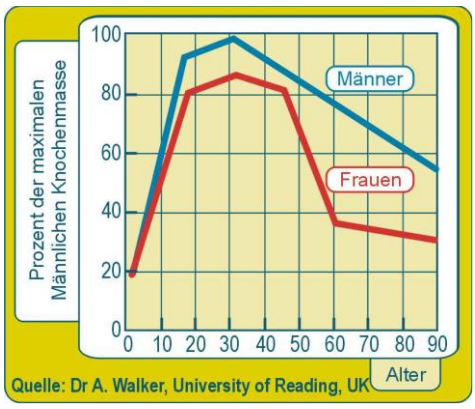
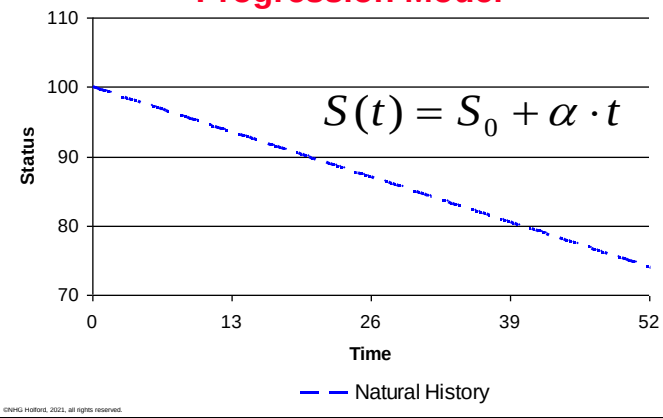
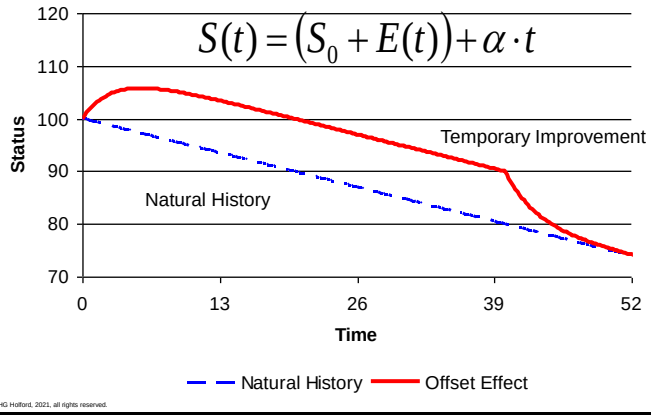
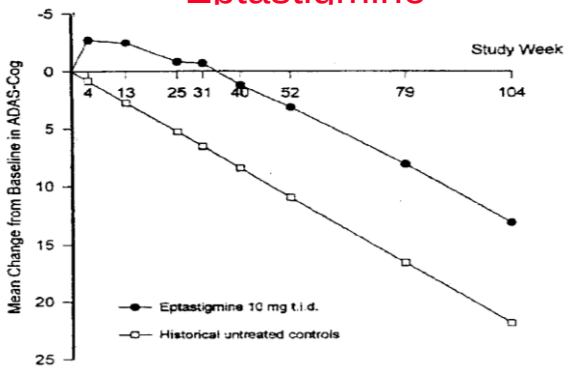
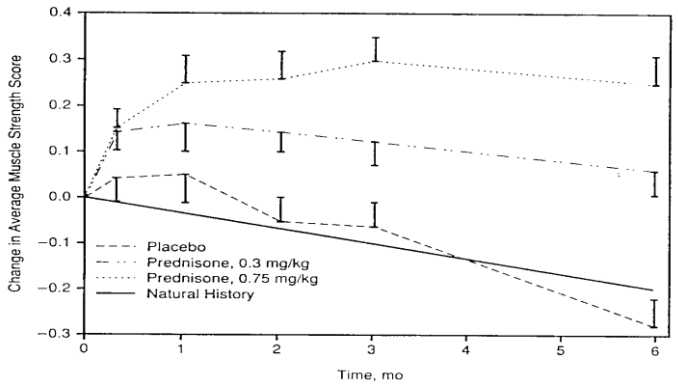
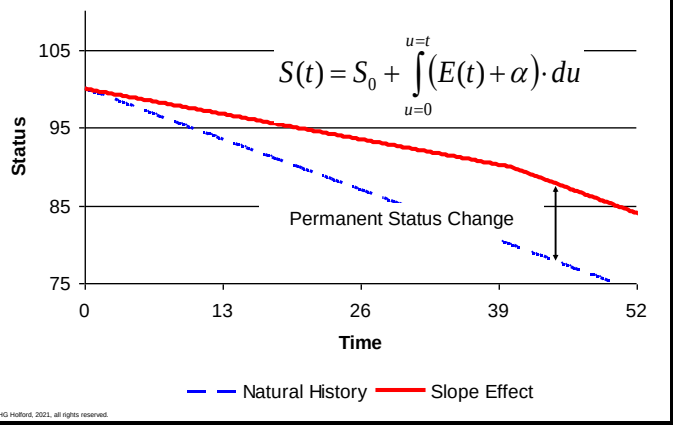
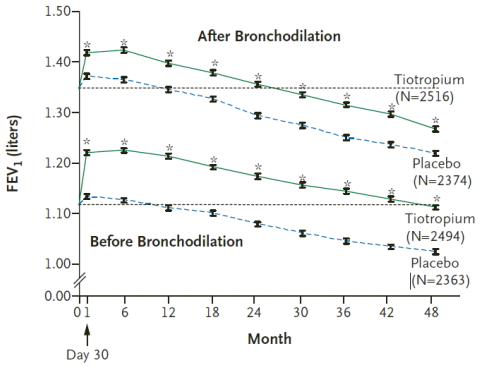
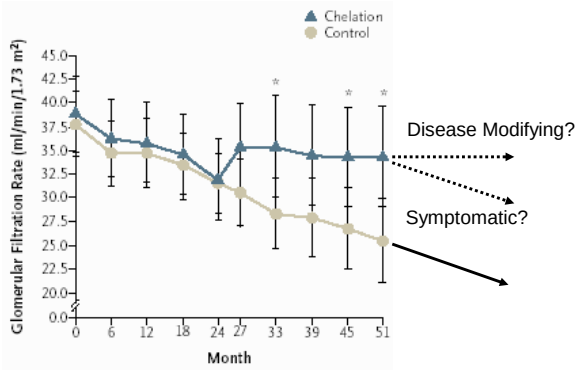
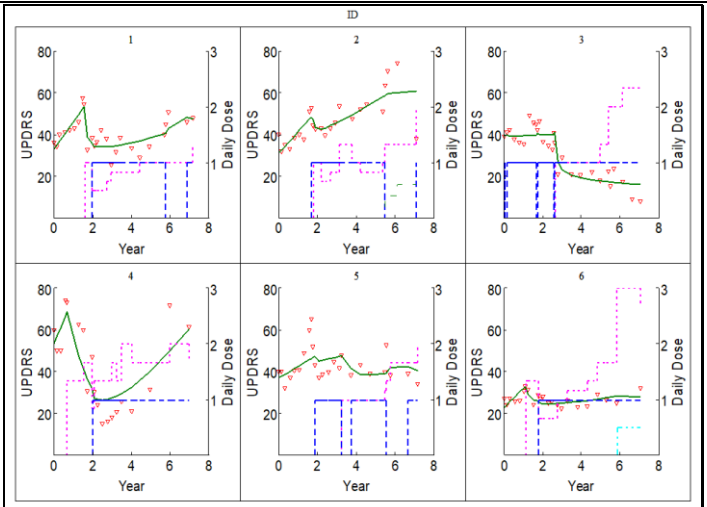
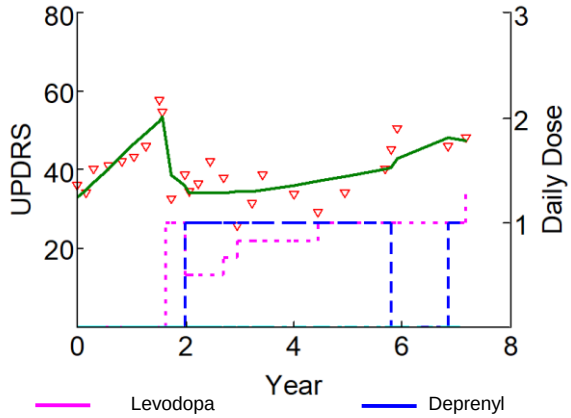
Slide 1	# Clinical Pharmacology ## Disease Progress and Drug Action Nick Holford Dept Pharmacology and Clinical Pharmacology University of Auckland	
Slide 2	Clinical Pharmacology = Disease Progress + Drug Action 	Clinical pharmacology can be described as the science of understanding disease progress (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 	

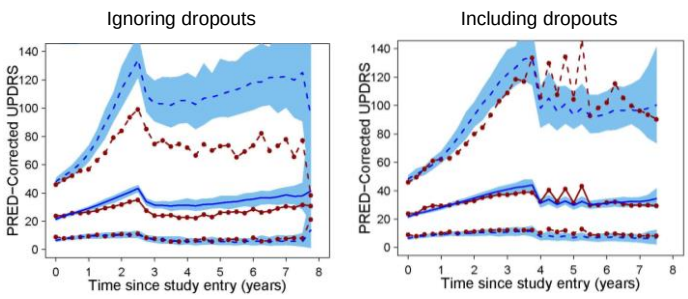
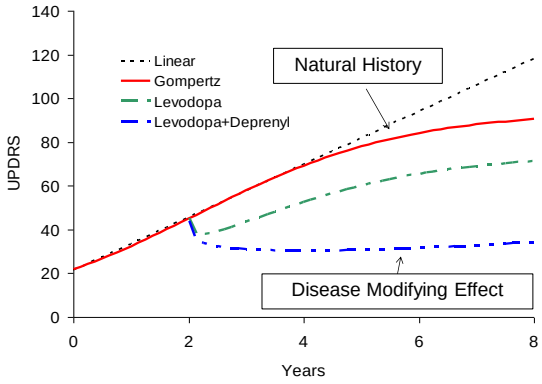
Slide 4	**Disease Progress Model** ➢ **Quantitative model that accounts for the time course of disease status, *S(t)*:** » ***"biomarkers"*** – **Signs** - physiological or biological measurements of disease activity » ***"clinical outcome"*** – **Symptoms** - measure of how a patient feels or functions – **Survival** - Dead or alive (or had a stroke or not, etc.) 	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**  	
Slide 6	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 	

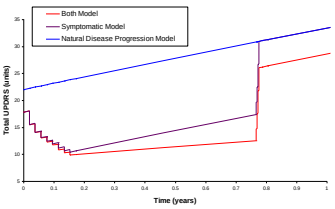
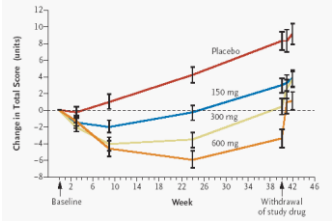
Slide 7	**The Link Between Biomarkers and Outcome Is Well Known**  	
Slide 8	**Linear (Natural History) Disease Progression Model**  	The simplest model to describe changing disease status with time is linear. In general if the change is relatively small in relation to the time scale of observation then any disease progress curve will be reasonably described by a linear function.
Slide 9	**Linear + Offset (Symptomatic)**  	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	 Imbimbo et al. Two-year treatment of Alzheimer's disease with eptastigmine. The Eptastigmine Study Group. Dementia and Geriatric Cognitive Disorders 1999;10(2):139-47. 	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	**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 12	**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 13	**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 14	**Slow Symptomatic or Disease Modifying?**  Lin J-L, Lin-Tan D-T, Kuang-Hong H, Chen-Chen Y. Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. New England Journal of Medicine 2003;348(4):277-286 	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 15	# 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.
Slide 16	 	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 17	# Symptomatic plus Disease Modifying?  	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 18	**Disease progress + Drug action + Dropouts Predicts DATATOP Cohort**  Model includes symptomatic and disease-modifying treatment effects 	
Slide 19	**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 Pharmacokinet Pharmacodyn. 2006;33(3):281-311. 	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 Pharmacokinet Pharmacodyn. 2006;33(3):281-311.
Slide 20	**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 	

Slide 21	**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 22	**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 150 mg/d	Medium 300 mg/d	High 600 mg/d
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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** | 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. 	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 23	**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 150 mg/d	Medium 300 mg/d	High 600 mg/d
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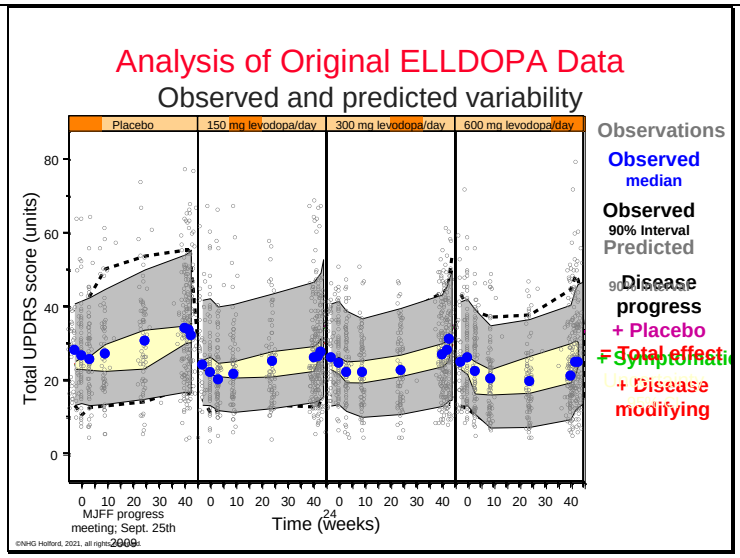
Observed Difference	**5.9 ± 1.2**	**5.9 ± 1.3**	**9.2 ± 1.3**
Predicted ELLDOPA	**5.1 ± 1.2**	**6.1 ± 1.3**	**9.2 ± 1.4**
Predicted DATATOP	**3.8 ± 1.4**	**5.9± 1.3**	**8.4 ± 1.3** | The Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004 December 9, 2004;351(24):2498-508. 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 	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 24		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 25

Disease Progress Models

- **Alzheimer's Disease**
  - » Progress: Linear
  - » Action: Offset
- **Parkinson's Disease**
  - » Progress: Non-Linear
  - » Action: Offset and Disease Modifying
- **Other Diseases**
  - » e.g. COPD, diabetes, hypertension
  - » Does treatment modify progression?

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 26

DATATOP Clinical Outcomes

Outcome	Definition	Number of outcomes
Death	Mortality at 8-years post study entry	98
Disability ADL15	Total ADL score ≥15	364
Cognitive Impairment MMSE24	Mini-mental state exam ≤24	89
Depression HAMD10	Hamilton-D score ≥10	183

Slide 27

Why do women live longer than men?

Slide 28

Hazards of life…

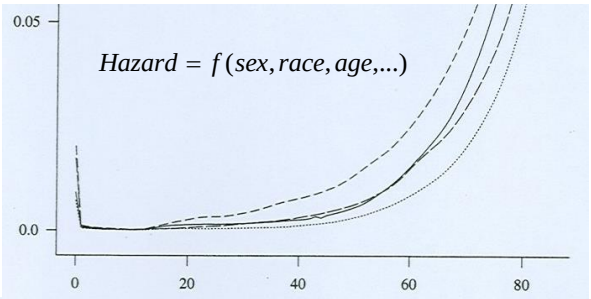


Figure 2.6 *Hazard functions for all cause mortality for the US population in 1989. White males (———); white females (·····); black males (- - - - - -); black females (—— ——).*

"… a bathtub-shaped hazard is appropriate in populations followed from birth."
Klein, J.P., and Moeschberger, M.L. 2003. *Survival analysis: techniques for censored and truncated data*. New York: Springer-Verlag.

The hazard describes the death rate at each instant of time. The shape of the hazard function over the human life span has the shape of a bathtub.
US mortality data shows the hazard at birth falls quickly and eventually returns to around the same level by the age of 60. The hazard is approximately constant through childhood and early adolescence. The onset of puberty and subsequent life style changes (cars, drugs,…) adopted by men increases the hazard to a new plateau which lasts for 10 to 20 years.
It would require a time varying model to describe how development (children) and ageing (adults) are associated with changes in death rate.

Slide 29

Hazard models link disease progress and clinical outcome probability

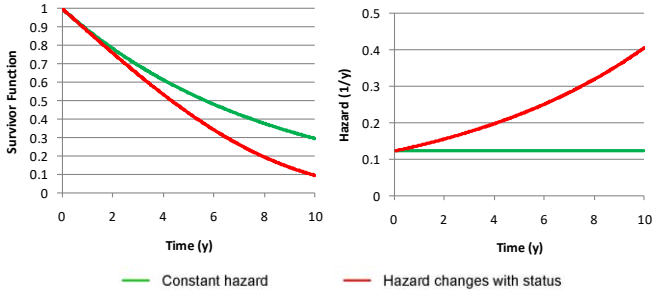
Survivor Function

$$S(t) = \Pr(T \geq t) = e^{-\int_0^t h(t)}$$

Hazard Function

$h(t)=\beta_0$

$h(t)= \beta_0 \cdot exp(\beta_{status} \cdot status(t))$



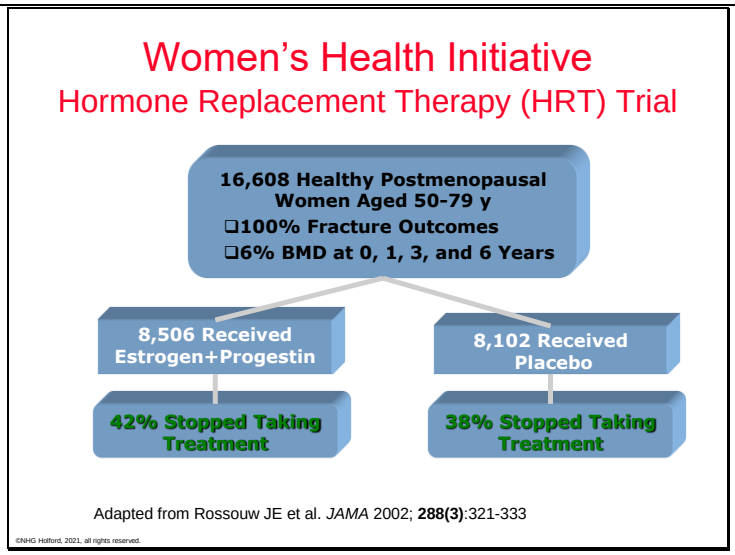
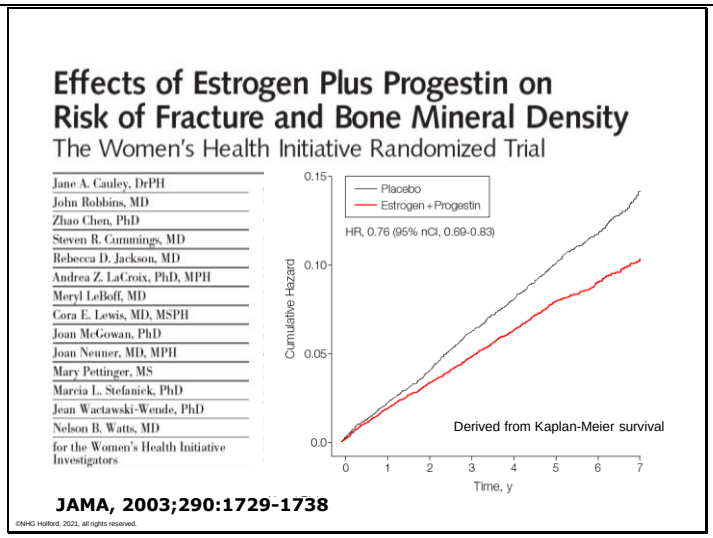
Slide 30

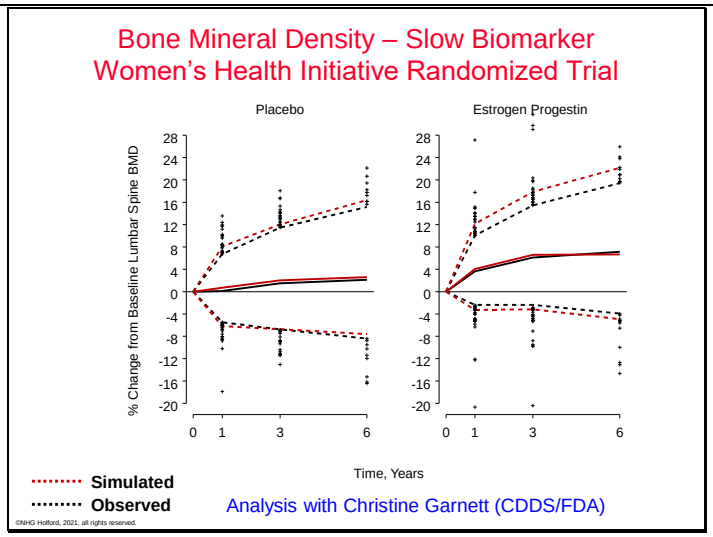
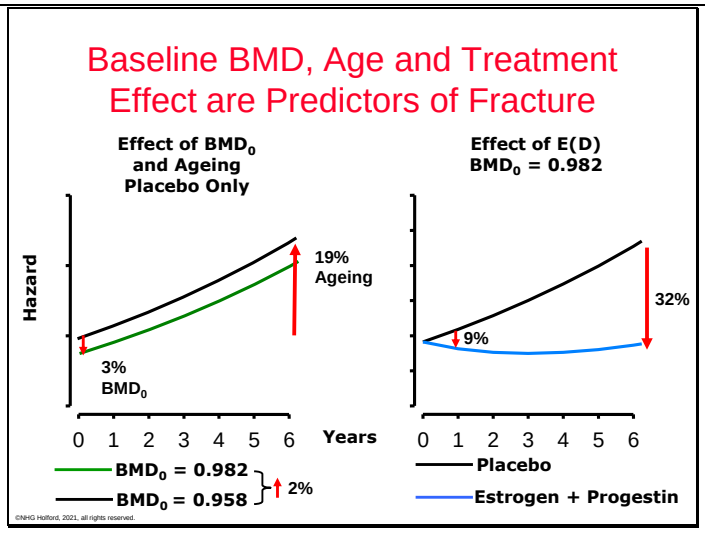
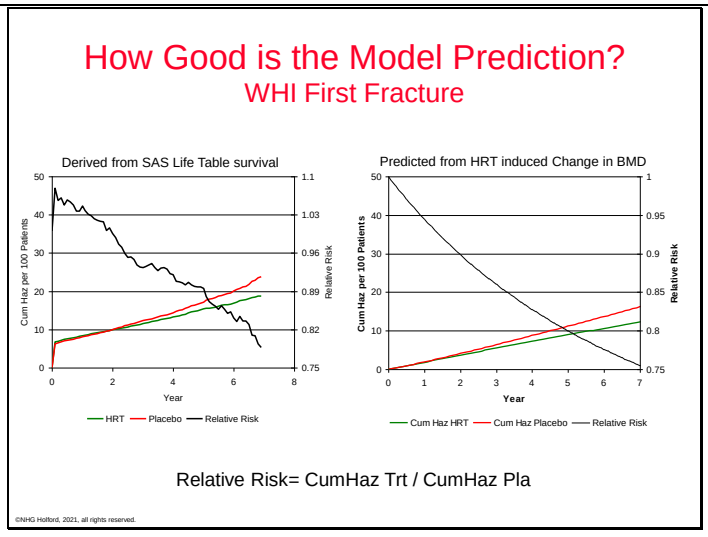
Hazard Changes for Parkinson's Outcomes

	Effects on Hazard (% difference from HR=1)			
Explanatory factors	**Death N=98**	**Disability N=364**	**Cognitive Impairment N=89**	**Depression N=183**
Age at study entry (per y)	↑ 7%	↑ 3%	↑ 8%	NS
Time since entry (per y)	↑14%	↓22%	NS	↓32%
Deprenyl[#] (10 mg/d)	↑152%	↓36%	NS	↓37%
Disease Status (per 10 units)	**UPDRS** ↑40%	**UPDRS** ↑175%	**PIGD** ↑335%	**UPDRS** ↑43%

 # = Independent of disease status effect **NS = not significant**

Slide 31	# Osteoporosis Disease Progression, Drug Action -- and Fractures 	
Slide 32	## The Link Between Bone Mineral Density and Outcome Is Well Known?  	
Slide 33	## BMD Changes and Fractures Risk ➢ Positive Correlation » Bisphosphonates » SERMs ➢ Negative Correlation » Fluoride ➢ Poor Correlation? » Calcitonin » Vitamin D and Ca++ *The link is controversial – especially for new mechanisms* *Correlation is the weakest form of understanding* *What can PKPD and disease progression modelling offer?* 	Bisphosphonates and estrogens have correlation between BMD change and fracture risk Calcitonin reduces fracture risk but does not change BMD Fluoride increases fracture risk and increases BMD Ca/vitamin D increases BMD without added reduction in fracture (hip and total fracture. JAMA 2006)

Slide 34		The WHI is a series of clinical trials designed to assess the risks and benefits of different strategies to reduce the incidence of heart disease, cancer, and fractures in postmenopausal women. One of the clinical trials in the WHI was the estrogen-progestin trial which randomized 16,600 women to either estrogen + progestin group or placebo. The trial was designed to follow these women for 9 years but after a mean follow-up of 5.2 y the study was stopped early due to increase incidence of breast cancer, heart disease and other AEs. All cause mortality was not significantly different. During the trial a substantial number of women stopped taking their assigned treatment, 42% in the estrogen-progestin arm and 38% in the placebo arm. However, these women still provided outcome data. By the end of the trial, fracture outcome was reported for all women. Bone mineral density was obtained from a 6% cohort of women. This means there was 1024 women with BMD measurements.
Slide 35		NOTE: Ca/vitamin D at doses administered show increases in BMD without added reduction in fracture (hip and total fracture) Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus Vitamin D Supplementation and the Risk of Fractures. N Engl J Med. 2006 February 16, 2006;354(7):669-83.

Slide 36		The Women's Health Initiative trial observed the time course of changes in bone mineral density in 1000 women who were treated with placebo or with hormone replacement therapy. Both groups were treated with vitamin D and calcium. Half of the placebo patients were given placebo vitamin D and calcium. This plot is a visual predictive check showing the median and 90% interval for the observed (black) and predicted (red) BMD changes. The increase in BMD in the placebo group (and some of the change in the HRT group) is attributable to treatment with vitamin D and calcium.
Slide 37		This is a deterministic simulation of the final fracture model using total body BMD NOTE: Ca/vitamin D at doses administered show increases in BMD without added reduction in fracture (hip and total fracture. JAMA 2006)
Slide 38		

Slide 39	## What Did We Learn? ➢ UPDRS is a predictor of several outcome events » Survival predicted by time course of disease progress » Deprenyl may have positive and negative benefits ➢ BMD is a predictor of fracture hazard » Slow increase in BMD due to treatment ➢ Biomarker link via hazard is a general mechanism for predicting outcome events » The missing link for translational research? ➢ Time cannot be ignored! 	The disease model contained a disease status model for BMD, a dropout model and a time-to-event model for fractures. Our modeling efforts have shown that: 1)Treatment increase BMD by 6%. But due to slow bone turnover, maximum treatment effect is not observed until 4-6 years after initiating treatment. 2)Women are more likely to stop treatment within the first year of the trial and taking E+P. Within the placebo and E+P arms, women with lower BMD are more likely to stop treatment. 3)We have shown that baseline BMD and changes in BMD due to treatment are predictors of osteoporotic fractures. Our results also showed that there was no effect of changes in BMD in the placebo group on fracture risk.
Slide 40	## Putting Time Back into The Picture "*Science is either stamp collecting or physics*" Ernest Rutherford