http://www.page-meeting.org/page/page2007/ModellingDiseaseProgression.pdf

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Modelling Disease Progression

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Outline

1. What is disease progress?
2. Models for disease progress
3. Models for drug action
4. Placebo effects
5. Practical Example

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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.

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Old Model - New Meaning

$$E = E0 + \frac{E\max \cdot Conc}{EC50 + Conc}$$

Disease Progress 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.

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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.

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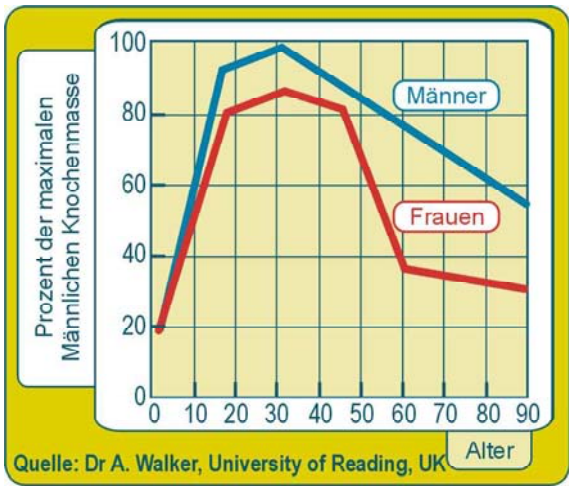

A biomarker description of disease progress.
Bone mineral density (Knochenmasse) measured in men (Manner) and women (Frauen) is shown over ages (Alter) ranging from 0 to 90. Most therapeutic studies on bone mineral density (BMD) cover less than 10 years so there is a limited understanding of drug effects 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.

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Components of a Disease Progression 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.
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 response as a separate component.
Simple disease progress models are described in 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.
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.

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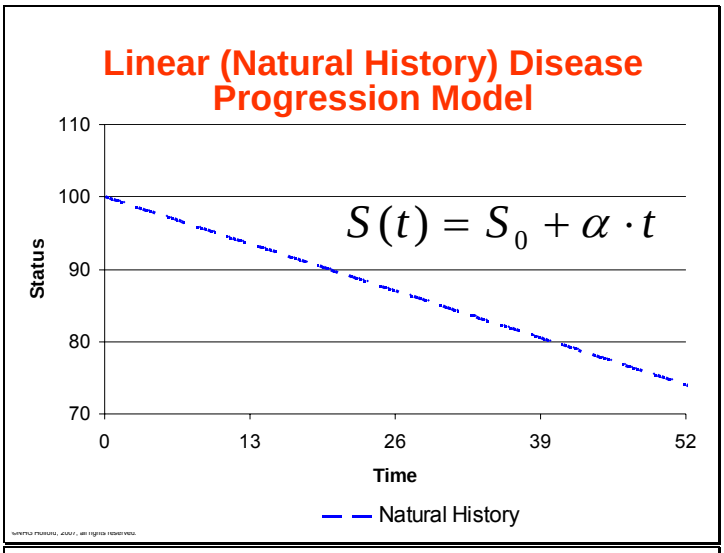

The simplest model to describe changing disease status with time is linear. In general if the change is relatively small in relation to the time scale of observation then any disease progress curve will reasonably described by a linear function.

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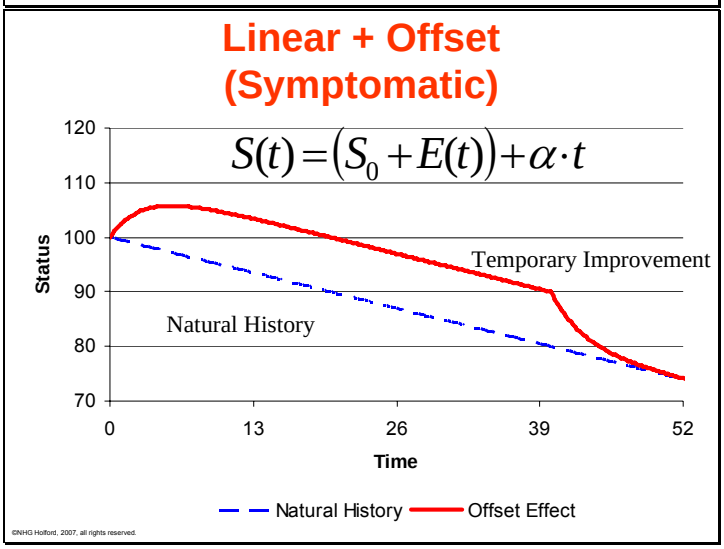

With any disease progress model it is possible to imagine a drug action that is equivalent to a change in the baseline parameter of the model. This kind of effect on disease produces a temporary offset. When treatment is stopped the response to the drug washes out and the status returns to the baseline. 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.

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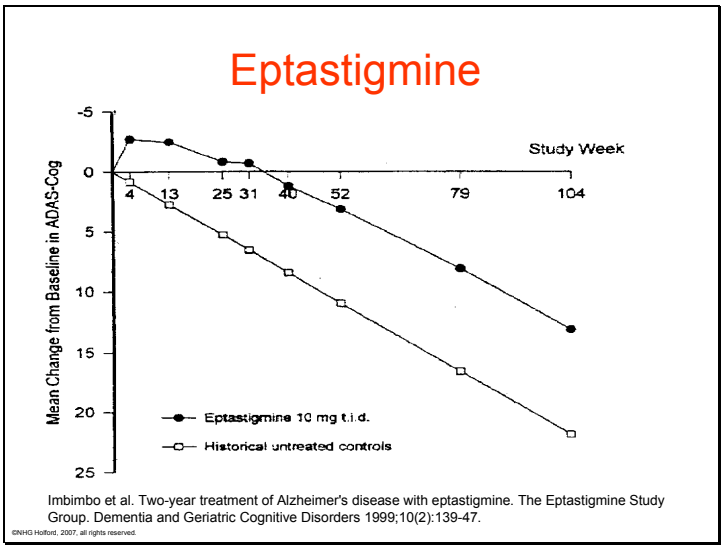

The action of cholinesterase inhibitors in Alzheimer's disease is very similar for all drugs in this class. There is a delayed onset of benefit taking 2 to 3 months to reach its peak followed by continuing progression of the disease at the same rate as expected from natural history progression. This 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.

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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.

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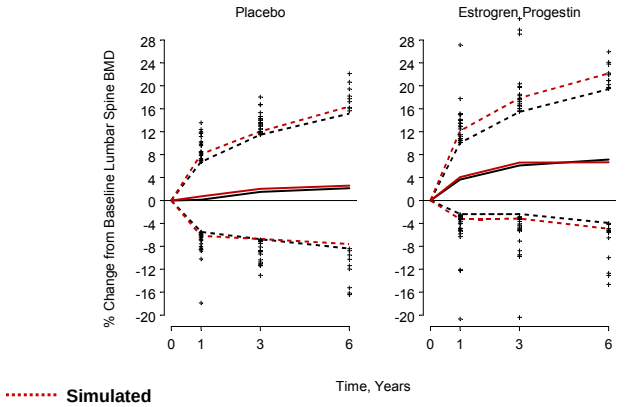
Bone Mineral Density – Slow Biomarker
Women's Health Initiative Randomized Trial



Analysis by Christine Garnett (CDDS/FDA)

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.

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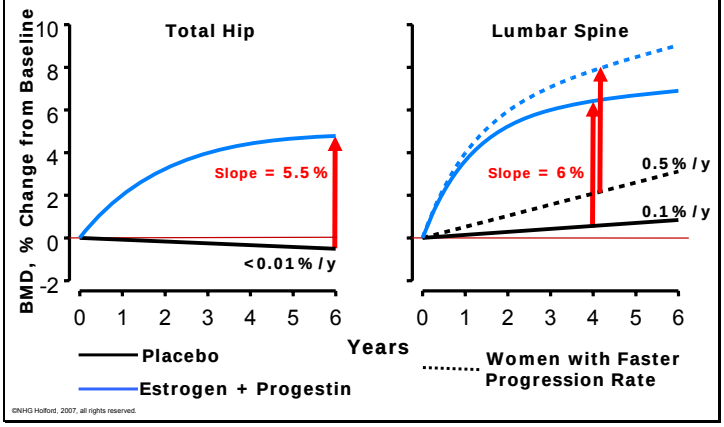
BMD Time Course

70 kg woman 13 years post menopause



These figures shows some key results for the Hip and Spine models which represent two different types of bone.
For the hip bone, there was a trend for bone loss with a progression rate of less than 0.01% per year. Maximum treatment effect was estimated to be 6% of baseline. But by year 6, 94% of treatment effect was observed. The effect compartment half-life at the hip was 1.53 years.
At the lumbar spine, women gained bone mass during the trial. Approximately 52% of the women's progression rate was 0.1% per year and the remaining women gained

bone with a rate of 0.5% per year. These two patterns of response may have been due to use of vitamin D and calcium. Some patients only received placebo vitamin D and calcium.
Maximum treatment effect from hormones was approximately 6% of baseline. The effect compartment half-life at the lumbar spine was 0.81 years. Due to the shorter equilibration T1/2, maximum treatment effect was observed by year 4 at the lumbar spine.

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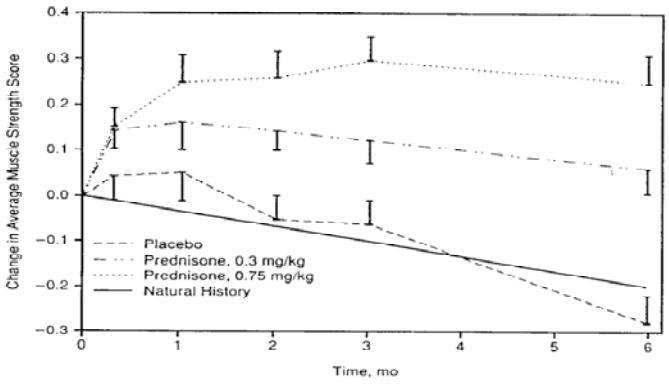
Linear + Offset + Placebo



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 response to placebo 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.

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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)*EXP(ETA(4))
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.

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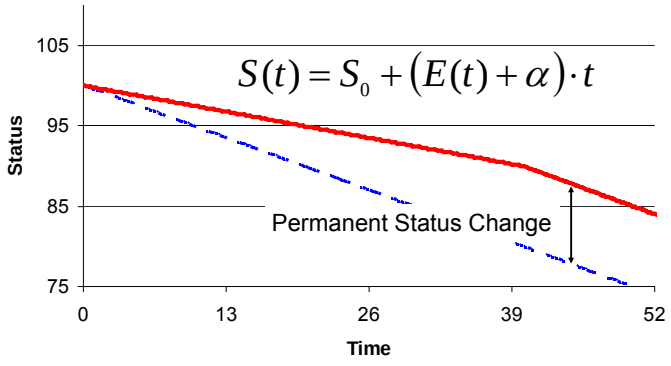
Linear + Slope (Protective)



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 permanent effect after stopping treatment is the hallmark of a protective action.

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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

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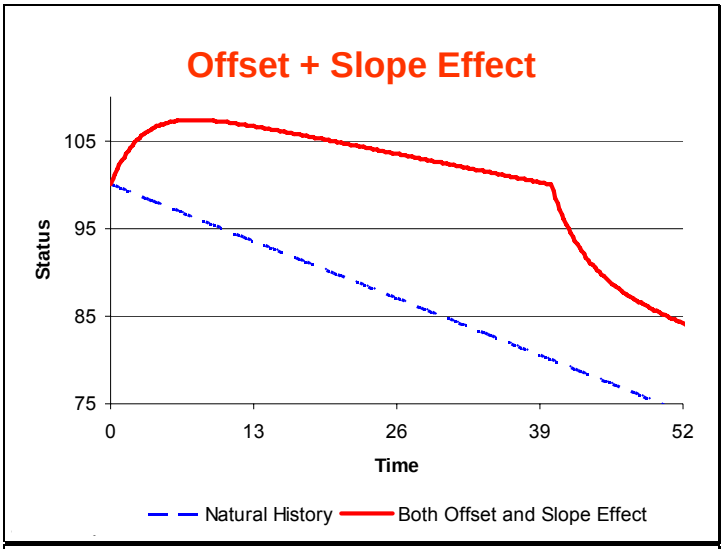

There is no reason to think that drug effects must be either offset or slope types. It is possible to have both kinds of effect due to the same drug.

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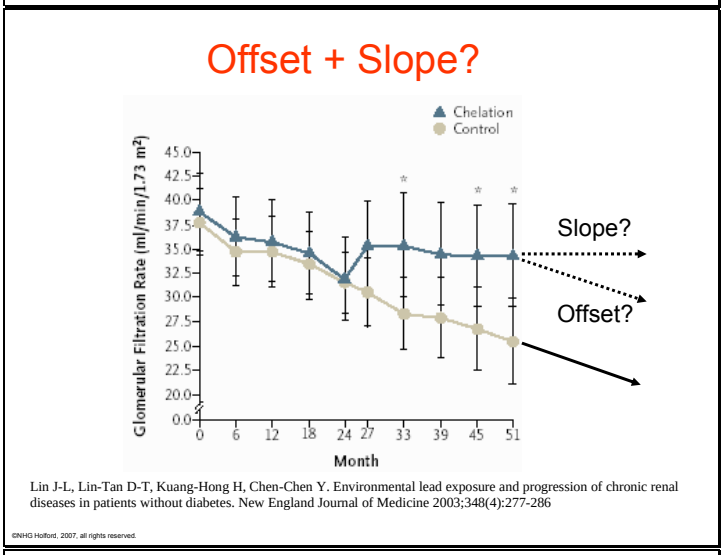

Lin J-L, Lin-Tan D-T, Kuang-Hong H, Chen-Chen Y. Environmental lead exposure and progression of chronic renal diseases in patients without diabetes. New England Journal of Medicine 2003;348(4):277-286

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 protective effect from a slow onset offset effect.

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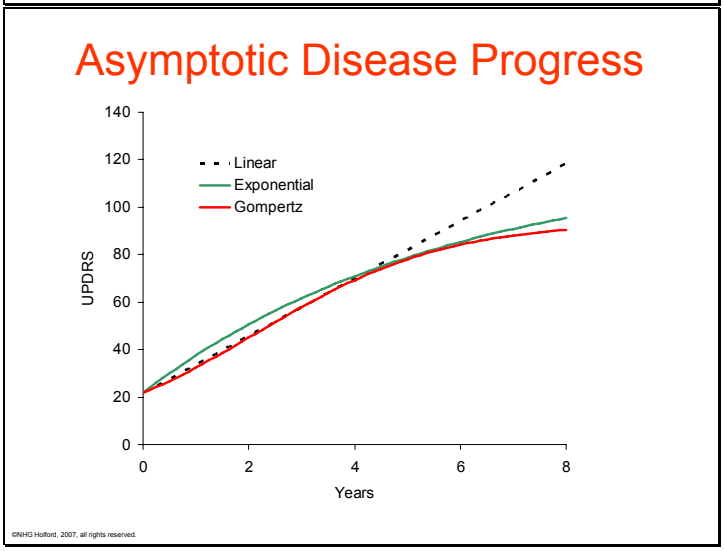

The shapes of the linear, exponential asymptote and Gompertz asymptote are shown based on estimates obtained in patient's with Parkinson's disease. The exponential and Gompertz models have different time courses. The exponential model has a more rapid initial slope.

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Asymptotic Disease Progress

Linear $$\frac{dS}{dt} = \alpha \cdot f(Rx)$$

Exponential $$\frac{dS}{dt} = \frac{\ln(2)}{Tprog} \cdot (Sss \cdot f(Rx) - S)$$

Gompertz $$\frac{dS}{dt} = \frac{1}{Tprog \cdot f(Rx)} \cdot (Sss - S) \cdot S$$

α = Linear progression rate
Tprog = Progression time constant
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 an offset drug effect.
A linear model has as slope parameter which is the basis for a protective 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.

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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.

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A Real Example

Disease Progression in Parkinson's Disease

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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.

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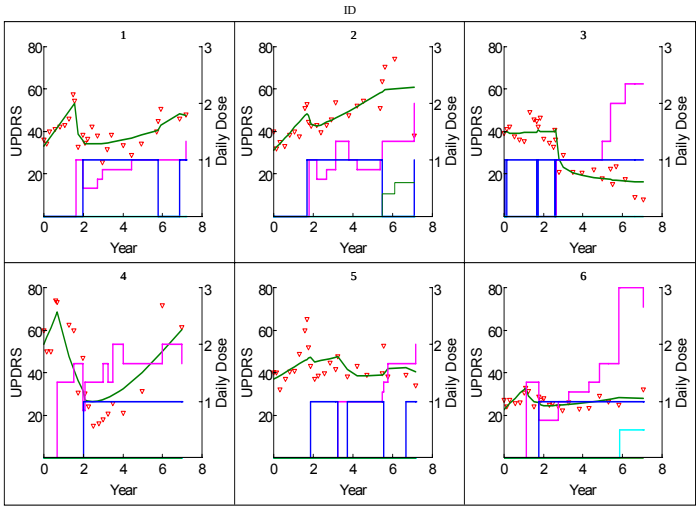

Disease status was followed with the Unified Parkinson's Disease Response Scale (UPDRS). The UPDRS patterns were quite variable from patient to patient. A major source of variability was the response to individual drug treatments.

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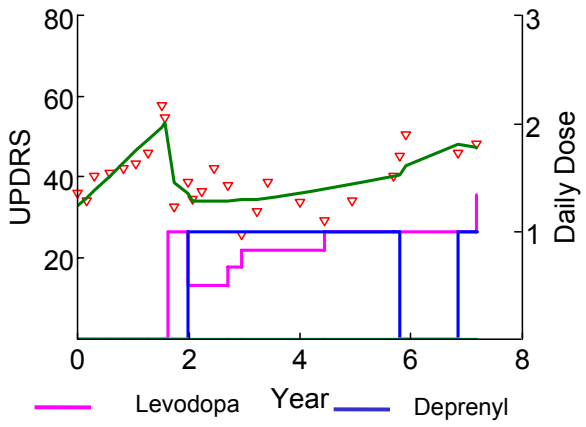
Offset + Slope Effect?



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.

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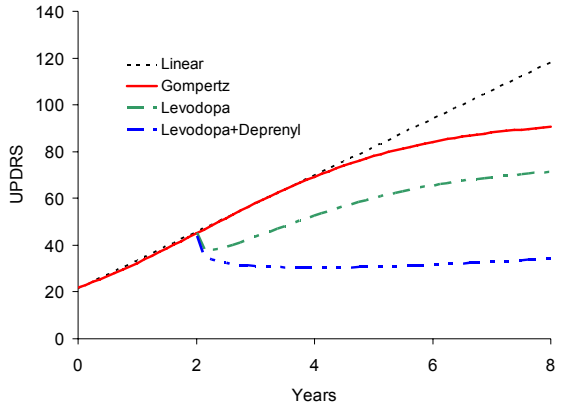
Offset and Protective Effects of Levodopa and Deprenyl



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.

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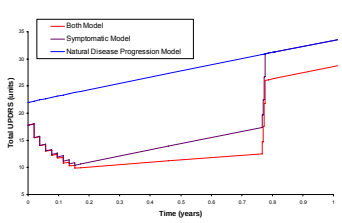
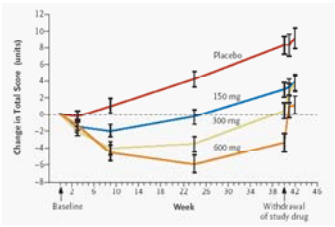
ELLDOPA Before and After



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 protective effect or a very slow loss of symptomatic effect.

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Clinical Trial Simulation

UPDRS total Mean Difference from Placebo
Reported ELLDOPA Observations
100 Simulated Trial Replications ± SD

	Low 150 mg/d	Medium 300 mg/d	High 600 mg/d
Observed Difference	5.9 ± 0.7	5.9 ± 0.8	9.2 ± 0.9
Predicted Difference	3.8 ± 1.4	5.9 ± 1.3	8.4 ± 1.3

Predictions made before ELLDOPA Results Reported

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.
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.

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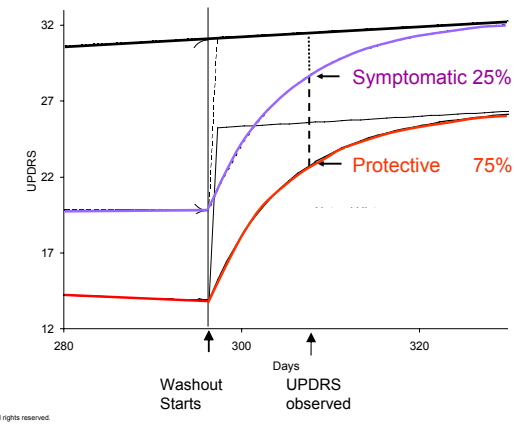
What Happened in ELLDOPA?



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 protective 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.
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.

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Disease Progress Models

- **Alzheimer's Disease**
  - Progress: Linear
  - Action: Offset
- **Post-Menopause Bone Loss**
  - Progress: Linear
  - Action: Offset? Slope?
- **Parkinson's Disease**
  - Progress: Non-Linear
  - Action: Offset and Protective

The time course of biomarkers in Alzheimer's disease, post-menopausal bone loss and Parkinson's disease has been used to identify the shape of the natural history curve for the biomarker. Drug actions can also be identifed. For post-menopausal bone loss the time course of response is very slow and it is not clear if the drug action is simply a slow offset effect of if there may also be protective actions as well.

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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.