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# Disease Progression and Models for Disease Progression

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# Outline

- Disease progression – general perspectives
- Modelling disease progression
- Drug effect and disease progression
- Example: Disease progression in osteoporosis

# Disease progression

*What does it mean?*

- Characterization of disease over time
  - Natural history of the disease
  - Uncontaminated by placebo or treatment response

*Why is it important?*

- Treatment response may be influenced by underlying disease
- By modelling it could be possible to separate between
  - Changes in disease
  - Placebo effect
  - Active drug effect
- Linking PKPD with disease models → better understanding of mechanism of drug action (and disease)
- Clinical trial simulation – predict outcome of a trial

# Handling of disease progression

## Traditional way

- assume no change in disease - success/failure is due to drug treatment only or
- let placebo response account for disease progression

## Better way

- parametric models describing change in disease over time
- based on biomarker



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## Time aspects

### Macroscopic - whole life - Chronic

- Relapses
- Seasonal variation (chronopharmacologic)

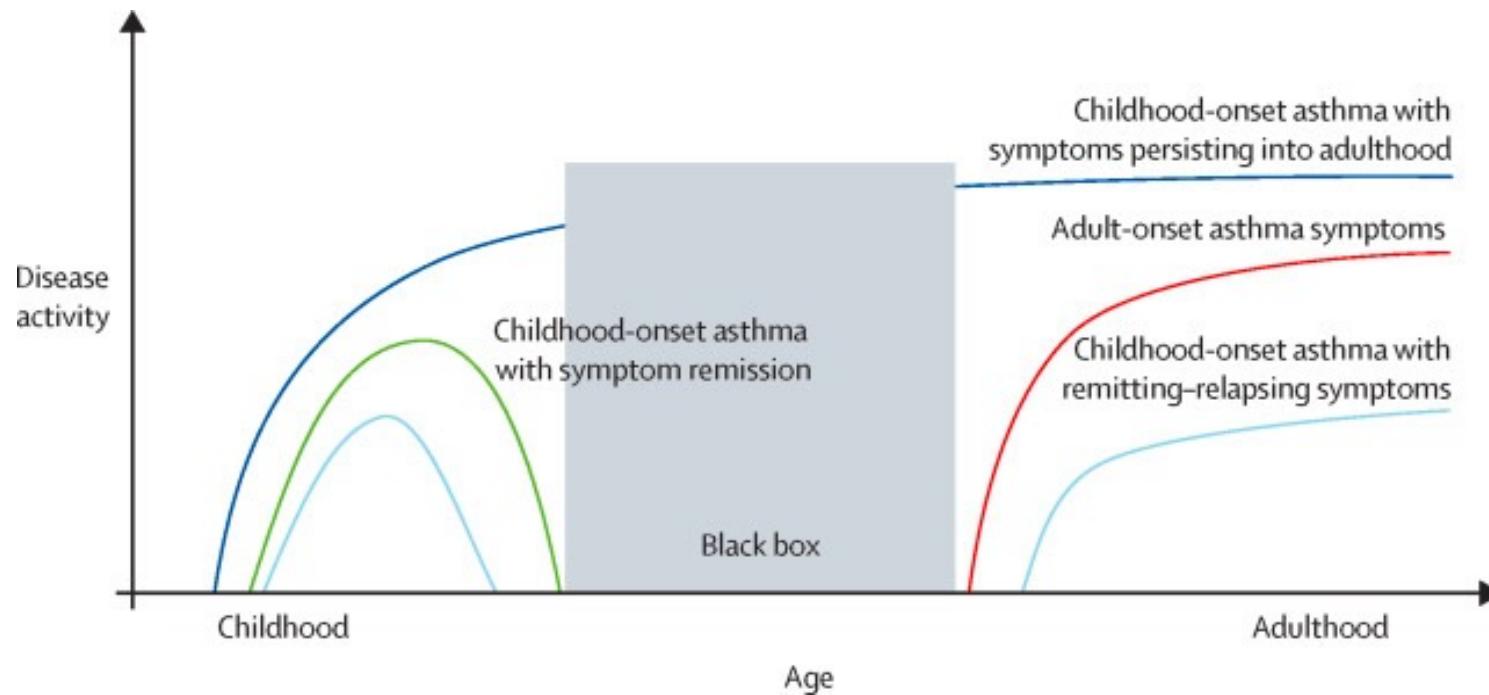
### Microscopic - within an attack - Acute

- Circadian variation
- Onset rate



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## Macroscopic aspect Asthma



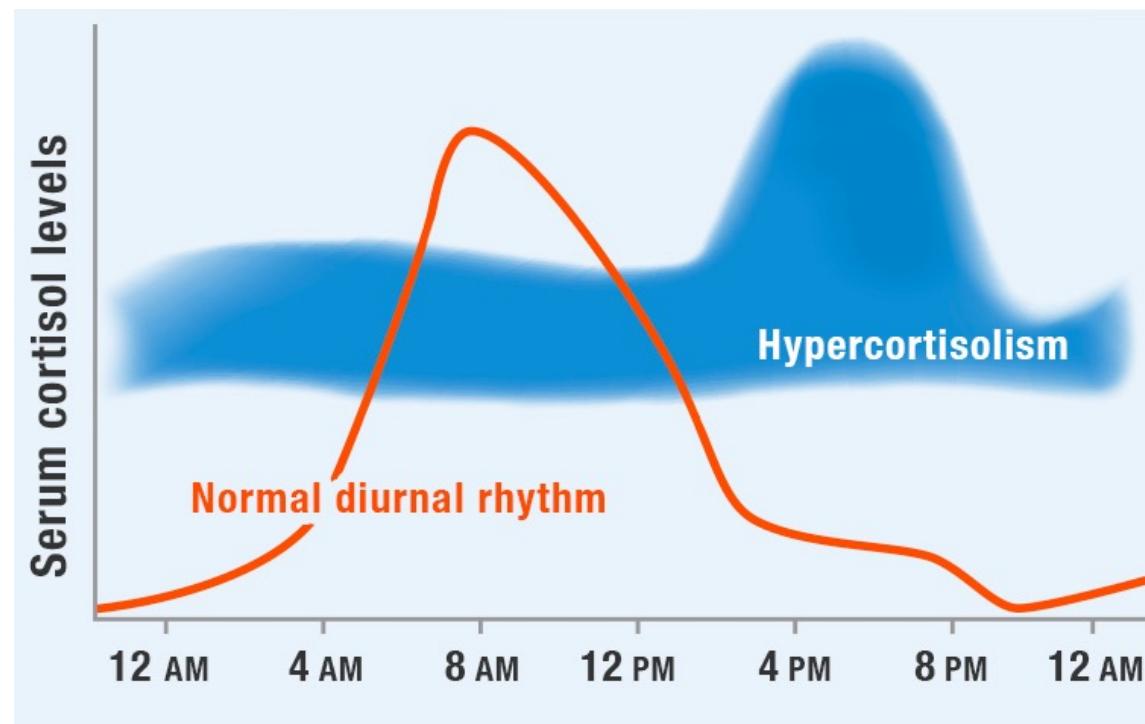
Fuchs et al., Lancet 2017



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## Microscopic aspect Cortisol

Diurnal rhythm



<https://www.cortisolmatters.com/about-hypercortisolism>

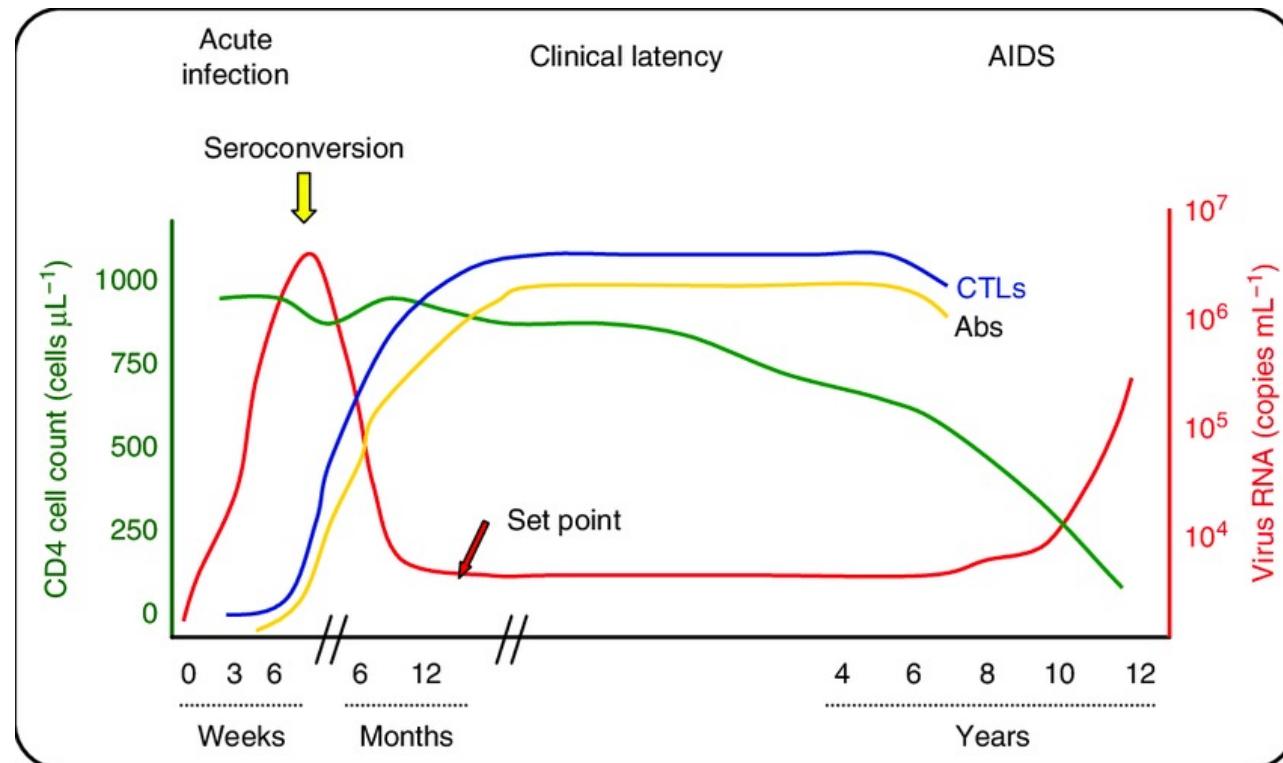


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HIV

HIV infect CD4+ T cells

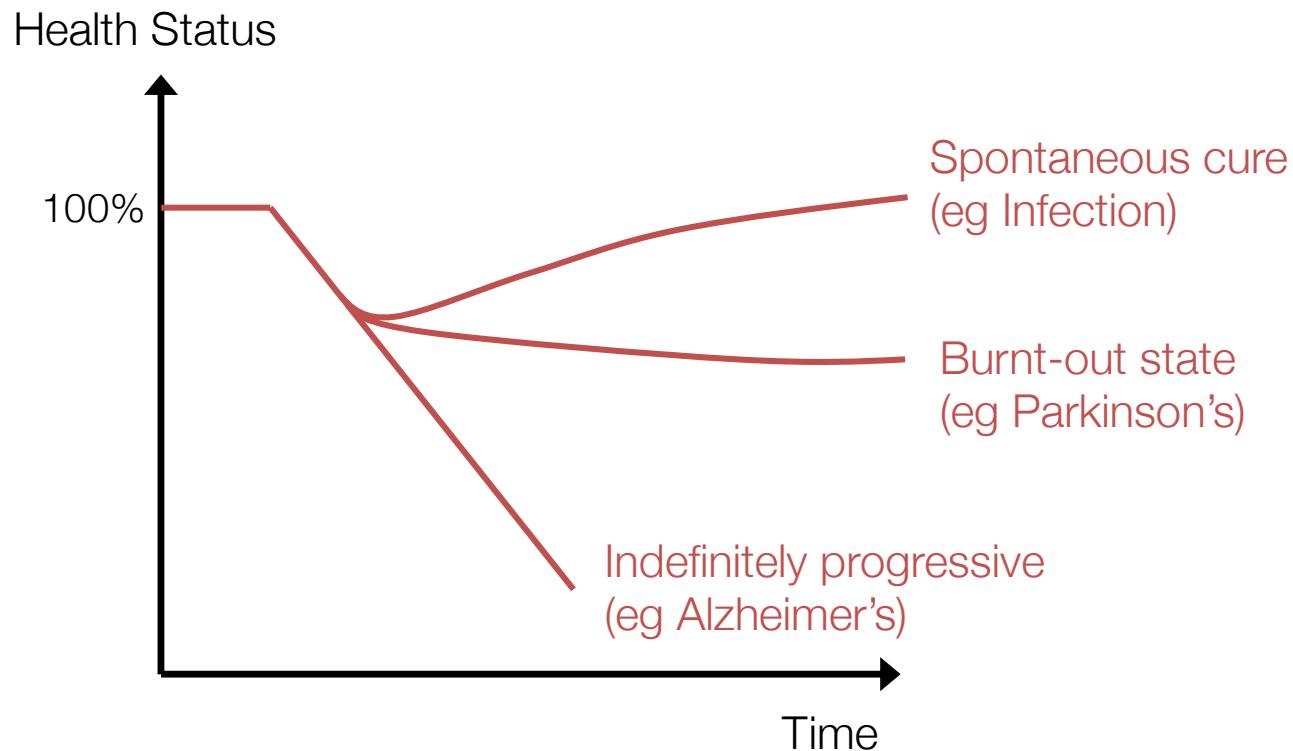
CTL = cytotoxic T lymphocyte  
Abs = Antibodies





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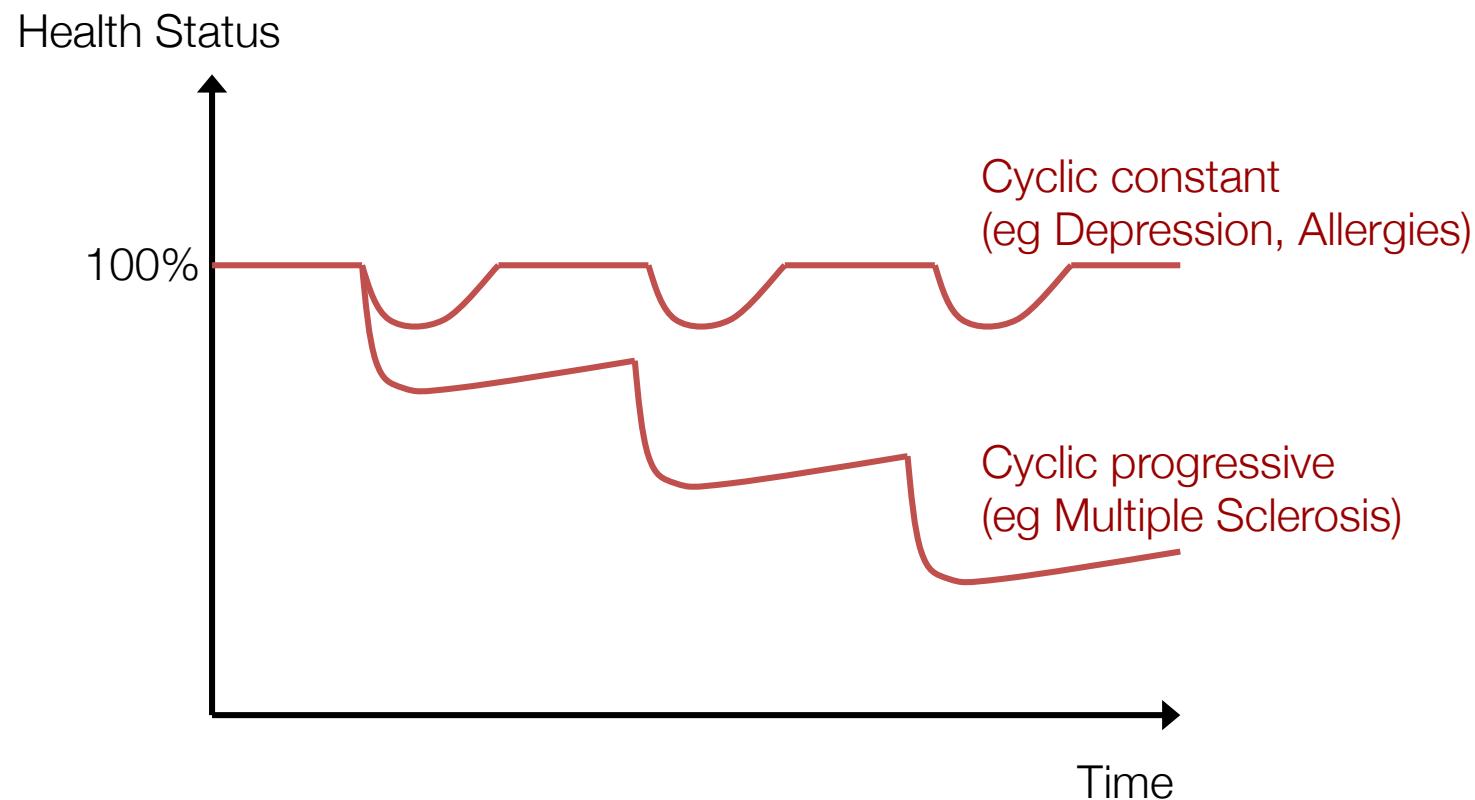
## Common types of disease progression





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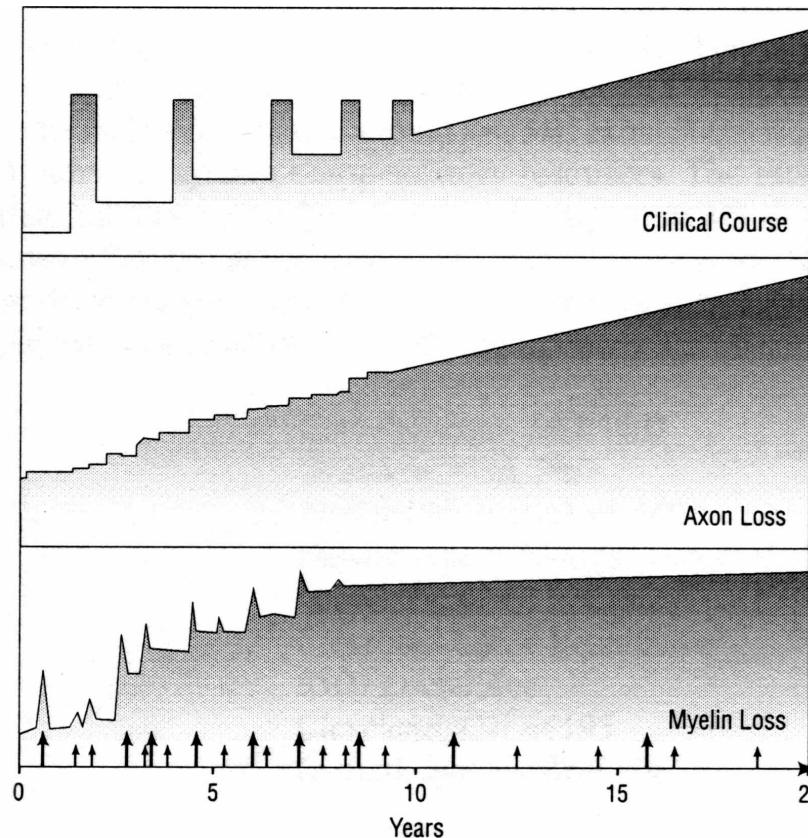
## Cyclic/relapsing diseases





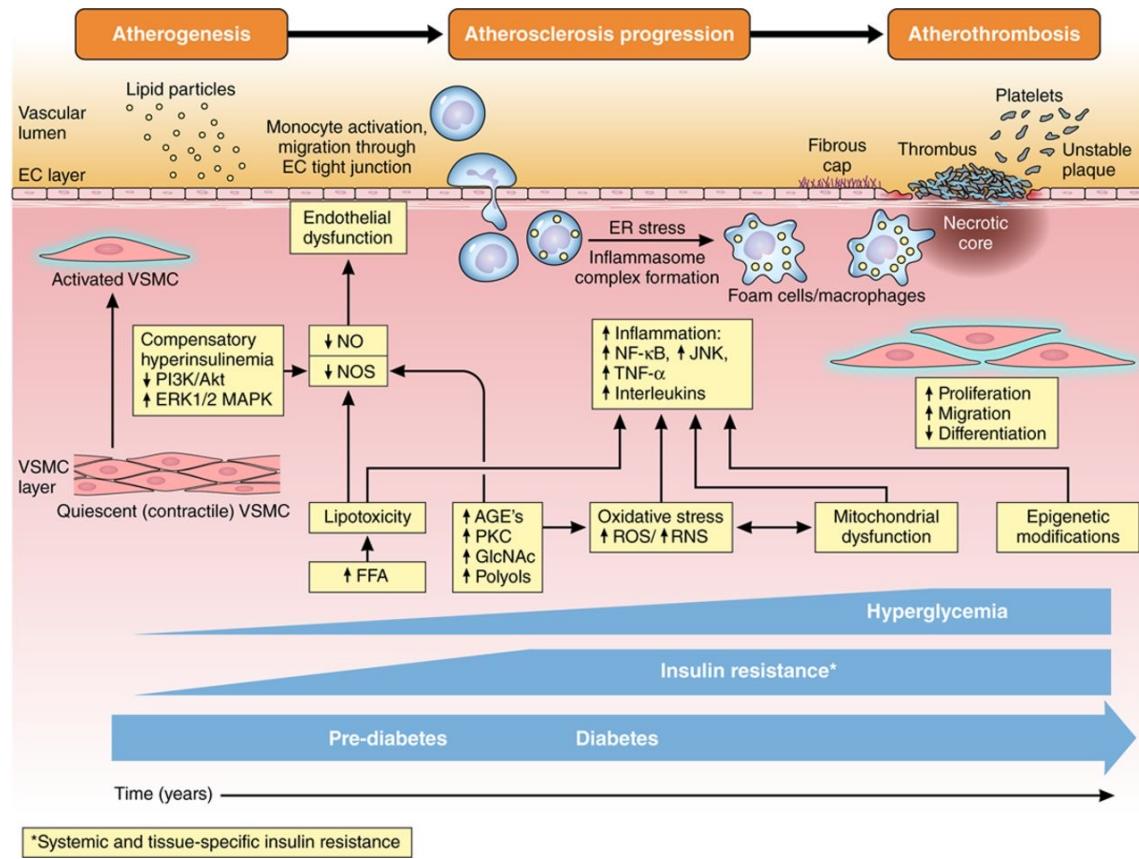
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# Relapsing-Progressing disease Multiple Sclerosis



Bjartmar et al. Arch Neurol 2001; 58:37-39

# Detailed description of Disease Diabetes Type II



Low Wang. Circulation 2016



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# Modelling disease progression

## Disease status (S)

S – Clinical measure of disease severity (Health state)

$S(t) = \text{Baseline } (S_0)$

- + Disease progression
- + Placebo response
- + Drug effects

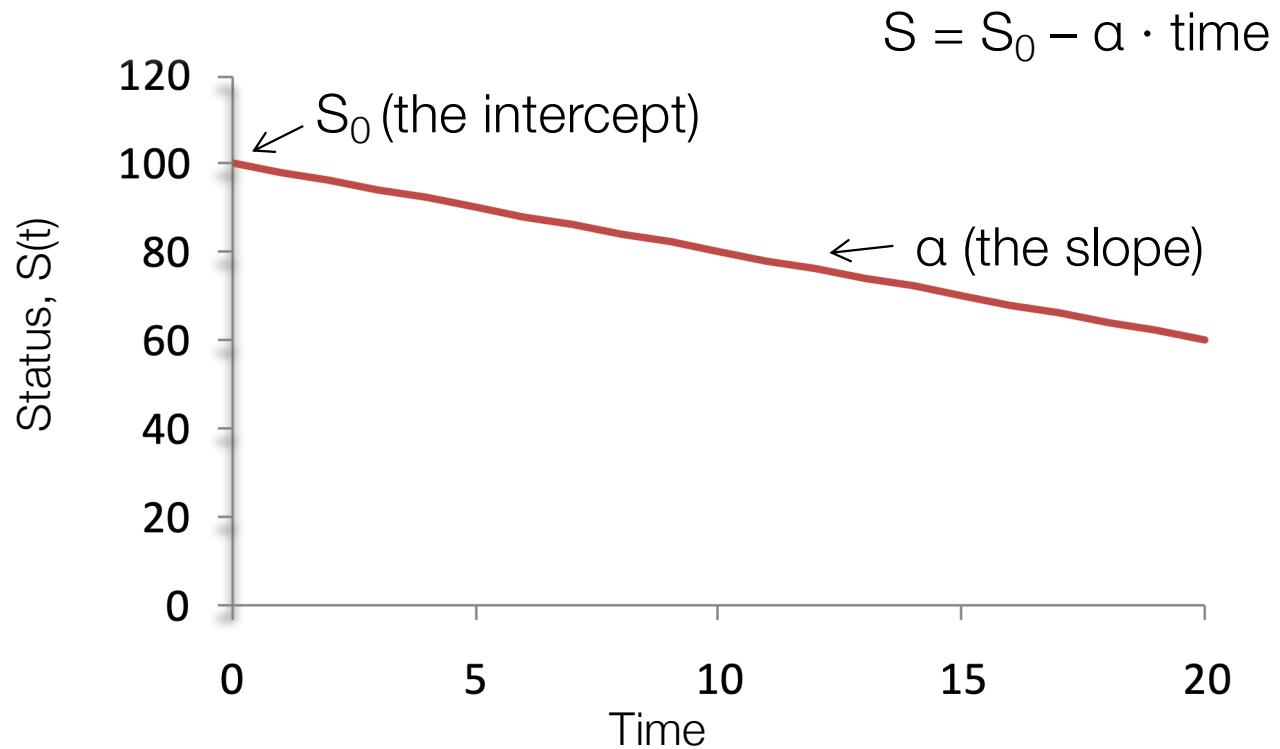
} Often difficult to separate  
based on collected data

- Objective/Subjective measure
- Time frame



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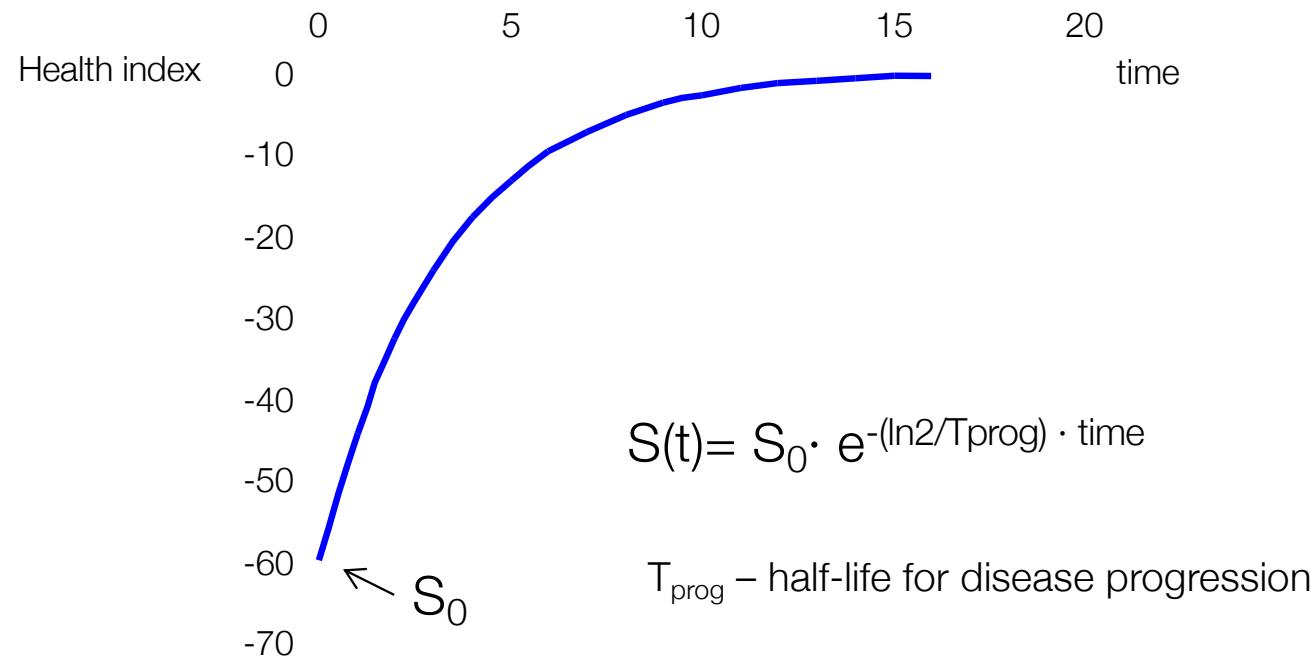
## Linear disease progression





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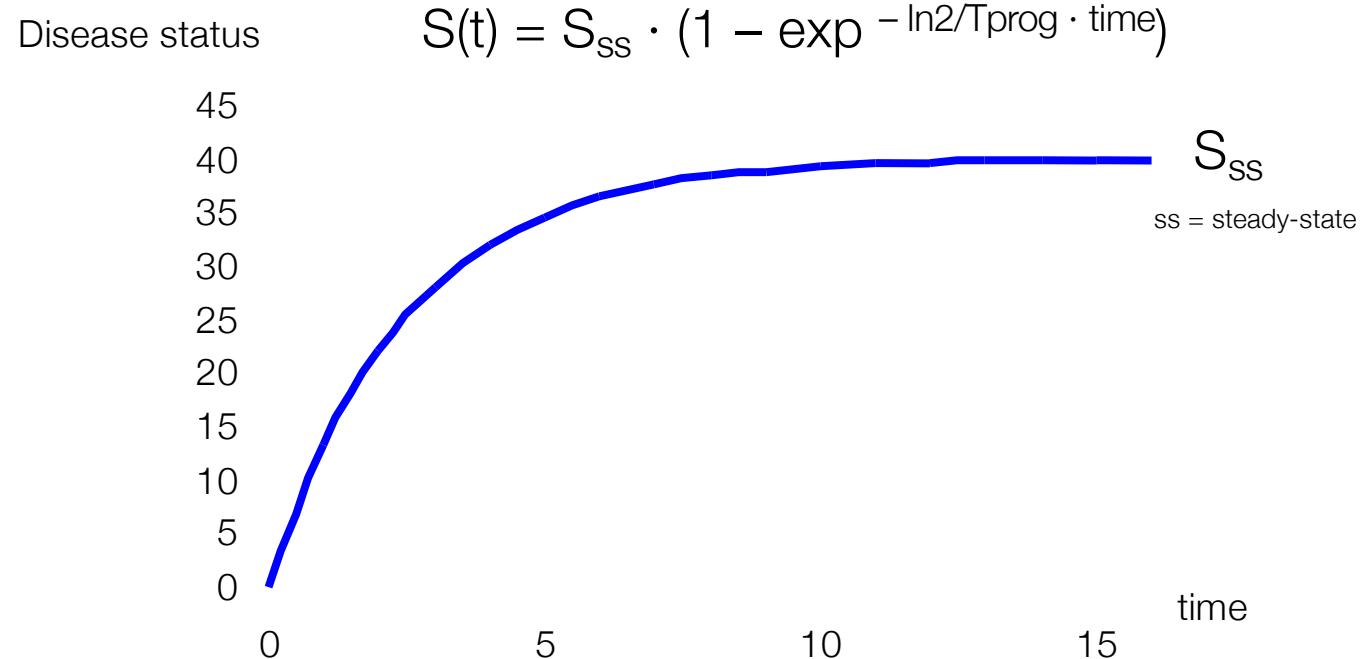
## Asymptotic progress model Spontaneous recovery





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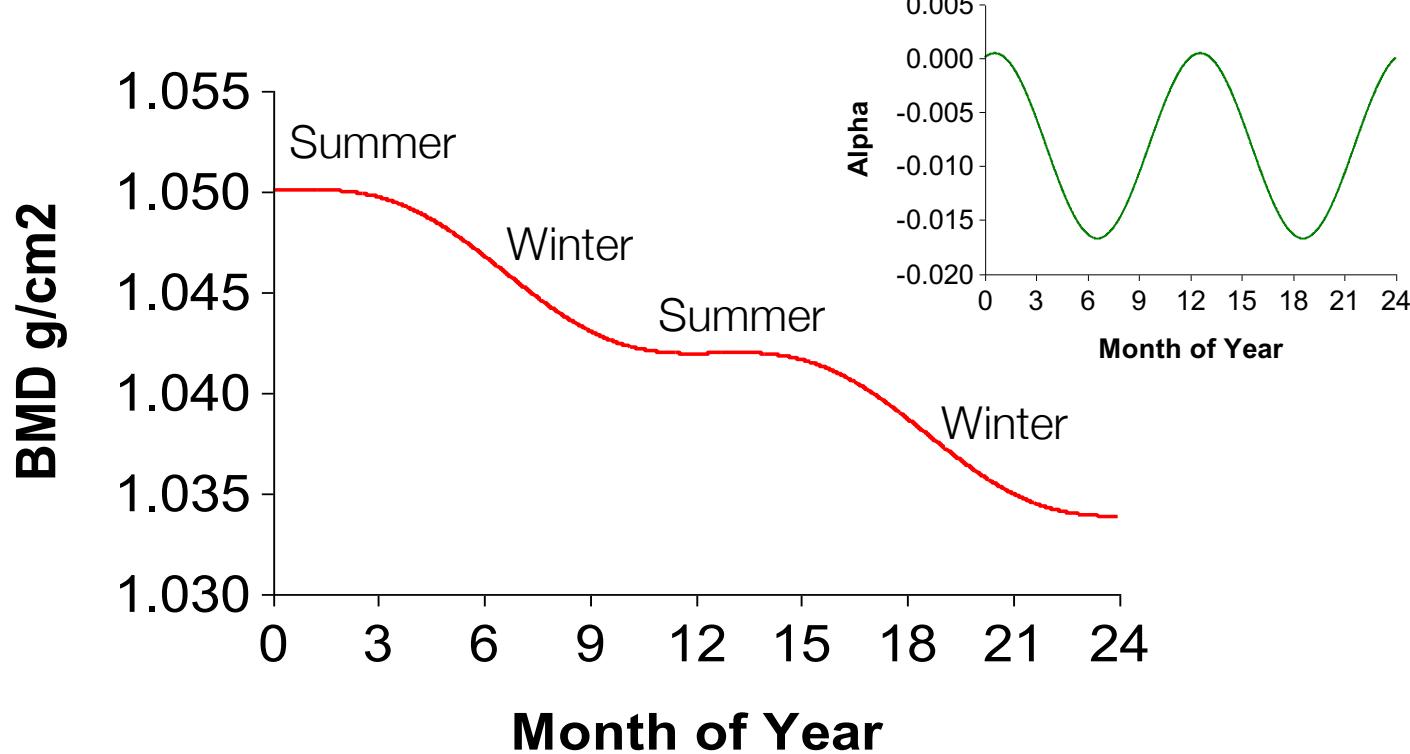
## Asymptotic progress model "burnt-out" state





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## Seasonal Variation in Bone Mineral Density (BMD)



Month 0 = Summer

Holford et al., ASCEPT, 2000



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# Drug effect on Disease Progression

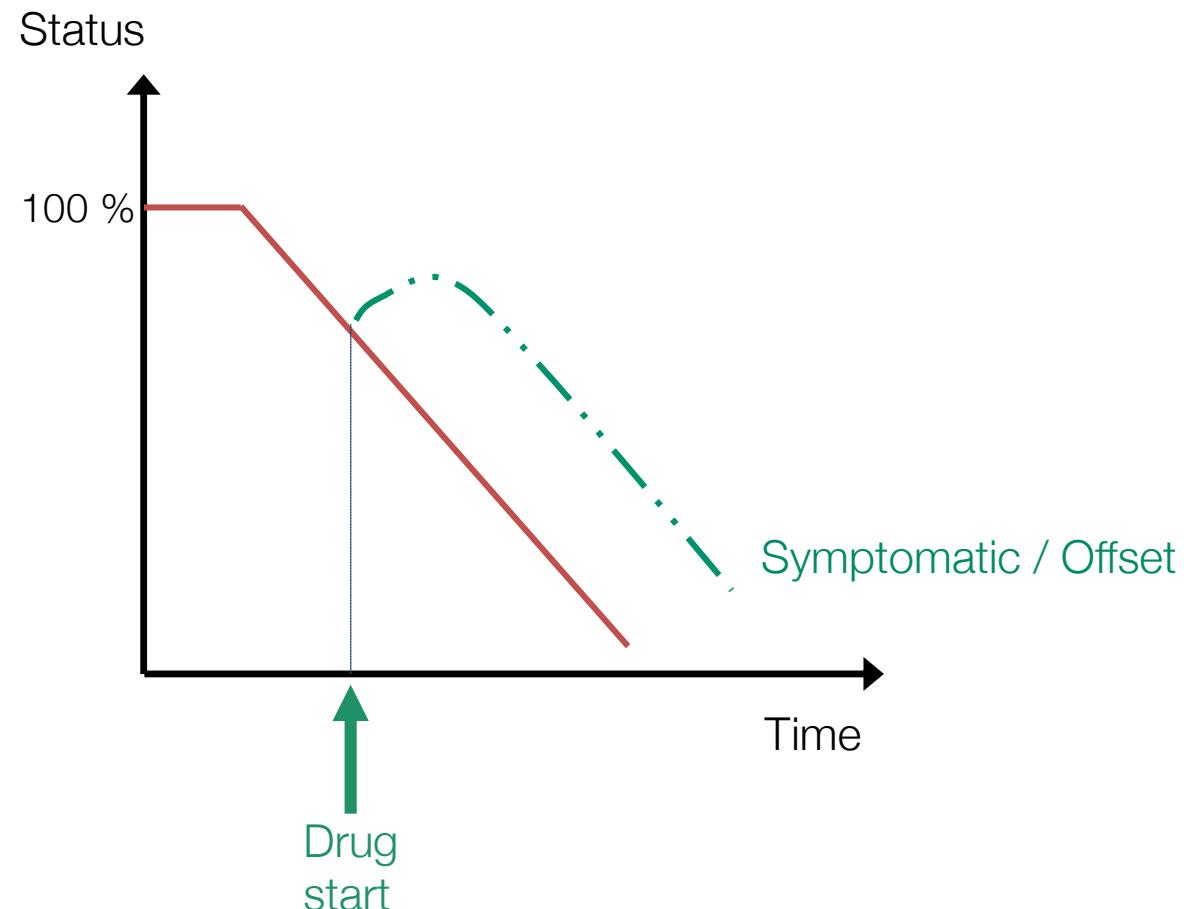
# Treatment effects

- Symptomatic drug effect
  - “Offset”
  - No effect on the process of disease progression
- Disease-modifying drug effect
  - Modifies the underlying process of disease
    - Curative/reversed disease process
    - Stopped disease process
    - Reduced rate of disease progression



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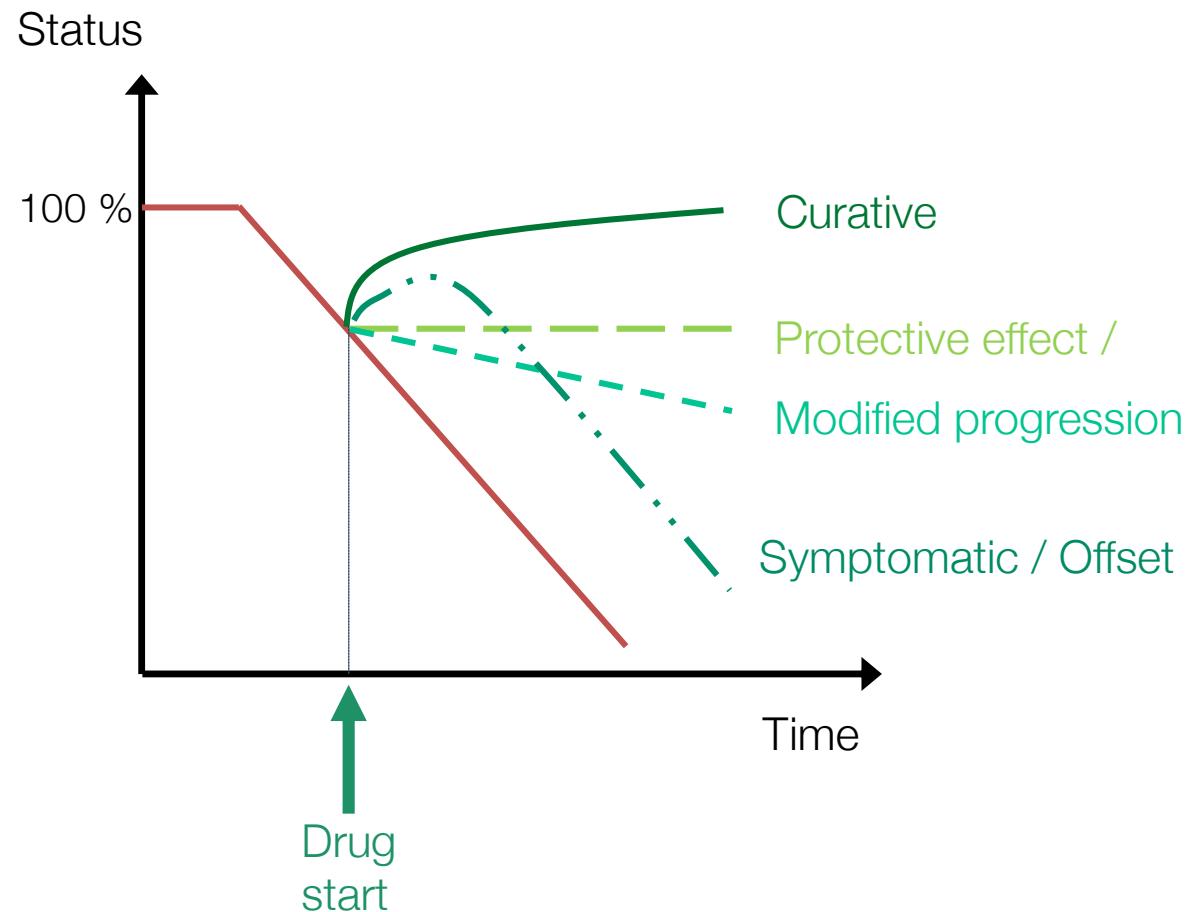
## Drug effects on disease progression





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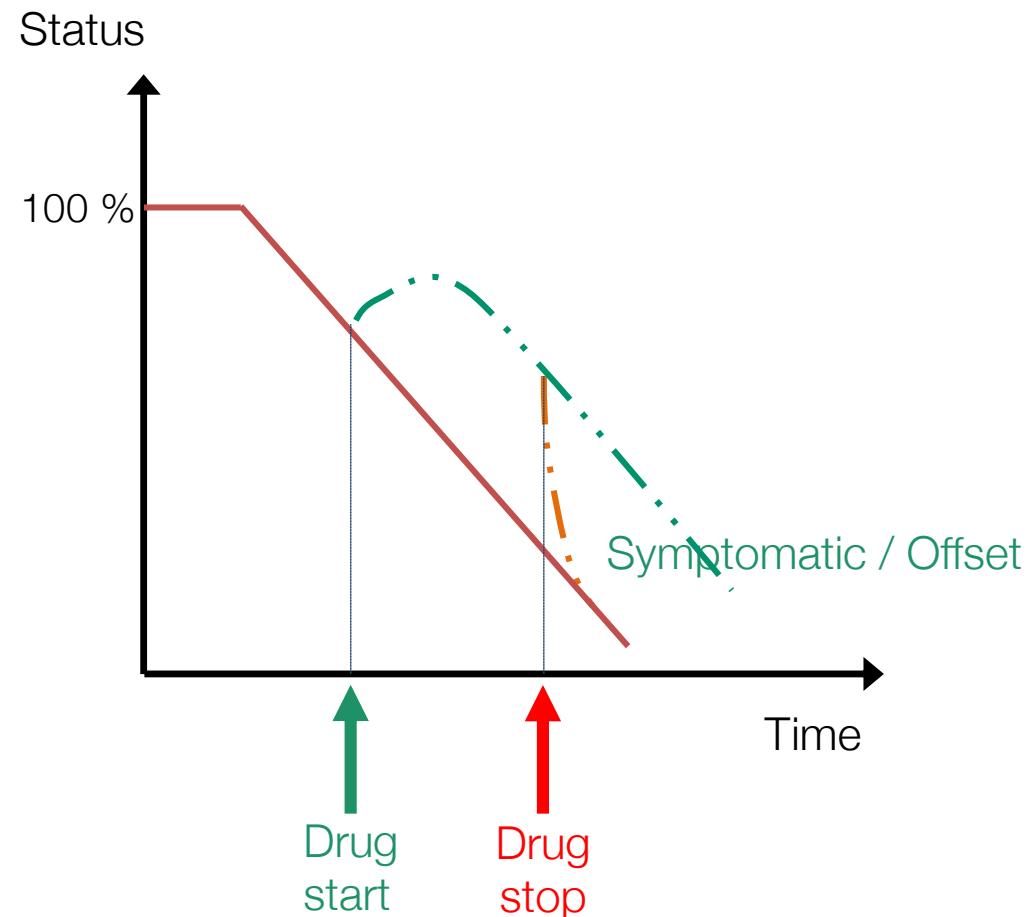
## Drug effects on disease progression





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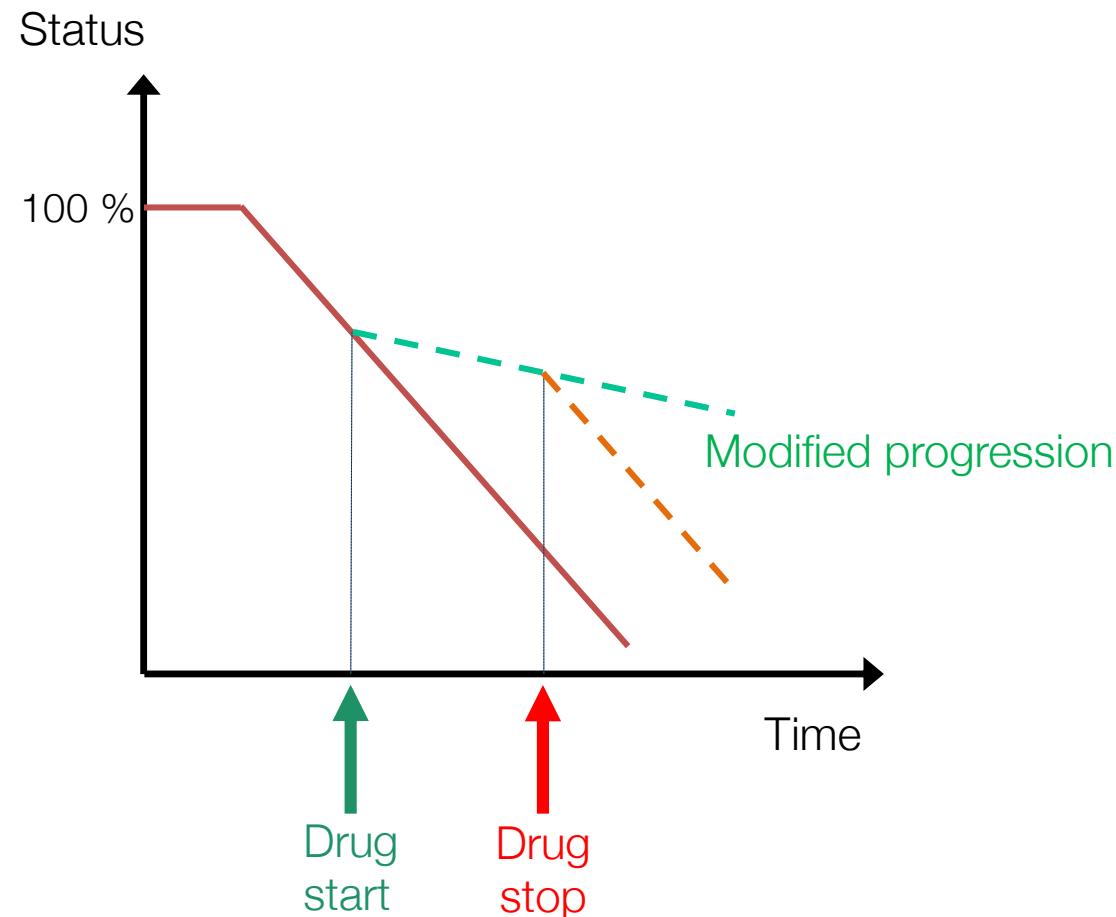
## Drug effects on disease progression





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## Drug effects on disease progression





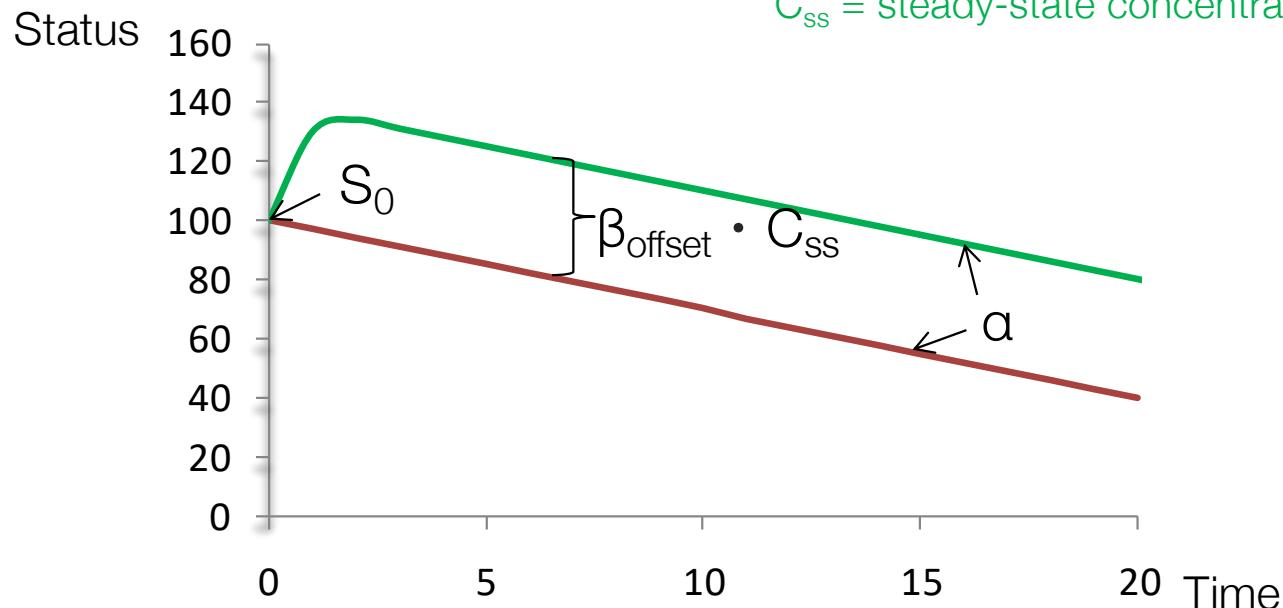
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## Linear disease progress model Offset/Symptomatic drug effect

$$S(t) = S_0 - a \cdot \text{time} + f(\text{drug})$$

e.g.  $f(\text{drug}) = \beta_{\text{offset}} \cdot C_{\text{ss}}$

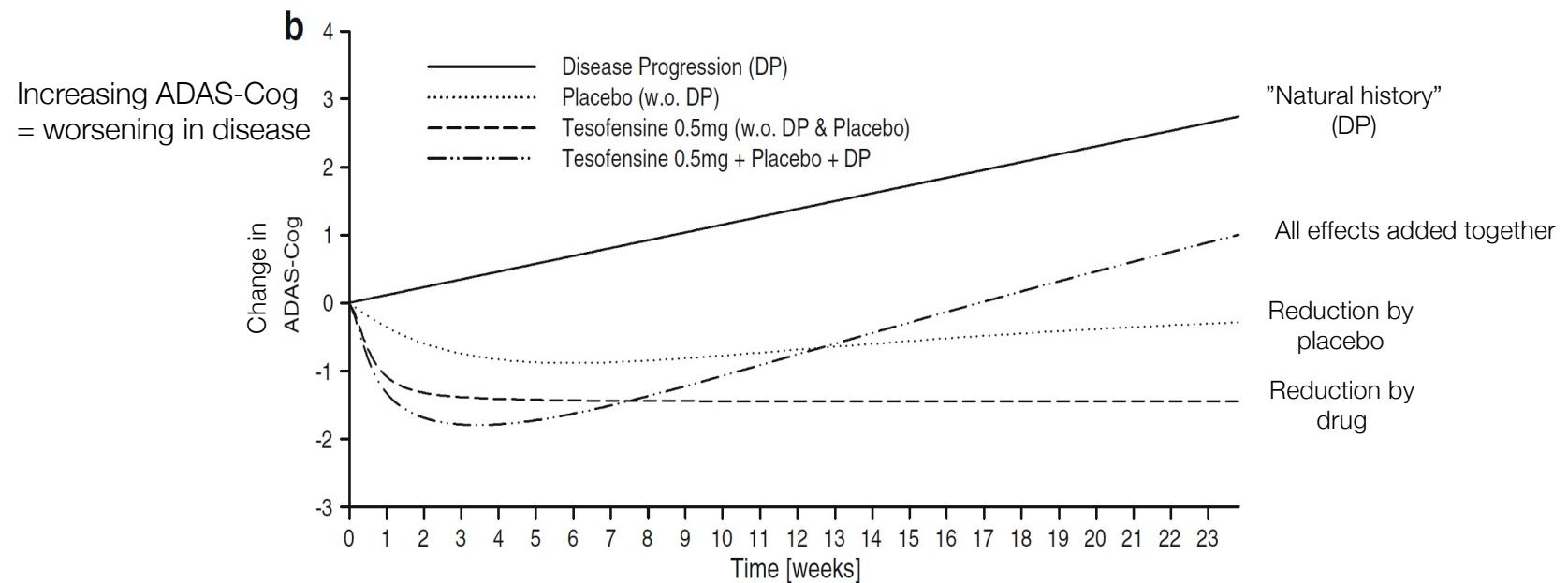
$C_{\text{ss}}$  = steady-state concentration



$f(\text{drug})$  can be Dose, concentration, AUC, effect compartment conc, ...

# Linear disease progression model Symptomatic drug effect of tesofensine in Alzheimer's disease

$$S(t) = \text{Baseline} + \text{Disease progression} + \text{Placebo response} + \text{Drug effect}$$



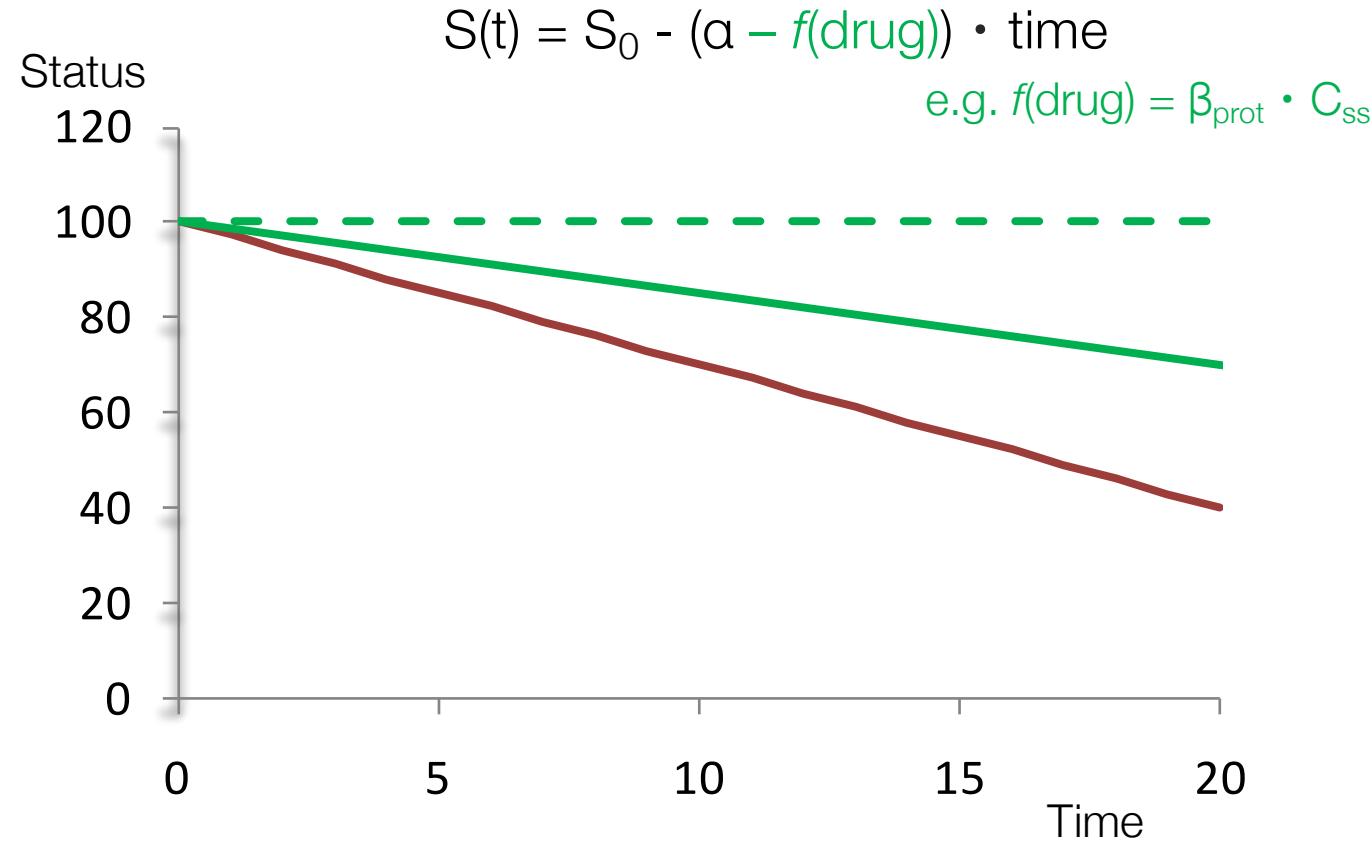
Tesofensine now investigated for obesity...

Lehr et al, AAPS J, 2010

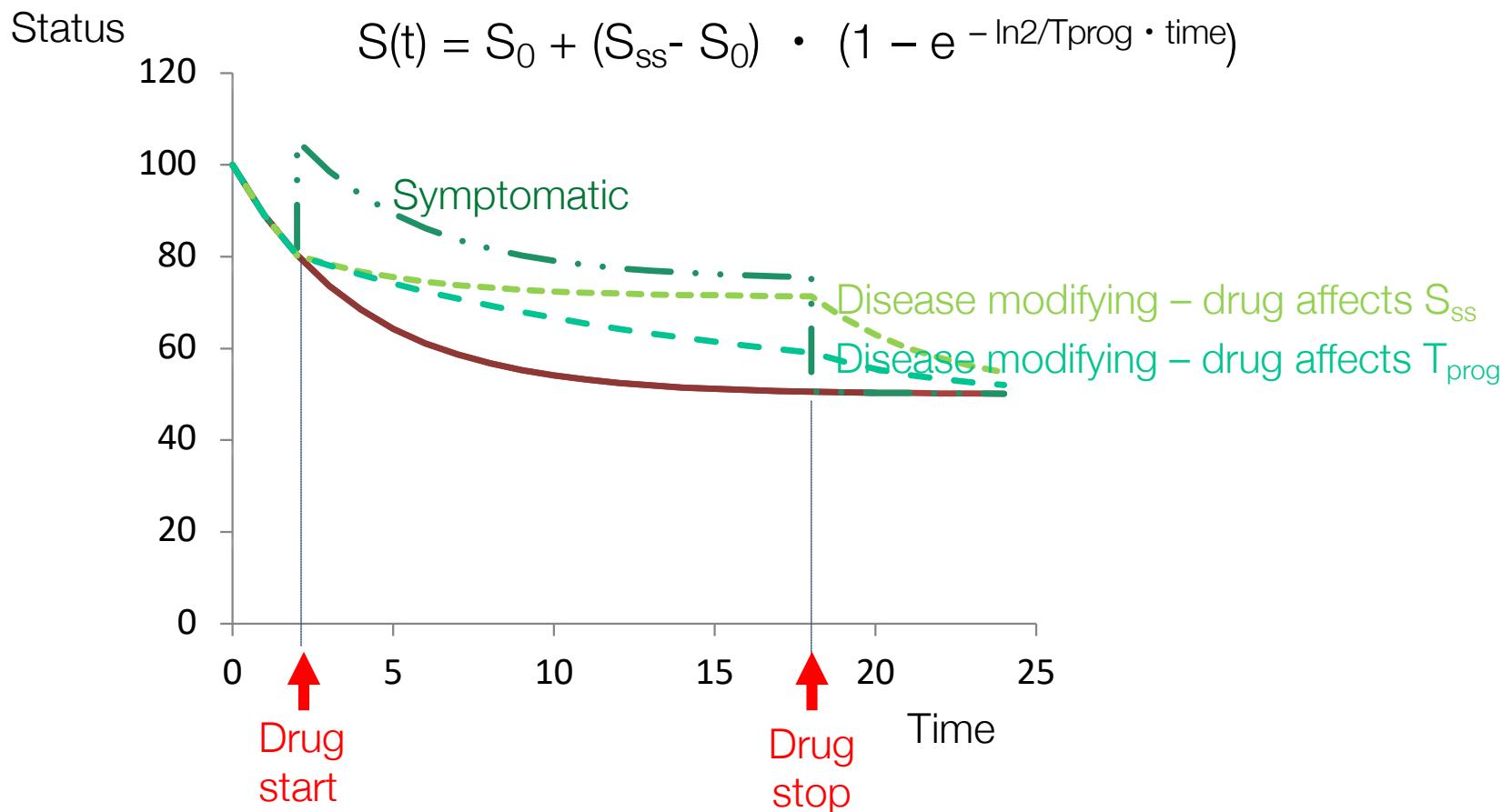


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## Linear disease progression model Modified progression/Protective drug effect



# Asymptotic disease progression model with drug effect





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# A more mechanistic view of disease progression (?)

Post et al., 2005  
Danhof et al., 2007

(a)

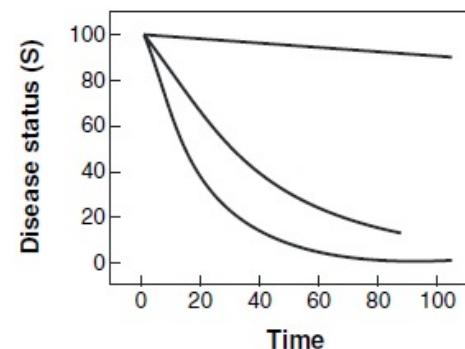
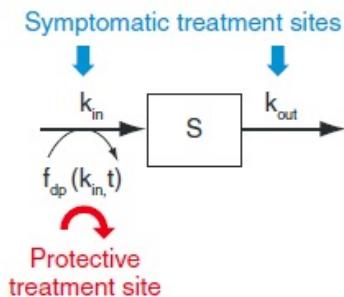
Homeostatic system: no disturbance



No change in status (S) if healthy

(b)

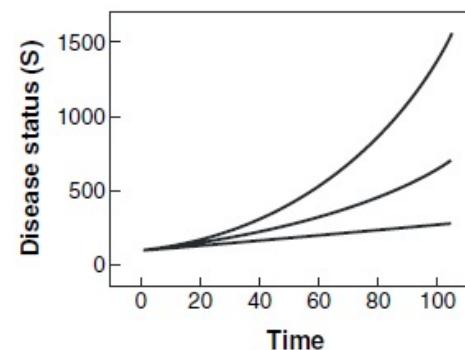
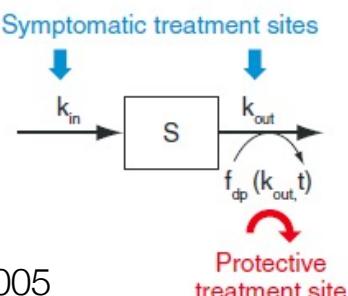
Type I disease system: decreasing system input function ( $k_{in}$ )



S reduces due to reduced “production”

(c)

Type II disease system: decreasing system output function ( $k_{out}$ )



S increases due to decreased “elimination”



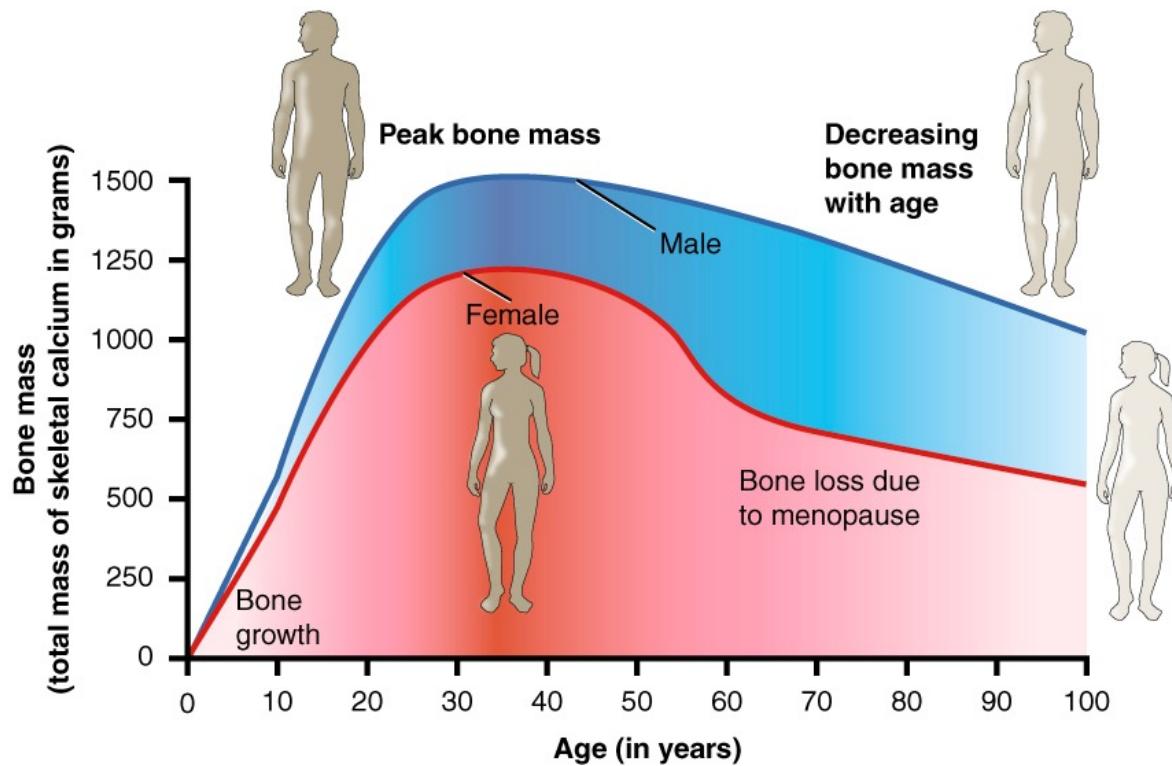
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# Disease progression in osteoporosis



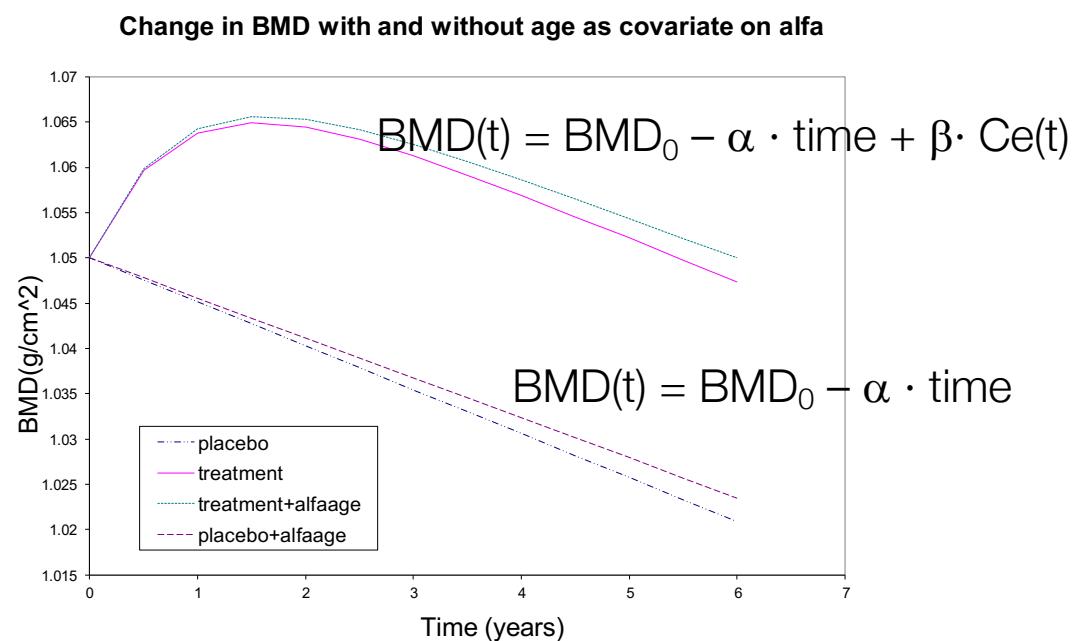
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# Disease progression in Osteoporosis



# Empirical disease progression model Bone Mineral Density (BMD)

Pamidronate (a bisphosphonate)



BMD = Bone  
Mineral Density

Ce = effect  
compartment  
concentration



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## Mechanistic model BMD

### Disease progression (=placebo)

$$\frac{dBMD}{dt} = R_{syn} - k_{loss} \cdot BMD$$

$$R_{syn} = R_{syn0} \cdot \left( 1 - \frac{1}{\text{Max prog}} \right) \cdot e^{-\frac{\ln(2)}{t_{50disprog}} \cdot \text{time}} + \frac{1}{\text{Maxprog}}$$

$$k_{loss} = \frac{\ln(2)}{t_{50loss}} \cdot \left( 1 + (\text{Max prog} - 1) \cdot \left( 1 - e^{-\frac{\ln(2)}{t_{50disprog}} \cdot \text{time}} \right) \right)$$

Synthesis rate ( $R_{syn}$ ) and rate constant of degradation ( $k_{loss}$ ) decreases and increases over time, respectively



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## Mechanistic model Drug effect of raloxifene – BMD

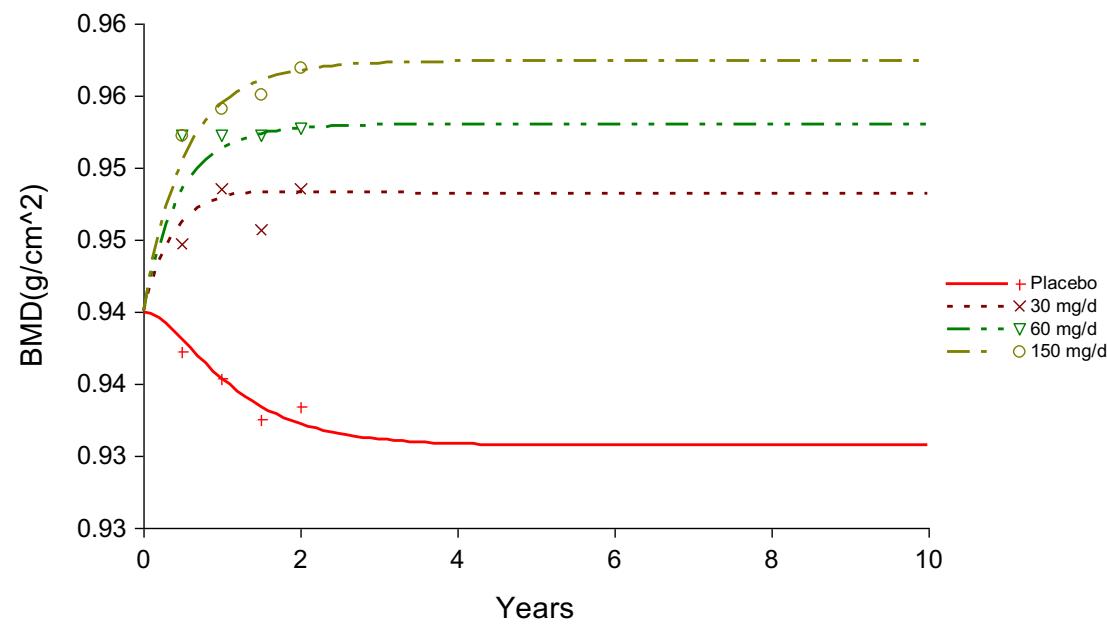
Raloxifene (Evista®) selective estrogen receptor modulator

$E_{max}$  model – Dose inhibit  $k_{loss}$

$$\frac{dBMD}{dt} = R_{syn} - k_{loss} \cdot \left( 1 - \frac{E_{max} \cdot Dose}{ED_{50} + Dose} \right) \cdot BMD$$

# Mechanistic model Drug effect of raloxifen – BMD

Raloxifen (Evista®) selective estrogen receptor modulator



## Conclusions

Difficult to study disease progression

Modelling has potential to separate placebo effects and disease progression

A better understanding of the disease, placebo response and drug effect leads to improved therapy



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## What was the muddiest point?



Write down in the chat (to me privately) on what part you had had most difficult to follow in the lecture