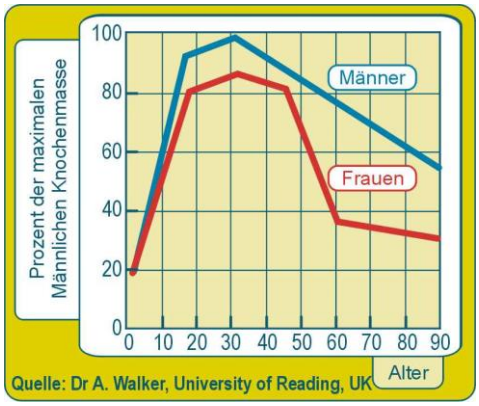
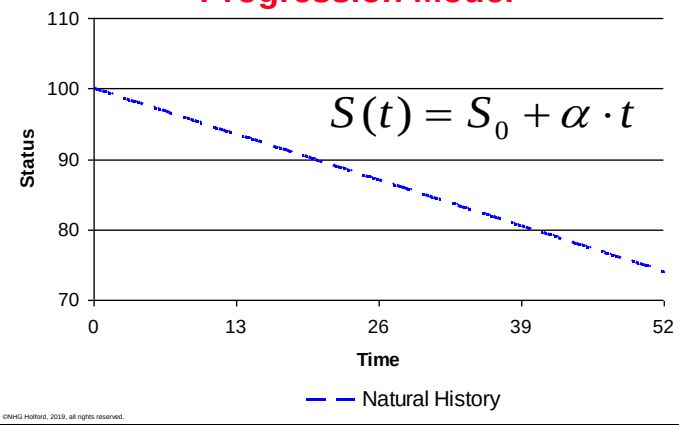
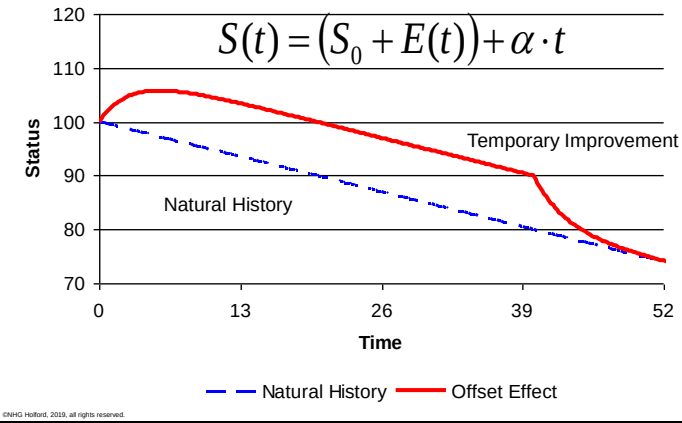
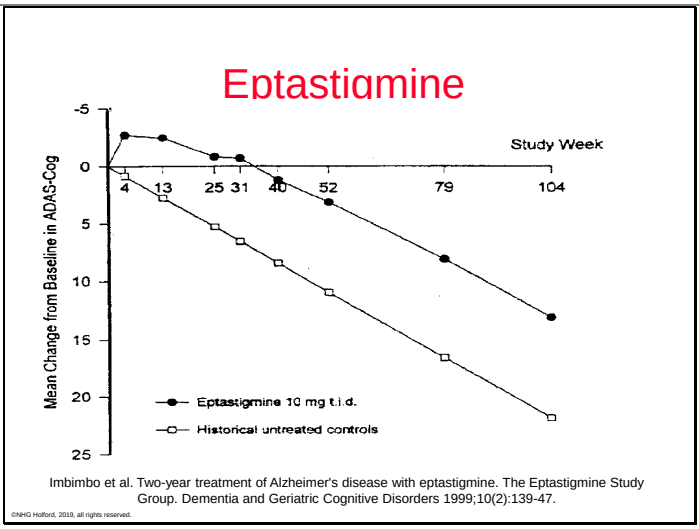
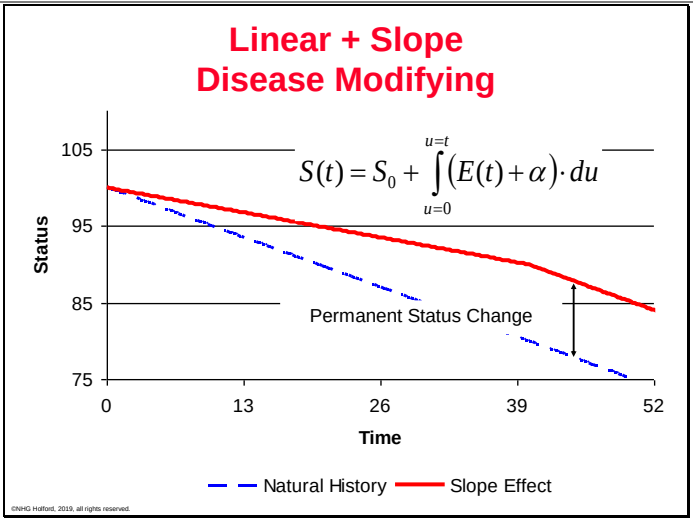
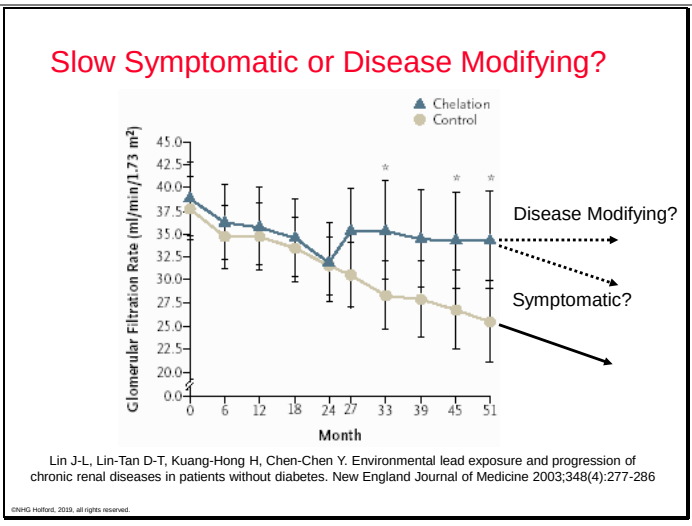
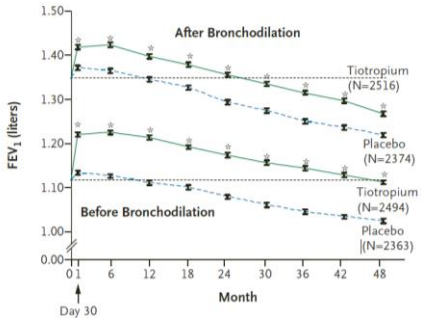
Slide 1	# Clinical Pharmacology ## Disease Progress and Drug Action Nick Holford Dept Pharmacology and Clinical Pharmacology University of Auckland	
Slide 2	# Outline 1. What is disease progress? ➢ Progress (status) and Process (mechanism) 2. Symptomatic or disease modifying? ➢ Can Regulatory Agencies help decide? 3. Disease modification ➢ Rheumatoid Arthritis, Multiple Sclerosis, COPD ? ➢ Parkinson's Disease – confirmed benefit of levodopa 	
Slide 3	# What is Clinical Pharmacology? Clinical Pharmacology = Disease Progress + Drug Action $$S(t) = S0 + \frac{Emax \cdot C(t)}{C50 + C(t)}$$ Disease Progress PKPD 	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.

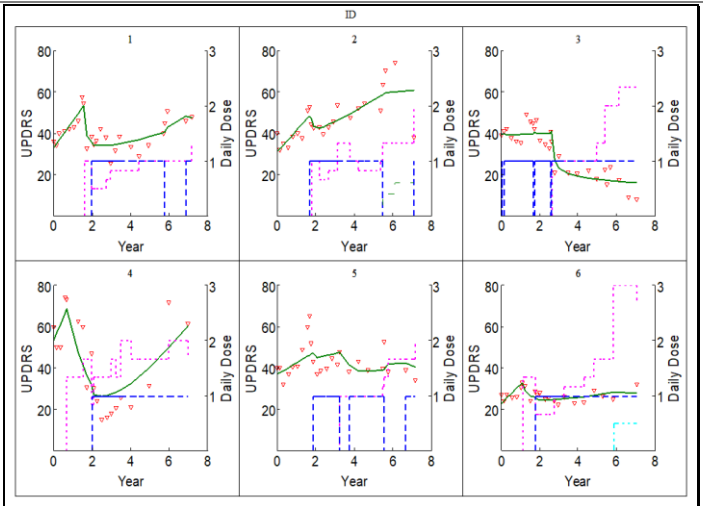
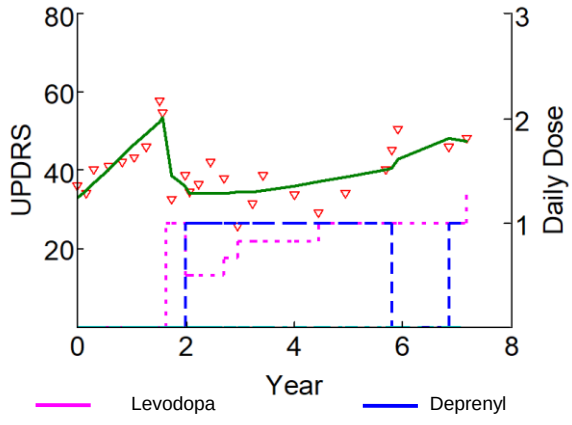
Slide 4	**Disease Progress Model** • **Quantitative model that accounts for the time course of disease status, *S(t)*:** » ***"biomarkers"*** – **Signs** - physiological or biological measurements of disease activity » ***"clinical outcome"*** – **Symptoms** - measure of how a patient feels or functions – **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  	The time course of changes in bone mass ("knockenmasse") with age ("alter") is shown in men (blue line) and women (red line). The source ("quelle") is cited as Dr A Walker from the University of Reading.
Slide 6	From Ann Walker <a.f.walker@reading.ac.uk> 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 Ann Walker Dr Ann Walker PhD MNIMH MCPP Nutritionist/Medical Herbalist Tel: +44 (0) 118 966 6930 "Discovering Herbal Medicine": 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 	

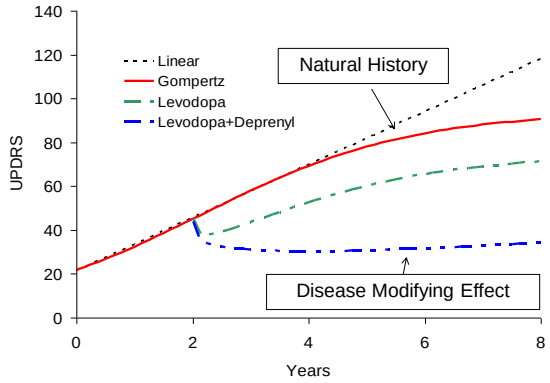
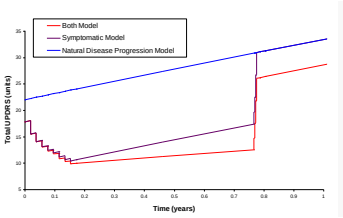
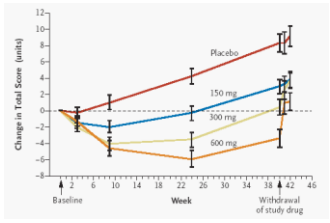
Slide 7	**The Link Between Biomarkers and Outcome Is Well Known**  	The link between low bone mineral density (biomarker) and the risk of bone fracture (outcome) is well known. This Swiss muesli was marketed with the claim that calcium and magnesium strengthen bone mass. Calcium and magnesium were added to the muesli in order to broaden its appeal to women concerned about developing osteoporosis.
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 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.

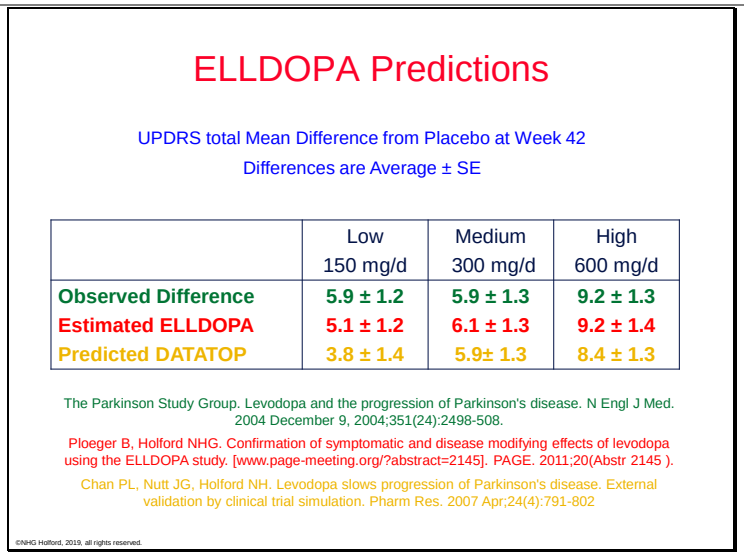
Slide 10	 Imbimbo et al. Two-year treatment of Alzheimer's disease with eptastigmine. The Eptastigmine Study Group. Dementia and Geriatric Cognitive Disorders 1999;10(2):139-47. 	The action of cholinesterase inhibitors in Alzheimer's disease is very similar for all drugs in this class. There is a delayed 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	 	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	 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.

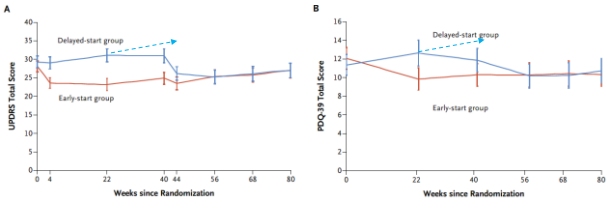
Slide 13	**Disease Progress and Process Models** ▪ Progress model describes the time course of disease status, *S(t)*  Holford NHG, Mould DR, Peck CC. Disease Progress Models. In: Atkinson A, editor. Principles of Clinical Pharmacology. San Diego: Academic Press; 2001. p. 253-62 ▪ Process model proposes an underlying mechanism to describe *S(t)*  $Rform(t) = Rform_0 \cdot \exp(-kf \cdot t) \quad Rloss(t) = Rloss_0 \cdot \exp(+kl \cdot t)$ Post TM, Freijer JI, DeJongh J, Danhof M. Disease system analysis: basic disease progression models in degenerative disease. Pharm Res. 2005;22(7):1038-49. ©NHG Holford, 2019, 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. 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. Post TM, Freijer JI, DeJongh J, Danhof M. Disease system analysis: basic disease progression models in degenerative disease. Pharm Res. 2005;22(7):1038-49.
Slide 14	**Disease Modifying - Can FDA Help Decide?** ▪ Rheumatoid Arthritis » Guidance for Rheumatoid Arthritis (2013) » No mention of disease modifying https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM354468.pdf » Webinar describing the guidance shows all drugs for RA as DMARDs (disease modifying anti rheumatic drugs) (2013) » No definition of DMARD https://www.fda.gov/downloads/drugs/ucm362589.pdf ©NHG Holford, 2019, all rights reserved.	DMARD=Disease Modifying Anti-Rheumatic Drug FDA describes drugs used to treat rheumatoid arthritis as DMARDs but does not define what disease modifying means in public documents.
Slide 15	**Disease Modifying - Can FDA Help Decide?** ▪ Multiple Sclerosis » Multiple Sclerosis Outcome Assessments Consortium Data Acquisition Highlights (2012) » No mention of disease modifying https://www.fda.gov/downloads/drugs/newsevents/ucm473655.pdf » "…all previous Phase 3 studies of disease modifying therapies (DMTs) in MS have included the effect on relapse rate as an efficacy endpoint." (2013) » No definition of DMT https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm374188.pdf ©NHG Holford, 2019, all rights reserved.	DMT=Disease Modifying Treatment FDA describes drugs used to treat multiple sclerosis as DMTs but does not define what disease modifying means in public documents.

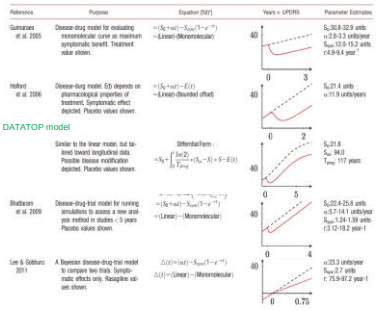
Slide 16	**Disease Modifying - Can EMA Help Decide?** ▪ Multiple Sclerosis » Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis » Mentions disease modifying therapies » No definition of disease modifying http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/10/WC500133438.pdf 	EMA has a Guideline on clinical investigation of medicinal products for the treatment of Multiple Sclerosis . Mentions disease modifying treatments but no definition of disease modifying.
Slide 17	**Chronic Obstructive Pulmonary Disease**  No sign of disease modification Winner of the prize for the most stars on a graph in the New England Journal of Medicine? 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 18	**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 with symptomatic and disease modifying effects of levodopa and deprenyl (selegeline). 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 19	 	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 20	**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 21	**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 22	**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 	The ELLDOPA study was based on the hypothesis that levodopa had toxic effects on dopaminergic neurones. If this hypothesis was true then it would suggest later treatment with levodopa would be preferable to earlier treatment.
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. An analysis of patients in the DATATOP cohort who stopped levodopa showed treatment effects took much longer than 2 weeks to wash out (Hauser & Holford 2002). 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. The DATATOP model based analysis predicted that the difference from placebo was due to a combination of symptomatic and disease modifying effects.

		Hauser RA, Holford NH. 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 24		The ELLDOPA study was simulated using the parameter estimates for disease progress and levodopa effects obtained from the ELLDOPA data (Estimated ELLDOPA). A similar simulation was performed using parameters predicted from the DATATOP cohort (Predicted DATATOP) and the levodopa washout study (Hauser & Holford 2002). The predicted difference from placebo in the three levodopa dose groups was very similar to the observed response. This is a form of external validation of the DATATOP model. It 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 model based analysis of the ELLDOPA data used the same model as DATATOP and confirmed similar symptomatic and disease modifying effects. Hauser RA, Holford NH. 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 Holford NH, 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. [DATATOP model and parameters] The Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med. 2004 December 9, 2004;351(24):2498-508. [ELLDOPA study] Ploeger B, Holford NHG. Confirmation of symptomatic and disease modifying effects of levodopa using the ELLDOPA study. [www.page-meeting.org/?abstract=2145]. PAGE. 2011;20(Abstr 2145). 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 25	**Ignoring Reality is not Science** The NEW ENGLAND JOURNAL of MEDICINE ESTABLISHED IN 1812 JANUARY 24, 2019 VOL. 380 NO. 4 Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease  Why did delayed start "placebo" patients get better? 41% (87 out of 210) in the "placebo" group took levodopa! ©NHG Holford, 2019, all rights reserved.	The LEAP trial (Verschuur et al. 2019) randomized Parkinson's patients to inactive ("placebo") or levodopa treatment for 40 weeks. At 40 weeks, patients still taking "placebo" were started on levodopa. 41% of patients in the "placebo" group were started on levodopa before 40 weeks for symptomatic reasons. The rate of UPDRS progression between 4 and 40 weeks was 50% slower in the early compared to the delayed start groups but not significantly different. The rate of UPDRS progression was reported as being faster in the delayed start group between 44 and 80 weeks which is not consistent with the figure (A) showing the time course. Verschuur CVM, Suwijn SR, Boel JA, Post B, Bloem BR, van Hilten JJ, et al. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease (LEAP). N Engl J Med. 2019;380(4):315-24
Slide 26	**Untenable Statistical Analysis Assumptions** VIEWPOINT The Final Nail in the Coffin of Disease Modification for Dopaminergic Therapies The LEAP Trial JAMA Neurology July 2019 Volume 76, Number 7 VIEWPOINT Harms From Uninformative Clinical Trials JAMA Published online July 25, 2019 The conclusions of the LEAP trial are invalid because of the intention to treat analysis. This ignores that 41% of patients assigned to inactive "placebo" treatment actually took levodopa. The LEAP trial should be the nail in the coffin for uninformative clinical trials using intention to treat analysis to understand biology and science! ©NHG Holford, 2019, all rights reserved.	Espay (2019) concludes there is no support for disease modifying benefits of levodopa but does not seem to be aware of the results of the DATATOP and ELLDOPA analyses which predict and confirm a disease modifying effect of levodopa (Holford et al. 2006, Chan et al. 2007, Ploeger & Holford 2011). Zarin et al. (2019) caution about the harm arising from uninformative clinical trials which may be uninformative because of inappropriate analysis. The LEAP trial (Verschuur et al. (2019) is uninformative because the intention to treat analysis wrongly assumes that all patients receiving inactive ("placebo") treatment in the first 40 weeks. In fact 41% of patients were switched to levodopa because of unacceptable progression of symptoms. This means these patients would have slower progression in the first 40 weeks and any disease modifying effects from levodopa would be carried forward to the second 40-80 week period. This necessarily reduces the difference between the delayed and early start groups when evaluated at 80 weeks. Holford NH, 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. 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. Ploeger B, Holford NHG. Confirmation of symptomatic and disease modifying effects of levodopa using the ELLDOPA study. [www.page-meeting.org/?abstract=2145]. PAGE.

		2011;20(Abstr 2145). Verschuur CVM, Suwijn SR, Boel JA, Post B, Bloem BR, van Hilten JJ, et al. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease (LEAP). N Engl J Med. 2019;380(4):315-24 Espay AJ. The Final Nail in the Coffin of Disease Modification for Dopaminergic Therapies: The LEAP Trial. JAMA Neurology. 2019;76(7):747-8 Zarin DA, Goodman SN, Kimmelman J. Harms From Uninformative Clinical Trials JAMA. 2019.
Slide 27	**Parkinson's Disease** The Parkinson Study Group DATATOP cohort is the only prospectively validated model for prediction of the disease modifying effect of dopaminergic treatment DATATOP model  Venuto CS, Potter NB, Ray Dorsey E, Kieburtz K. A review of disease progression models of Parkinson's disease and applications in clinical trials. Mov Disord. 2016;31(7):947-56. 	Venuto CS, Potter NB, Ray Dorsey E, Kieburtz K. A review of disease progression models of Parkinson's disease and applications in clinical trials. Mov Disord. 2016;31(7):947-56.
Slide 28	**Conclusions** ▪ Disease progression captures changes in disease status with time ▪ Looking at graphs of disease time course can help understand natural history and effects of treatment ▪ Model based description can distinguish symptomatic from disease modifying effects of treatment ▪ Disease progression can help understand and predict disease outcome events ▪ Avoid intention to treat analysis for scientific investigation 	