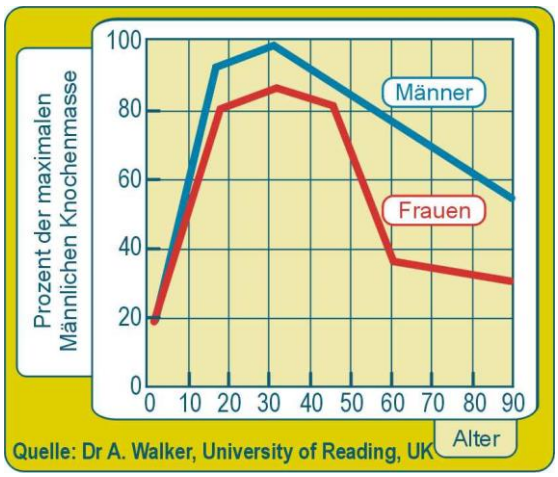
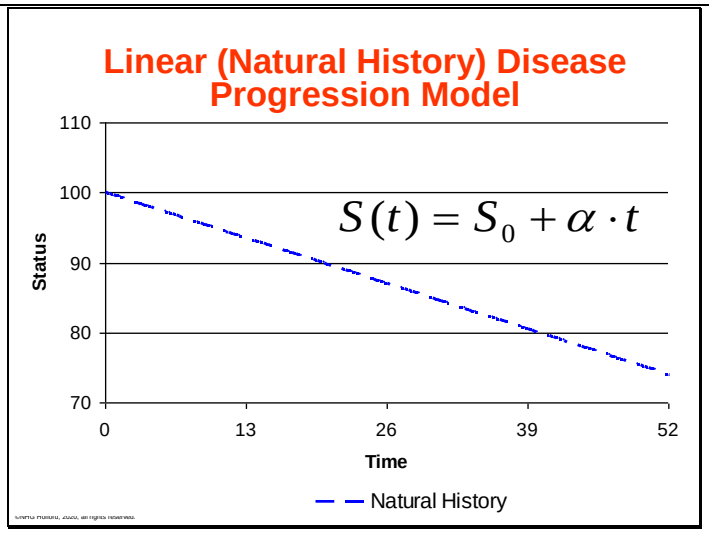
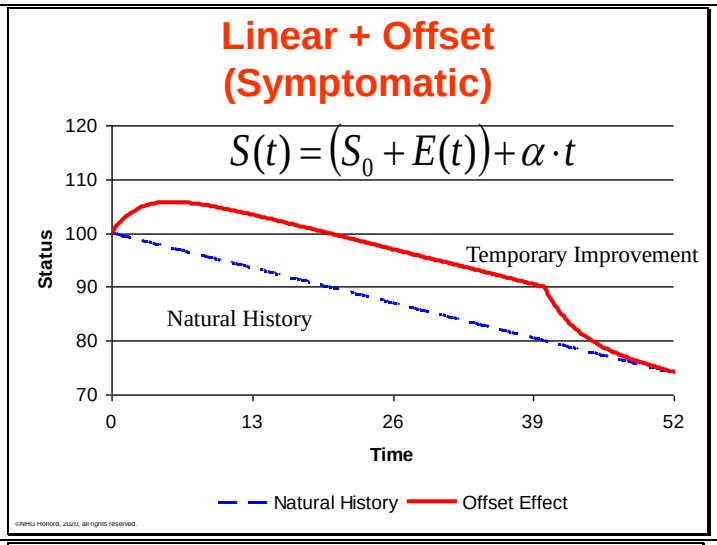
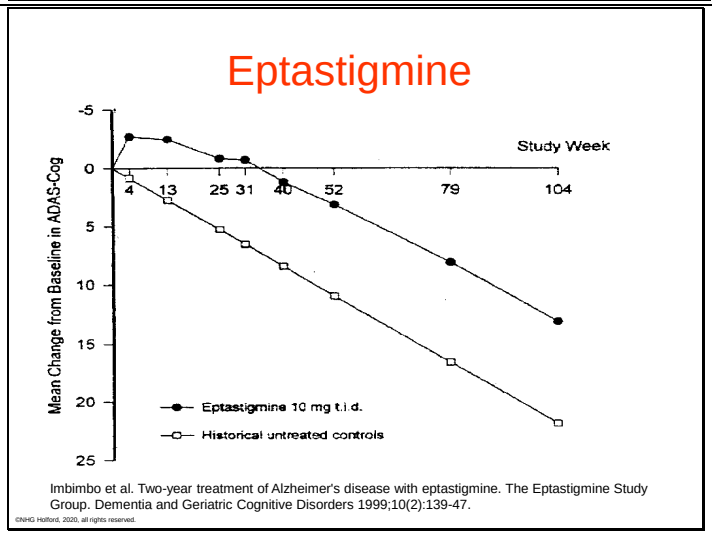
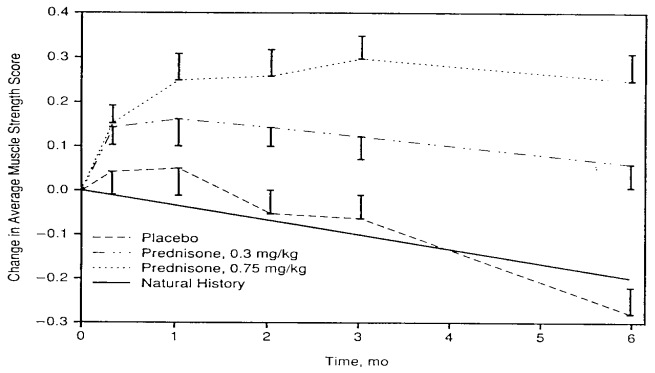
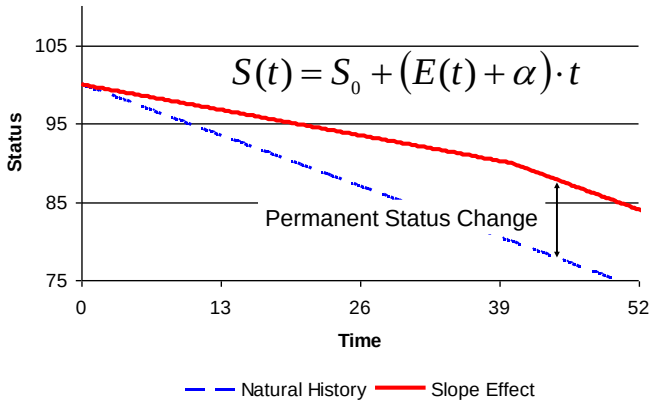
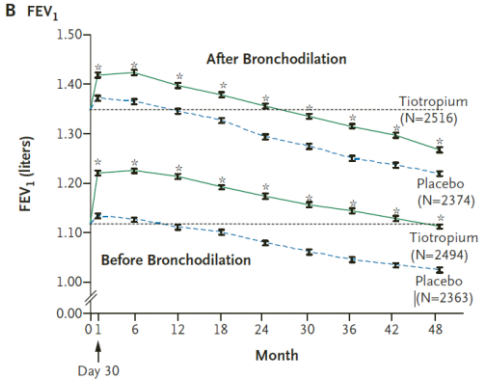
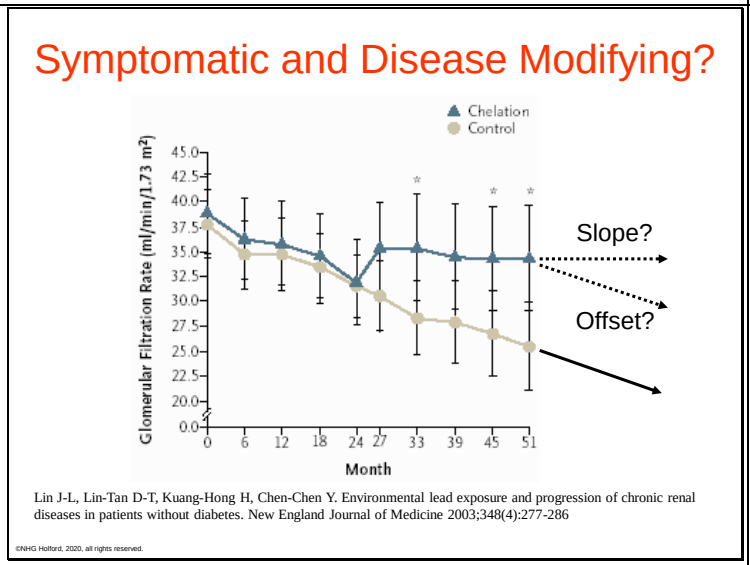
Slide 1	**Disease Progress** Nick Holford Dept Pharmacology and Clinical Pharmacology University of Auckland	
Slide 2	Outline 1. What is disease progress? 2. Models for disease progress 3. Models for drug action 4. Placebo effects 5. Practical Example 	Disease progression describes the natural history of disease without treatment. The word 'progression' implies a direction of change – usually with worsening severity. Disease progress refers to a description of disease progression plus changes attributable to treatments and placebo responses.
Slide 3	Clinical Pharmacology = Disease Progression + Drug Action 	Clinical pharmacology can be described as the science of understanding disease progress which is the result of disease progression (clinical) and and drug action (pharmacology). Disease progression 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. Holford N. Clinical pharmacology = disease progression + drug action. Br J Clin Pharmacol. 2015;79(1):18-27

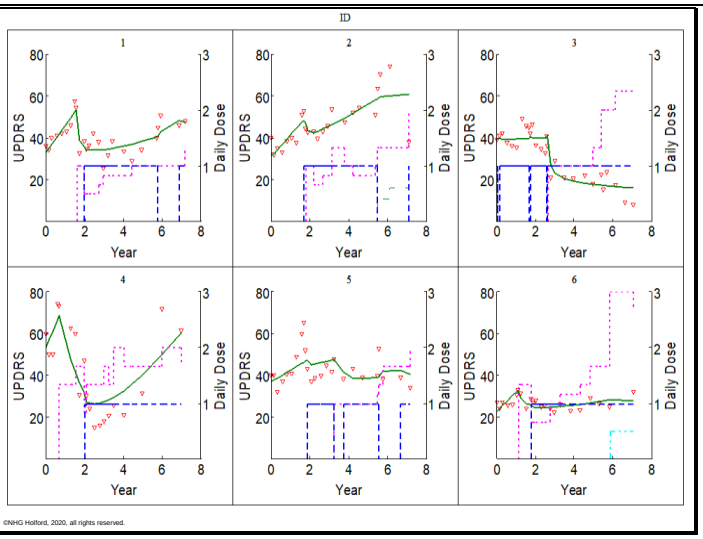
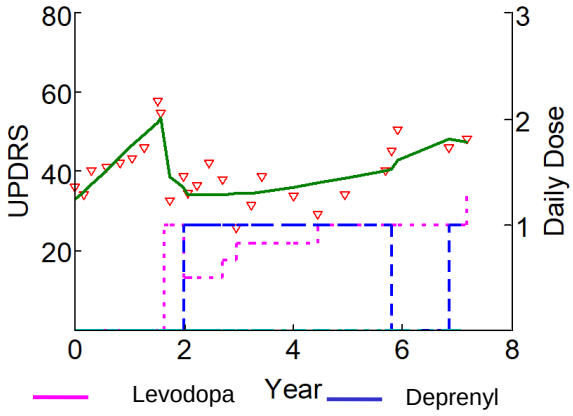
Slide 4	**Old Model - New Meaning** $$E = E0 + \frac{E\max \cdot Conc}{EC50 + Conc}$$ Disease Progression Drug Action 	Early approaches (e.g. Holford & Sheiner 1981) describing the time course of drug effect distinguished a constant baseline response (E0) from a varying concentration related response (e.g. the Emax model). The constant baseline parameter describes the response in the absence of drug and is the simplest form of disease progress model. The use of the symbol E0 for the baseline response was not a good choice because the effect (E) when concentration is zero must be zero i.e. E0 is not the drug effect when concentration is zero but is the biological response (biomarker) that is being observed. Holford NHG, Sheiner LB. Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin Pharmacokinet. 1981;6(6):429-53.
Slide 5	**Disease Progression Model** • **Quantitative model that accounts for the time course of disease status, *S(t)*:** – ***"clinical outcome"*** • **Survival** - Dead or alive (or had a stroke or not, etc.) • **Symptoms** - measure of how a patient feels or functions – ***"biomarkers"*** • **Signs** - physiological or biological measurements of disease activity 	A more appropriate 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 6	 	A biomarker description of disease progression. Bone mineral density (Knochenmasse) measured in men (Manner) and women (Frauen) is shown over ages (Alter) ranging from 0 to 90. Most therapeutic studies on bone mineral density (BMD) cover less than 10 years so there is a limited understanding of drug effects on disease progression. Note that this figure suggests that the rate of loss of BMD slows in older woman – as it must because BMD cannot go negative.

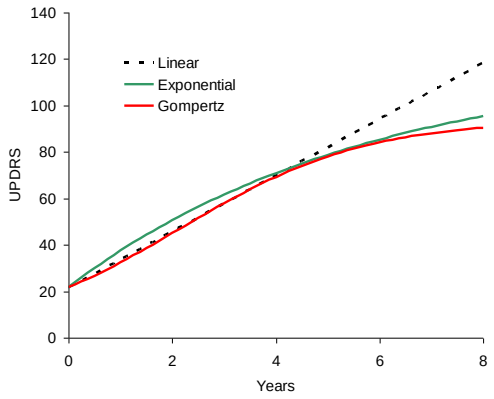
Slide 7	From [redacted] Subject: **Re: Bone mass in humans** 19/03/2009 11:01 p.m. To: Nick Holford Dear Nick Holford Thank you for drawing my attention to this. This is not my work and neither is it my research area. I have never had any contact with this food manufacturer. Yours sincerely On Mar 4 2009, Nick Holford wrote: Dear Dr I came across the figure shown below on the back of a Swiss muesli 	
Slide 8	The Link Between Biomarkers and Outcome Is Well Known  	
Slide 9	**Components of a Disease Progress Model** • Baseline Disease State • Natural History • Active Treatment Response • Placebo Response ***S(t) = S0 +Nat. Hx. + Active + Plac*** 	Disease progress models start with a baseline disease status, S0. The change from baseline in the absence of drug treatment describes the natural history of the disease (disease progression). When drugs are used then the active effect of the drug modifies disease status. In clinical trials it is also necessary to consider the placebo (or nocebo) response to inactive treatment as a separate component. Some disease progress models are described in Holford NHG, Mould DR, Peck CC. Disease progress models. In: Atkinson A, editor. Principles of Clinical Pharmacology. 2nd ed. San Diego: Academic Press; 2007. p. 313-21. More complex effects based on turnover models have been described in Post TM, Freijer JI, DeJongh J, Danhof M. Disease system analysis: basic disease progression models in degenerative disease. Pharm Res. 2005 Jul;22(7):1038-49.

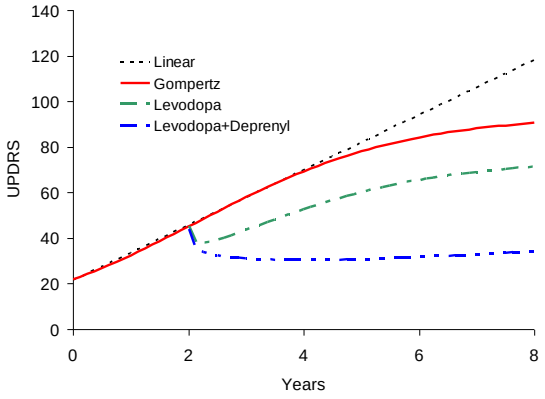
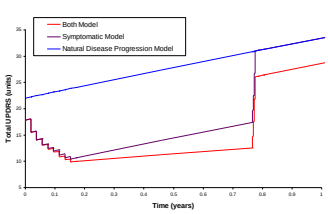
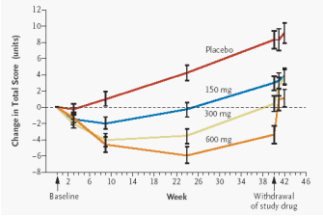
Slide 10		The simplest model to describe changing disease status with time is linear. In general if the change is relatively small in relation to the time scale of observation then any disease progress curve will reasonably described by a linear function.
Slide 11		With any disease progress model it 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 12		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 protective effect it is small and hard to detect without withdrawal of treatment.

Slide 13	**Linear + Offset + Placebo**  Griggs RC, Moxley RT, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, et al. Prednisone in Duchenne Dystrophy: A randomized, controlled trial defining the time course and dose response. Archives of Neurology 1991;48:383-88 	Muscular dystrophy causes a progressive loss of muscle strength. This graph shows the author's belief that the natural history is essentially linear over 6 months. The effects of two doses of prednisone demonstrate a delayed onset of effect but no change in the rate of progression after the maximum effect is achieved. This seems to be an example of an offset type of drug effect. The placebo response to inactive treatment is also delayed but differs from prednisone by loss of effect and return to the natural history rate of progression. The difference in time course of drug action, placebo response and natural history components allows these three phenomena to distinguished.
Slide 14	**Linear + Slope (Disease Modifying)**  	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 15	**Symptomatic or Disease Modifying?**  Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2008;359(15):1543-54. 	The FEV1 is a measure of airway resistance. Tiotropium is an inhaled anti-cholinergic bronchodilator. FEV1 was measured before and after bronchodilatation with inhaled salbutamol (albuterol). Patients with chronic obstructive pulmonary disease (COPD) treated with placebo or with tiatropium show an initial symptomatic response which appears to be maintained in the tiatropium treated group. There is no indication of a disease modifying effect. Before bronchodilation, the annual rates of decline were the same in the tiotropium group and the placebo group: 30±1 ml per year. After bronchodilation, the annual rate of decline was 40±1 ml per year in the tiotropium group, as compared with 42±1 ml per year in the placebo group. Results of this kind of trial looking for disease modifying effects are still controversial because of naïve data analysis approaches that cannot distinguish symptomatic from disease modifying effects. Niewoehner DE. TORCH and UPLIFT:

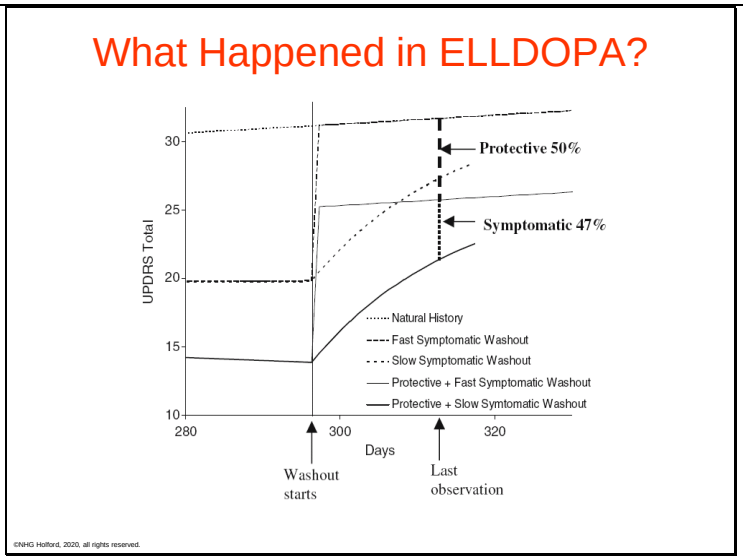
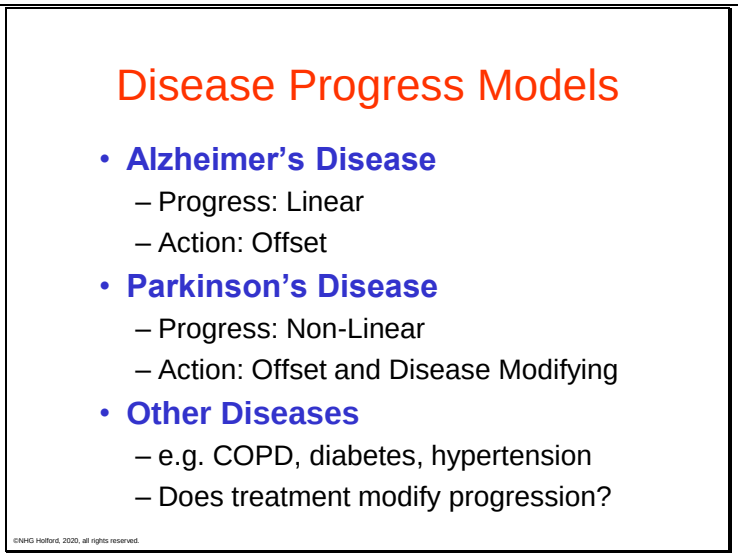
		what has been learned from the COPD "mega-trials"? COPD. 2009;6(1):1-3.
Slide 16		A trial was undertaken in Taiwan in patients with moderate renal functional impairment. After 2 years of follow up they were randomized to treatment with a lead chelating agent. Patients who received chelation treatment 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. “64 subjects with an elevated body lead burden were randomly assigned to the chelation control groups. For three months, the patients in the chelation group received lead-chelation therapy with calcium disodium EDTA, and the control group received placebo. During the ensuing 24 months, repeated chelation therapy was administered weekly to 32 patients with high-normal body lead burdens (at least 80 µg but less than 600 µg) unless on repeated testing the body lead burden fell below 60 µg; the other 32 patients served as controls and received weekly placebo infusions for 5 weeks every 6 months.”

Slide 17	# 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 	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 Pharmacokinet Pharmacodyn. 2006 Jun;33(3):281-311. Holford NHG. Disease progression and neuroscience. Journal of Pharmacokinetics and Pharmacodynamics. 2013;40:369-76.
Slide 18	 	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 19	# Offset + Slope Effect?  	The first patient in the DATATOP cohort shows the patterns that were eventually used to build a disease progression 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 progression model is most suitable but it could be linear. Testing different model led to the conclusion that the disease progression approached an asymptote using a Gompertz model.

Slide 20	**Asymptotic Disease Progression**  	The exponential asymptotic model has its fastest change at early times with continuously decreasing rate of change as the asymptote is reached. A sigmoidal shape with the maximum rate of change in the middle of the curve is obtained with a Gompertz function. The Gompertz function has a long history for describing survival time distributions and for tumour growth curves. The shapes of the linear, exponential asymptote and Gompertz asymptote are shown based on estimates obtained in patient's with Parkinson's disease. The initial dip in the Gompertz curve relative to the exponential curve could be due to a transient placebo response.
Slide 21	**Asymptotic Disease Progression** Linear $\frac{dS}{dt} = \alpha \cdot f(Ce)$ Exponential $\frac{dS}{dt} = \frac{\ln(2)}{Tprog} \cdot (Sss \cdot f(Ce) - S)$ Gompertz $\frac{dS}{dt} = \frac{1}{Tprog \cdot f(Ce)} \cdot (Sss - S) \cdot S$ α = Linear progression rate Tprog = Progression half-life (exponential) or time constant (Gompertz) Sss = Asymptotic 'burnt out' steady state 	Each parameter in a disease progress model represents a possible site of action for a drug. All models have a baseline parameter which can be thought of as the basis for a symptomatic drug effect. A linear model has as slope parameter which is the basis for a disease modifying drug effect. Asymptotic disease progress models may have two parameters – an asymptote representing the eventual steady state for the disease and a time related parameter determining the time to the asymptote. Drug effects on either of these parameters can lead to a disease modifying effect. Note that the Tprog parameter for the exponential model is the half-life of progression to the asymptote. But the Tprog parameter for the Gompertz model is a second order time constant. Interpretation of its value has to refer to the disease status e.g. if Tprog is 20 years and the disease status has a value of 10 then progression at that status has a time constant of 2 years (Tprog/status). If the status is chosen at the mid point between S0 and Sss it corresponds to the status expected after one half-life with the exponential model. In that case a half-time of progression can be calculated e.g. if the mid-point status is 40 then the time constant is 0.5 and the equivalent half-life is ln(2)*0.5 or 0.347.

Slide 22	**Offset and Disease Modifying Effects of Levodopa and Deprenyl**  	The effects of levodopa and deprenyl are shown. Both have offset effects and disease modifying 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.
Slide 23	**ELLDOPA Before and After**  Design  Results The Parkinson Study Group. Levodopa and the Progression of Parkinson's Disease. N Engl J Med 2004;351(24):2498-2508 	The Parkinson Study Group which performed the DATATOP study was interested in asking if levodopa changes the rate of progression of Parkinson's disease. They designed a trial that was simple in principle but it rested on a key assumption that symptomatic effects of levodopa would wash out within 2 weeks of stopping treatment. When treatment was stopped after 9 months there was a loss of UPDRS response over the next 2 weeks but it did not approach the response seen in a parallel placebo treated group. The marked difference from placebo could be due to a true disease modifying effect or a very slow loss of symptomatic effect.
Slide 24	**ELLDOPA predicted from DATATOP** UPDRS total Mean Difference from Placebo Reported ELLDOPA Observations 100 Simulated Trial Replications (average ± se) Predictions made before ELLDOPA Results Reported 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. 	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. It confirms the predictions of the DATATOP model in the short term (just over 9 months). 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. Note: SEs for observed differences have been corrected. Published SEs in Chan et al. 2007 were incorrect.

	Low 150 mg/d	Medium 300 mg/d	High 600 mg/d
Observed Difference	5.9 ± 1.2	5.9 ± 1.3	9.2 ± 1.3
Predicted Difference	3.8 ± 1.4	5.9 ± 1.3	8.4 ± 1.3

Slide 25		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 26		The time course of biomarkers in Alzheimer's disease and Parkinson's disease has been used to identify the shape of the natural history curve for the biomarker. Drug actions can also be identified. Disease modifying effects of treatment in other major diseases are still under debate.

Slide 27	**General References** 1. Chan PLS, Holford NHG. Drug treatment effects on disease progression. Annu Rev Pharmacol Toxicol. 2001;41:625-59. 2. Holford NHG, Mould DR, Peck CC. Disease Progress Models. In: Atkinson A, editor. Principles of Clinical Pharmacology. San Diego: Academic Press; 2001. p. 253-62. 3. Post TM, Freijer JI, DeJongh J, Danhof M. Disease system analysis: basic disease progression models in degenerative disease. Pharm Res. 2005 Jul;22(7):1038-49. 4. Ploeger BA, Holford NH. Washout and delayed start designs for identifying disease modifying effects in slowly progressive diseases using disease progression analysis. Pharm Stat. 2009 Jul-Sep;8(3):225-38. 5. Vu TC, Nutt JG, Holford NHG. Progression of motor and nonmotor features of Parkinson's disease and their response to treatment. Br J Clin Pharmacol. 2012;74(2):267-83. 6. Holford N. Clinical pharmacology = disease progression + drug action. Br J Clin Pharmacol. 2015;79(1):18-27 	

Slide 28	**Offset Model Code**
	`$ERROR`
	`CE=F ; Immediate Effect PK`
	`S0=THETA(1)*EXP(ETA(1))`
	`ALPHA=THETA(2)*(1+ETA(2)) ; Note proportional ETA`
	`BETA=THETA(3)*(1+ETA(3))`
	`;Offset Drug Action`
	`Y=S0 + ALPHA*TIME + BETA*CE + EPS(1)`
	
		This code assumes that the drug action is described by a PK model for concentration which has an immediate effect. Any PK model can be used and a delayed effect could be modelled by using an effect compartment model.
		The drug action is added to the baseline (S0) in order to produce an offset effect.
		Note that the rate of progression of disease (alpha) and the effect of the drug (beta) may be either positive or negative in an individual patient. It is important not to use an exponential model for the random effects so that both patterns of progress and drug action can be described.

Slide 29	**Placebo Model Code**
	`$ERROR`
	`CE=F ; Immediate Effect PK`
	`S0=THETA(1)*EXP(ETA(1))`
	`ALPHA=THETA(2)*(1+ETA(2))`
	`BETA=THETA(3)*(1+ETA(3))`
	`;Single 'Placebo dose'`
	`DOSEP=THETA(4)*(1+(ETA(4)) ; allow placebo or nocebo change`
	`TELP=THETA(5)*EXP(ETA(5))`
	`TEQP=THETA(6)*EXP(ETA(6))`
	`;First Order input and elimination 'Bateman' function`
	`KELP=LOG(2)/TELP ; placebo 'elimination'`
	`KEQP=LOG(2)/TEQP ; placebo 'absorption'`
	`TWOEXP=EXP(-KELP*TIME)-EXP(-KEQP*TIME)`
	`PLACBO=DOSEP*KEQP/(KEQP-KELP)*TWOEXP`
	`Y=S0 + ALPHA*TIME + BETA*CE + PLACBO + EPS(1)`
	
		It is reasonable to suppose that the start of a clinical trial is the stimulus for the placebo response. The placebo response can by imagined to be due to the time course of placebo 'concentration' after a 'placebo dose' at time zero (the start of the trial). A basic pharmacokinetic first order absorption and elimination model can be used to describe the placebo time course. Differences in height of response between patients are determined by the apparent placebo 'dose'. Differences in the rate of appearance and loss of response are determined by the 'absorption' and 'elimination' half-lives. This type of placebo model function has been used to describe the placebo response in Alzheimer disease trials. Holford NHG, Peace KE. Methodologic aspects of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. Proc Natl Acad Sci U S A. 1992;89:11466-70.

Slide 30	**Slope Effect Code**
	
	`$PK`
	`S0=THETA(1)*EXP(ETA(1))`
	`ALPHA=THETA(2)*(1+ETA(2))`
	`BETA=THETA(3)*(1+ETA(3))`
	`CL=THETA(4)*EXP(ETA(4))`
	`V=THETA(5)*EXP(ETA(5))`
	
	`; Must use differential equations for SLOPE effect`
	
	`$DES`
	`CE=A(1)/V`
	`DADT(1) = -CL*CE ; PK model`
	`DADT(2) = BETA*CE + ALPHA ; Slope Action`
	
	`$ERROR`
	`DISPRG=A(2)`
	`Y=S0 + DISPRG + EPS(1)`
	
		Note that protective effect models must be coded as differential equations because drug concentration (CE) varies with time

Slide 31	**Asymptotic Progress Code**
	
	`$PK`
	`S0=THETA(1)*EXP(ETA(1)) ; baseline`
	`SSS=THETA(2)*(1+ETA(2)) ; asymptote steady state status`
	`DLTA= SSS - S0 ; change from baseline to asymptote`
	`THALF=THETA(3)*EXP(ETA(3)) ; half-life of asymptotic process`
	`BETA=THETA(4)*(1+ETA(4)) ; drug effect parameter`
	`CL=THETA(5)*EXP(ETA(5)) ; PK model clearance`
	`KPROG=LOG(2)/THALF`
	
	`$DES`
	`CE=A(1)`
	`STATUS=A(2)`
	`DADT(1) = -CL*CE ; PK model`
	`DADT(2) = KPROG*(DLTA*(1+BETA*CE) - STATUS) ; exponential asymptote`
	
	`$ERROR`
	`DISPRG=A(2)`
	`Y=S0 + DISPRG + EPS(1)`
	
		The drug effect is shown as an action on the steady state asymptote (SSS). Alternatively it could have been on the exponential rate constant (Kprog) or on both SSS and Kprog.