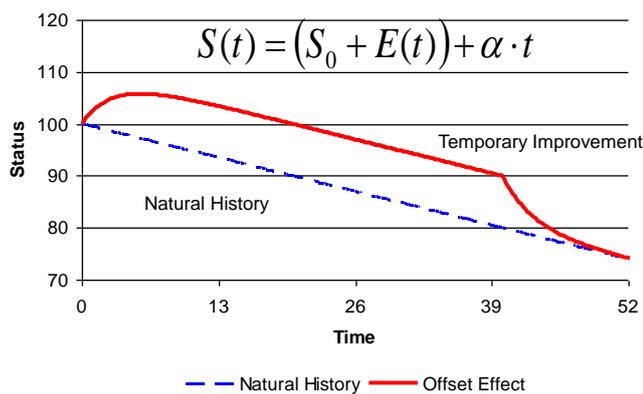


©NHG Hofstad, 2017, all rights reserved.

The simplest model to describe changing disease status with time is linear. In general if the change is relatively small in relation to the time scale of observation then any disease progress curve will reasonably described by a linear function.

Slide 9

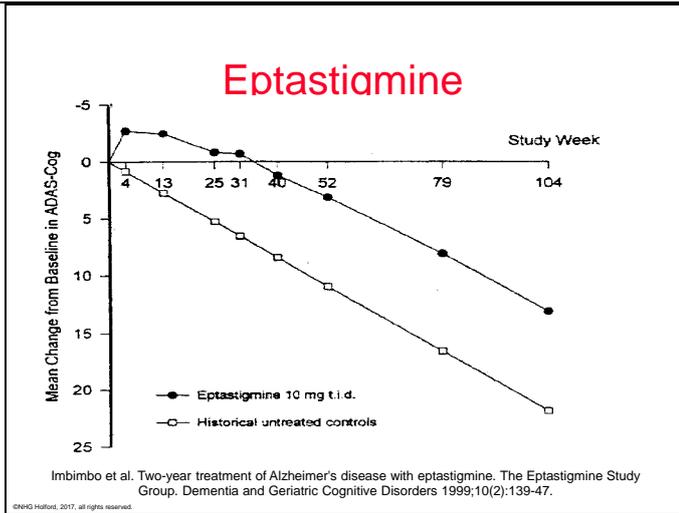
### Linear + Offset (Symptomatic)



©NHG Hofstad, 2017, all rights reserved.

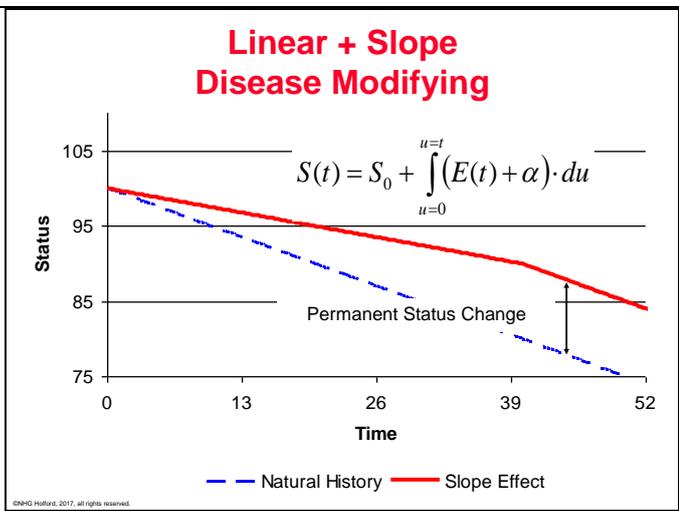
With any disease progress model it is possible to imagine a drug action that is equivalent to a change in the baseline parameter of the model. This kind of effect on disease produces a temporary offset. When treatment is stopped the response to the drug washes out and the status returns to the baseline. In many cases it is reasonable to suppose that the processes governing a delay in onset of drug effect will also affect the loss of effect but the offset effects of levodopa treatment in Parkinson's disease are one exception to this assumption.

Slide 10



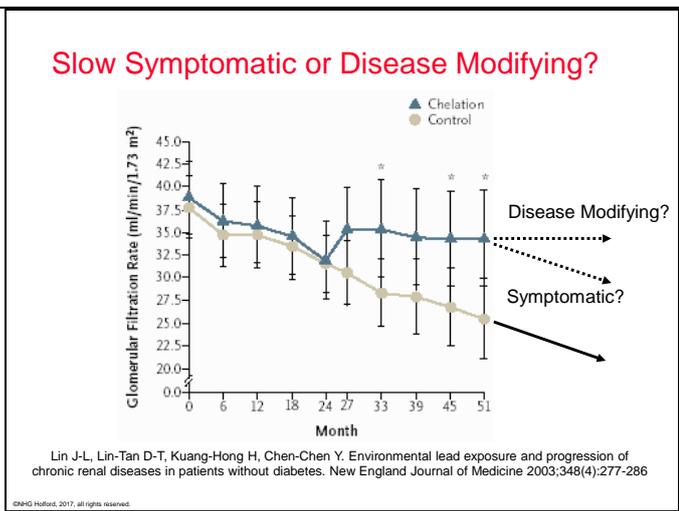
The action of cholinesterase inhibitors in Alzheimer's disease is very similar for all drugs in this class. There is a delayed onset of benefit taking 2 to 3 months to reach its peak followed by continuing progression of the disease at the same rate as expected from natural history progression. This is clear example of an offset type of drug action. If there is a disease modifying effect it is small and hard to detect without withdrawal of treatment.

Slide 11



Drug effects on the slope of a linear model lead to permanent changes in the disease status which are not reversed when treatment is stopped. The persistent change after stopping treatment is the hallmark of a disease modifying action if the natural history is linear.

Slide 12



A trial was undertaken in China in patients with moderate renal functional impairment. After 2 years of follow up they were randomized to treatment with a lead chelating agent. Patients who received chelation treatment had a rapid improvement in function which could be described by an offset effect. There was also a marked slowing of the rate of decline of renal function. This could be described by a slope effect but without washout of treatment it is not possible to distinguish a true disease modifying effect from a slow onset offset effect.

Slide 13

## Parkinson Study Group DATATOP Cohort

Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism

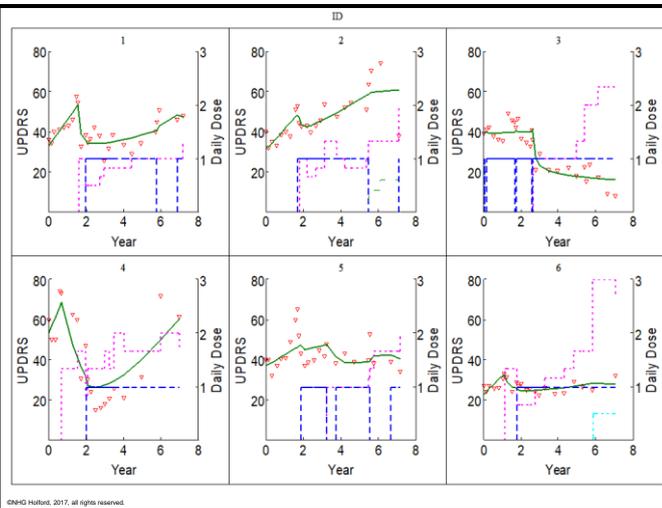
PKPD of anti-parkinsonian treatment  
and Parkinson's disease over 7 years  
in 800 patients

The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. The New England Journal of Medicine 1989;321:1364-1371

©NHG Holford, 2017, all rights reserved.

The DATATOP study was performed over 2 year period but patients enrolled in the study were subsequently followed up for 8 years. The time course of disease status in Parkinson's disease and the effects of treatment were described by a disease progress model. The NM-TRAN code for this analysis can be found in Holford et al. 2006. Holford NHG, Chan PL, Nutt JG, Kieburtz K, Shoulson I. Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments. J Pharmacokinetics Pharmacodyn. 2006 Jun;33(3):281-311.

Slide 14

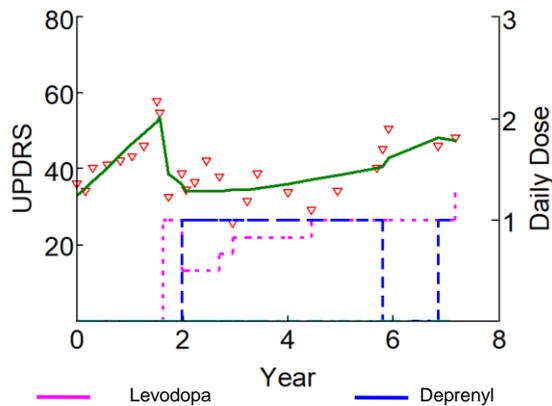


©NHG Holford, 2017, all rights reserved.

Disease status was followed with the Unified Parkinson's Disease Response Scale (UPDRS). The UPDRS patterns were quite variable from patient to patient. A major source of variability was the response to individual drug treatments.

Slide 15

### Symptomatic plus Disease Modifying?

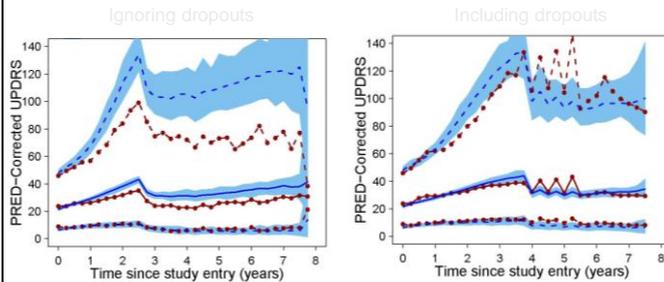


©NHG Holford, 2017, all rights reserved.

The first patient in the DATATOP cohort shows the patterns that were eventually used to build a disease progress and drug action model. The initial rate of progression seems to be slowed when treatment with levodopa and deprenyl is used. In addition there is a marked symptomatic effect which is primarily attributable to levodopa. It is not obvious what disease progress model is most suitable but it could be linear. Testing different model led to the conclusion that the disease progress approached an asymptote using a Gompertz model.

Slide 16

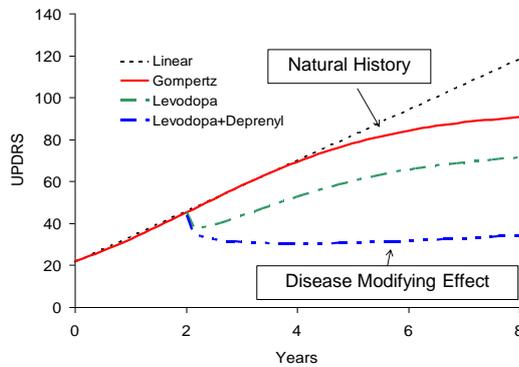
### Disease progress + Drug action + Dropouts Predicts DATATOP Cohort



©NHG Holford, 2017, all rights reserved.

Slide 17

### Combined Effects of Levodopa and Deprenyl



Holford NHG, Chan PL, Nutt JG, Kieburtz K, Shoulson I. Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments. J Pharmacokinetic Pharmacodyn. 2006;33(3):281-311.

©NHG Holford, 2017, all rights reserved.

The effects of levodopa and deprenyl are shown. Both have offset effects and protective effects which was described by an action on the time constant of a Gompertz asymptotic model. See Holford et al 2006 for details of the model code. Holford NHG, Chan PL, Nutt JG, Kieburtz K, Shoulson I. Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments. J Pharmacokinetic Pharmacodyn. 2006;33(3):281-311.

Slide 18

### Adverse Effects of LevoDOPA

Parkinson disease, the effect of levodopa, and the ELLDOPA trial  
Stanley Fahn  
Archives of Neurology; May 1999; 56, 5; Health & Medical Complete  
Pg. 529

NEUROTHERAPEUTICS

SECTION EDITOR: IRA SHOUKSON, MD

#### Parkinson Disease, the Effect of Levodopa, and the ELLDOPA Trial

Stanley Fahn, MD

The introduction of effective doses of levodopa for the treatment of Parkinson disease (PD)<sup>1,2</sup> was a revolutionary step in overcoming symptoms of a progressive neurodegenerative disease. This took place a little more than 30 years ago, and still, today, levodopa remains the most effective drug for the reversal of symptoms of PD.<sup>1,2</sup> If there were no associated adverse effects with long-term use, treatment of PD would be a simple matter. But most of the physician's effort in providing optimum care of patients with PD is in trying to overcome all too common adverse effects of levodopa.

©NHG Holford, 2017, all rights reserved.

Slide  
19

## Does L-DOPA Increase Progression of Parkinson's?

Table 2. Reasons for Delaying Levodopa Treatment\*

| Responses                      | How Likely Is It That Levodopa |  |
|--------------------------------|--------------------------------|--|
|                                | Enhances Progression of PD?    | Is Responsible for Motor Fluctuations? |
| Extremely likely               | 1.7                            | 13.5                                   |
| Very likely                    | 3.4                            | 28.6                                   |
| <b>Likely</b>                  | <b>16.8</b>                    | <b>26.1</b>                            |
| <b>Equally Likely/Unlikely</b> | <b>25.2</b>                    | <b>16.0</b>                            |
| <b>Unlikely</b>                | <b>32.0</b>                    | <b>10.1</b>                            |
| Very unlikely                  | 13.5                           | 4.2                                    |
| Extremely unlikely             | 7.6                            | 1.7                                    |

\* Results of survey of 120 neurologists, given as percentage. Boldface rows represent cluster of responses indicating uncertainty (clinical equipoise) about likelihood of levodopa enhancing progression of Parkinson disease (PD).

©NHG Holland, 2017, all rights reserved.

Slide  
20

## Earlier vs Late L-DOPA

### A CONTROLLED CLINICAL TRIAL TO DETERMINE IF LEVODOPA ALTERS THE NATURAL HISTORY OF PD: THE ELLDOPA TRIAL

The Parkinson Study Group has been awarded a grant (NS34796) from the National Institutes of Health to conduct a controlled clinical trial in patients with newly diagnosed PD to determine whether levodopa slows or hastens the progression of PD. This Earlier vs Later L-DOPA (ELLDOPA) study is a placebo-controlled, randomized, double-blind clinical trial.

The *primary objective* will be achieved by comparing the rates of progression of PD as measured by the change in the Unified Parkinson's Disease Rating Scale (UPDRS) in untreated subjects with early PD receiving placebo or levodopa. Three dosages of carbidopa-levodopa will be used, namely, 32.5/150 mg/d, 75/300 mg/d, and 150/600 mg/d, to obtain a dose-response curve.

©NHG Holland, 2017, all rights reserved.

Slide  
21

## ELLDOPA Study

ELLDOPA – Earlier vs Later L-DOPA

### Control

- Placebo

### Levodopa

- Low dose - 0.15 g/day
- Medium dose - 0.3 g/day
- High dose - 0.6 g/day

*Group size - 90 patients per group*

Fahn S. Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Earlier vs Later L-DOPA. Archives of Neurology 1999;56(5):529-35

©NHG Holland, 2017, all rights reserved.



Slide  
25

# Clinical Trial Simulation To The Rescue

*Pharmaceutical Research* (© 2007)  
DOI: 10.1007/s11095-006-9202-3

Research Paper

## Levodopa Slows Progression of Parkinson's Disease. External Validation by Clinical Trial Simulation

Phylinda L. S. Chan,<sup>1</sup> John G. Nutt,<sup>2</sup> and Nicholas H. G. Holford<sup>1,2,4</sup>

**Conclusions.** This simulation work confirmed the conclusion of the DATATOP analysis finding that levodopa slows disease progression. The simulation results also showed that a dose-related increased rate of progression in Parkinson's disease, obscured by symptomatic benefit, is very unlikely. Finally, the simulation results also shown that 2 weeks washout period was not adequate to completely eliminate the symptomatic benefits of levodopa.

©NHG Holford, 2017. All rights reserved.

Chan PL, Nutt JG, Holford NH. Levodopa slows progression of Parkinson's disease: external validation by clinical trial simulation. *Pharm Res.* 2007;24(4):791-802.

Slide  
26

## ELLDOPA predicted from DATATOP Model

UPDRS total Mean Difference from Placebo at Week 42  
Predictions from clinical trial simulation (100 replicates)  
Differences are Average ± SE

|                             | Low<br>150 mg/d  | Medium<br>300 mg/d | High<br>600 mg/d |
|-----------------------------|------------------|--------------------|------------------|
| <b>Observed Difference</b>  | <b>5.9 ± 1.2</b> | <b>5.9 ± 1.3</b>   | <b>9.2 ± 1.3</b> |
| <b>Predicted Difference</b> | <b>3.8 ± 1.4</b> | <b>5.9 ± 1.3</b>   | <b>8.4 ± 1.3</b> |

The Parkinson Study Group. Levodopa and the progression of Parkinson's disease. *N Engl J Med.* 2004 December 9, 2004;351(24):2498-508.

Chan PL, Nutt JG, Holford NH. Levodopa slows progression of Parkinson's disease. External validation by clinical trial simulation. *Pharm Res.* 2007 Apr;24(4):791-802.

©NHG Holford, 2017. All rights reserved.

The ELLDOPA study was prospectively simulated using the model for disease progress and levodopa effects obtained from the DATATOP cohort. The predicted difference from placebo in three levodopa dose groups was very similar to the observed response. This is a form of external validation of the DATATOP model. This is a very strong test of the value of the model developed from DATATOP because it predicted the outcome of a trial with a very different design.

Chan PL, Nutt JG, Holford NH. Levodopa slows progression of Parkinson's disease. External validation by clinical trial simulation. *Pharm Res.* 2007 Apr;24(4):791-802.

Slide  
27

## ELLDOPA predicted from ELLDOPA Model

UPDRS total Mean Difference from Placebo at Week 42  
Predictions from clinical trial simulation (100 replicates)  
Differences are Average ± SE

|                            | Low<br>150 mg/d  | Medium<br>300 mg/d | High<br>600 mg/d |
|----------------------------|------------------|--------------------|------------------|
| <b>Observed Difference</b> | <b>5.9 ± 1.2</b> | <b>5.9 ± 1.3</b>   | <b>9.2 ± 1.3</b> |
| <b>Predicted ELLDOPA</b>   | <b>5.1 ± 1.2</b> | <b>6.1 ± 1.3</b>   | <b>9.2 ± 1.4</b> |
| <b>Predicted DATATOP</b>   | <b>3.8 ± 1.4</b> | <b>5.9 ± 1.3</b>   | <b>8.4 ± 1.3</b> |

The Parkinson Study Group. Levodopa and the progression of Parkinson's disease. *N Engl J Med.* 2004 December 9, 2004;351(24):2498-508.

Ploeger B, Holford NHG. ELLDOPA revisited: estimating the combined symptomatic and disease modifying effects of levodopa using disease progression analysis. In preparation. 2010

Chan PL, Nutt JG, Holford NH. Levodopa slows progression of Parkinson's disease. External validation by clinical trial simulation. *Pharm Res.* 2007 Apr;24(4):791-802.

©NHG Holford, 2017. All rights reserved.

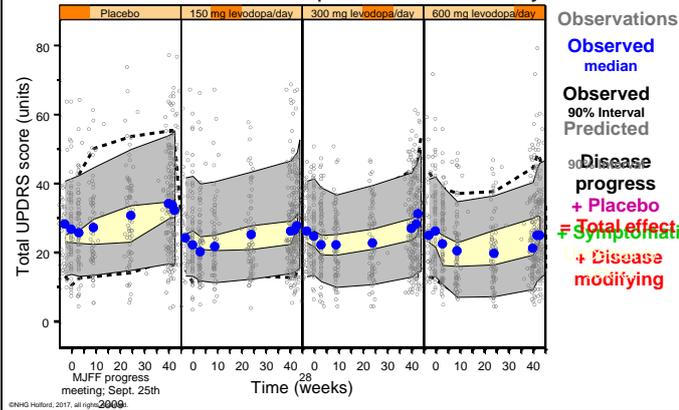
The ELLDOPA study was simulated using the model for disease progress and levodopa effects obtained from the ELLDOPA data (Predicted ELLDOPA) and the DATATOP cohort (Predicted DATATOP). The predicted difference from placebo in three levodopa dose groups was very similar to the observed response. This is a form of external validation of the DATATOP model. This is a very strong test of the value of the model developed from DATATOP because it predicted the outcome of a trial with a very different design.

The Parkinson Study Group. Levodopa and the progression of Parkinson's disease. *N Engl J Med.* 2004 December 9, 2004;351(24):2498-508. Ploeger B, Holford NHG. ELLDOPA revisited: estimating the combined symptomatic and disease modifying effects of levodopa using disease progression analysis. In preparation. 2010

Chan PL, Nutt JG, Holford NH. Levodopa slows progression of Parkinson's disease. External validation by clinical trial simulation. *Pharm Res.* 2007 Apr;24(4):791-802

Slide 28

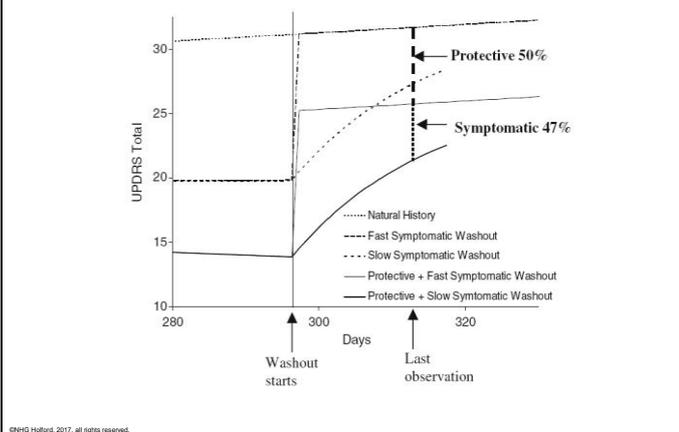
### Analysis of Original ELLDOPA Data Observed and predicted variability



The ELLDOPA trial included 4 treatment groups and the data from the placebo the low, medium and high levodopa treatment groups are shown as gray symbols in this plot. The observed median trend in these data is shown as these blue symbols whereas the observed variability for 90% of the population are shown as these dashed lines. The median trend is the result of the progression of the disease, which is assumed to be linear with a slope of nearly 12 units per year. There is a placebo effect, which is most visible in the placebo group, but also takes place in the other treatment groups. This placebo effect slowly washes in. It is transient and disappears over time. Part of the treatment effect is symptomatic, which has a rapid onset and washes out when the treatment stops after 9 months. The symptomatic effect has an Emax of 70% of baseline and an ED50 of 540 mg/d. This symptomatic effect does not describe the complete response. An additional disease modifying effect is required, which reduces the rate of progress by 32%. The median response predicted by the disease model closely resembles the observations, as the median observations fall within the 95% confidence interval (yellow area) of the predicted total effect. The same holds true for the observed variability for the total effect, which is represented by the gray area, which closely matched by the predicted variability.

Slide 29

### What Happened in ELLDOPA?



Using the parameters describing the washout of levodopa symptomatic effects obtained from a small group of patients originally in the DATATOP cohort (Hauser & Holford 2002) along with the disease progress and levodopa symptomatic and disease modifying effects it was possible to predict the symptomatic contribution to the observed difference from placebo after 2 weeks of levodopa washout. This is an example of the utility of modelling both disease progress and drug action. Not only can trial results be predicted but also the results can be interpreted in a more meaningful way. The DATATOP model was used to explain how much of the effect observed after washout of levodopa could be attributed to residual symptomatic effects (47%) compared to the disease modifying effect (50%). The sum of the effects does not add to 100% because the numbers are derived from stochastic simulations for each fast and slow symptomatic washout curves.

Hauser RA, Holford NHG. Quantitative description of loss of clinical benefit following withdrawal of levodopa-carbidopa and bromocriptine in early Parkinson's disease. *Mov Disord.* 2002;17(5):961-8.

Slide  
30

## Conclusion

- Levodopa does not accelerate disease progression
- Modelling of offset and slope effects allows the confounded results of the ELLDOPA trial to be separated
- Levodopa slows disease progression in a dose-related fashion