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Placebo Response

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Clinical Pharmacology
=
Disease Progress + Drug Action

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Components of a Disease Progress Model

- Baseline Disease State
- Natural History
- Active Treatment Response
- Placebo Response

$$S(t) = S_0 + \text{Nat. Hx.} + \text{Active} + \text{Placebo}$$

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Disease progress models start with a baseline disease status, S_0 . The change from baseline in the absence of drug treatment describes the natural history of the disease (disease progression). When drugs are used then the active effect of the drug modifies disease status. In clinical trials it is also necessary to consider the placebo response as a separate component. Some disease progress models are described in Holford NHG, Mould DR, Peck CC. Disease progress models. In: Atkinson A, editor. Principles of Clinical Pharmacology. 2nd ed. San Diego: Academic Press; 2007. p. 313-21. More complex effects based on turnover models have been described in Post TM, Freijer JI, DeJongh J, Danhof M. Disease system analysis: basic disease progression models in degenerative disease. Pharm Res. 2005 Jul;22(7):1038-49.

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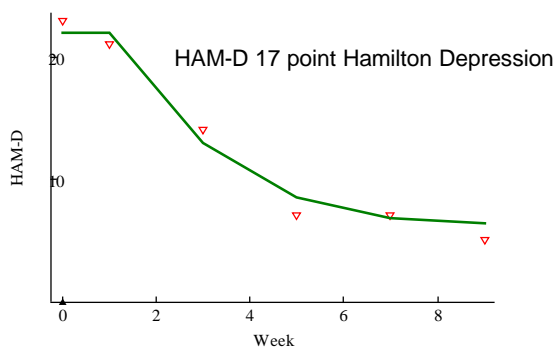
Response to Inactive Treatment

- PLACEBO
“I will please” -- Response improvement
- NOCEBO
“I will harm” -- Response worsens

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Placebo Response

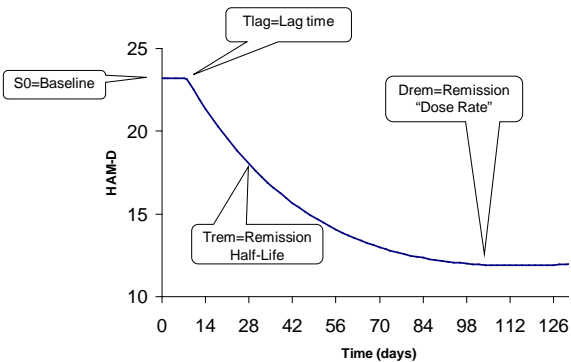


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Some clinical responses will show a natural history pattern which approaches an asymptote. For example, pain scores after abdominal surgery typically decrease over a few days and approach zero. The asymptote may be non-zero as shown in the figure. This illustrates the improvement in the Hamilton Depression (HAM-D) rating scale after administration of a placebo in an anti-depressant clinical trial. It is a matter of personal preference whether one calls this a change due to disease progress or a change due to placebo treatment. In this particular case the two mechanisms are indistinguishable.

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Placebo Response “Constant input with first order elimination”



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Disease Progress and Placebo Models for Depression Response

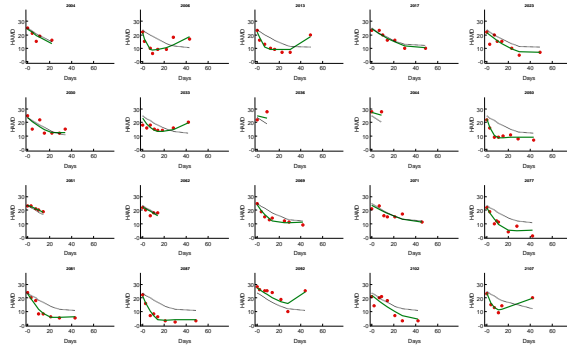
Models	Equations
Disease Progress	$S(t) = S_0$
Placebo Response	$Placebo(t) = Drem \cdot (1 - e^{-\ln(2)/Trem \cdot (t - Tlag)})$
HAM-D Time Course	$HAMD(t) = S(t) + Placebo(t)$

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An application of an exponential model with a nonzero asymptote is shown here. The disease progress model is assumed to remain constant and the change with time is attributed to a placebo response. An exponential model with an asymptote of $Drem$ (the size of the remission expressed as the placebo 'dose') and a half-life $Trem$ (the half-life of remission induced by placebo) is used to describe the placebo response. There is a delay before the onset of the placebo effect which can be described with $Tlag$ (lag time).

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Placebo

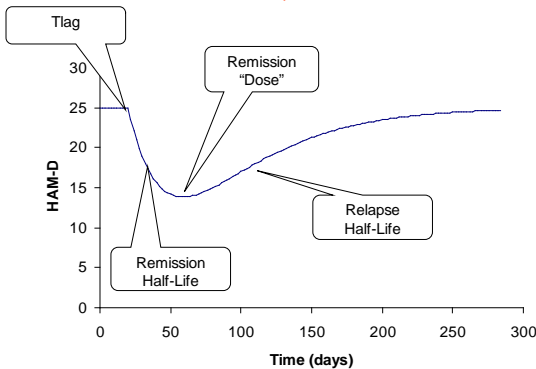


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The placebo response in anti-depressant trials is not always monophasic. Sometimes it is possible to discern a relapse (i.e. worsening of HAM-D) during the trial. The relapse component of the response can be described by a simple change to the asymptotic progress model.

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Placebo Response Model Bateman "first order absorption and elimination"



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Placebo Bateman Model

$$Placebo(t) = \frac{Drem \cdot Krem}{(Krem - Krel)} \cdot (e^{-Krel \cdot (t-Tag)} - e^{-Krem \cdot (t-Tag)})$$

$$HAMD(t) = S0 + Placebo(t)$$

$S0$ = Baseline HAM - D

Tag = Placebo onset lag - time

$Drem$ = Remission Dose

$Trem$ = Remission Half - life

$Trel$ = Relapse Half - life

$$Krem = \frac{\ln(2)}{Trem}$$

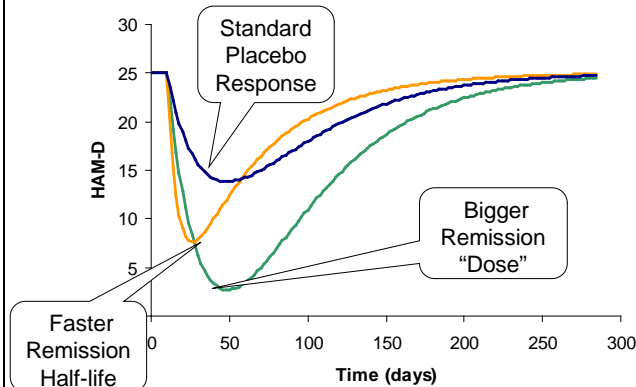
$$Krel = \frac{\ln(2)}{Trel}$$

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A two exponential model with a biphasic pattern is known as the Bateman function.

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Inverse Bateman Placebo Response Profiles



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What is the Time Course of Placebo Response?

- Placebo Arm of Double Blind Randomized Phase II Study of New Potential Anti-Depressants
 - Total 582 patients, 3864 observations
 - Drug X, Study A (154 patients)
 - Drug X, Study B (141 patients)
 - Drug Y, Study C (149 patients)
 - Drug Y, Study D (138 patients)

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Time Course of Placebo Response in Depression

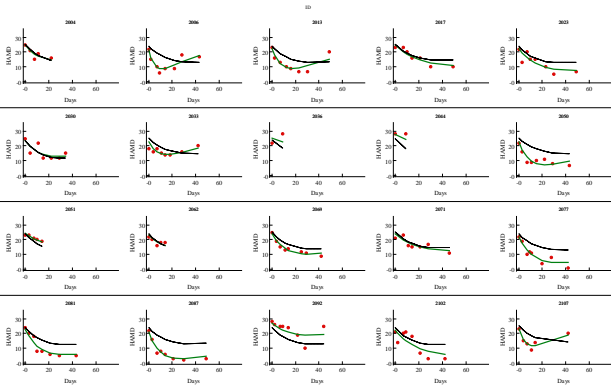
Parameter	Estimate	Units
Baseline	24	HAM-D
Lag time	4.7	days
Remission amplitude	20.6	HAM-D
Remission half-life	60	days
Relapse half-life	280	days

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Drug X

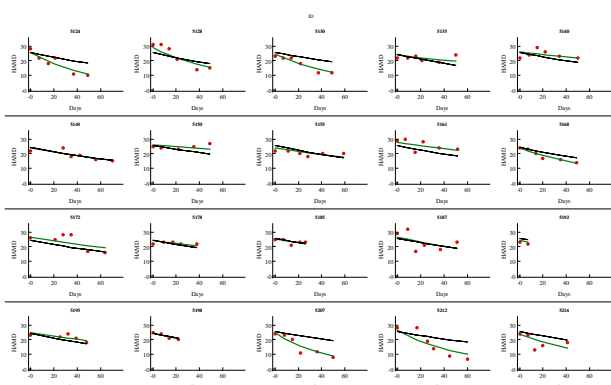


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Inverse Bateman

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Drug Y



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Inverse Bateman

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Relapse Mixture Model

- Assume some patients relapse (get worse while on placebo treatment)
- Assume patients who do not relapse have infinite relapse half-life
- Probability of patient having a relapse is estimated using a mixture model

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Relapse Probability

Study A	98%
Study B	45%
Study C	29%
Study D	18%

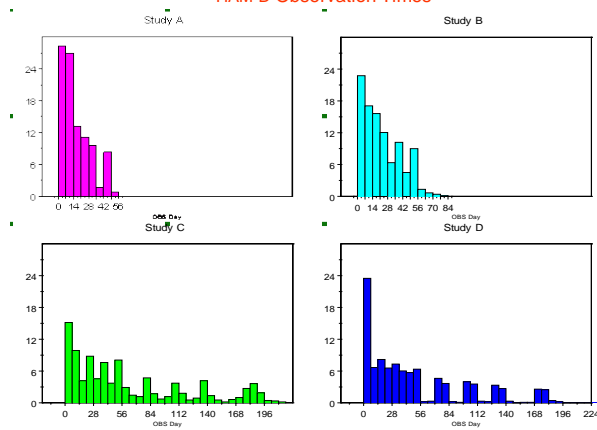
Why are relapse probabilities different?

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Is It a Design Issue? HAM-D Observation Times



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Observation Effect Model

- Each HAM-D observation is a “dose” of placebo
- Placebo “conc” rises and falls like oral drug absorption model
- Placebo “conc” shortens remission and relapse half-lives

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Observation Effect on Placebo Response

Parameter	Estimate
Placebo onset half-life	0.12 days
Placebo elimination half-life	31 days
Placebo effect on remission	-40%
Placebo effect on relapse	-64%

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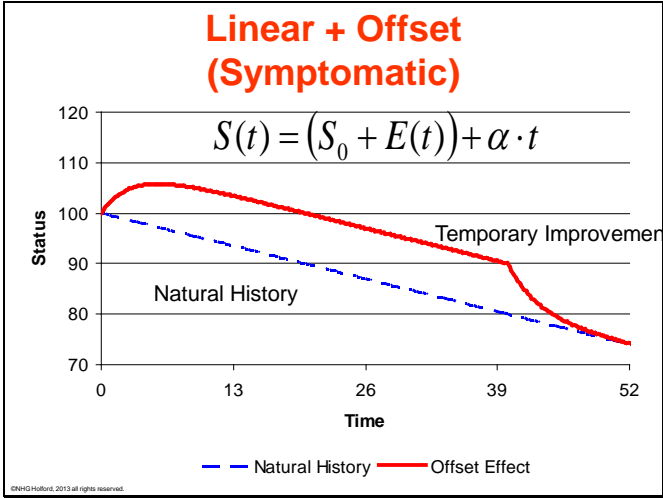
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Disease Progression and Placebo Response

- Requires assumption about shape of disease progression (natural history)
- Commonly disease progression is linear
- Placebo (or nocebo) observed response will be the sum of disease progression and the placebo (nocebo) time course

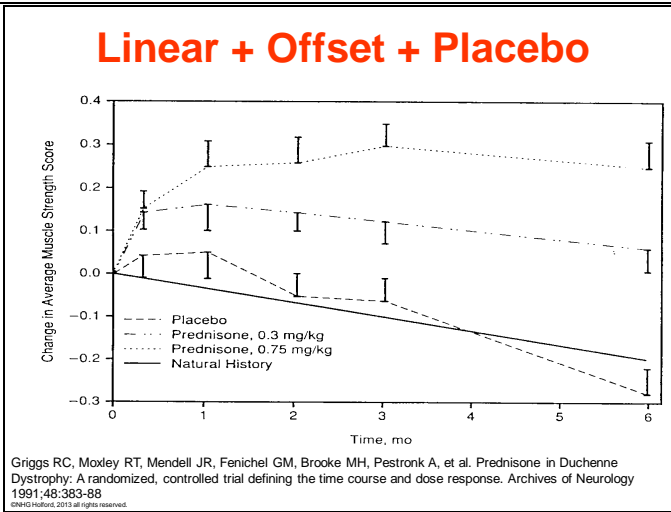
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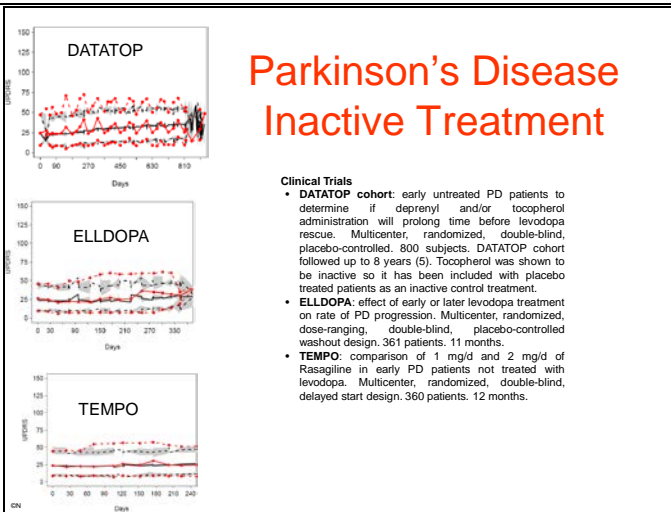
With any disease progress model it is possible to imagine a drug action that is equivalent to a change in the baseline parameter of the model. This kind of effect on disease produces a temporary offset. When treatment is stopped the response to the drug washes out and the status returns to the baseline.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

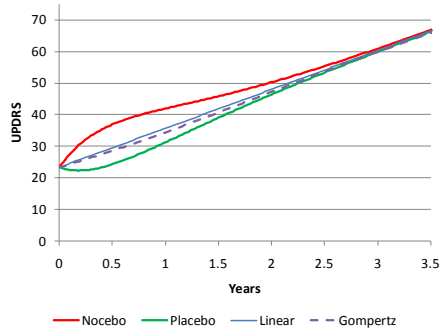
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(This section contains no text, only the clinical trial details from the figure.)

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Disease Progression And Placebo/Nocebo in Parkinson's Disease



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Parkinson's Disease Placebo and Nocebo

Parameter	Description	Units	Average	RSE	2.5% ile	97.5% ile
POP_S0	Baseline UPDRS	u	23.1	0.019	22.2	24.0
POP_ALPHA	Progression rate	u/y	12.7	0.100	10.6	15.6
POP_PMAX	Maximum 'placebo' benefit	u	-5.09	-0.288	-8.22	-3.12
POP_TAB	'Placebo absorption' half-life	day	202	0.438	111	469
FTEL	'Placebo elimination' half-life fraction of POP_TAB	x 100	0.805	2.64	0.005	4.11
Probability	Probability of positive response (PMAX)	.	0.162	0.298	0.066	0.254

Pmax for placebo is negative to describe improvement in response with inactive treatment

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Placebo Response Summary

- A part of the disease progress model
- Usually requires an assumption about the natural history
- May be a key part of the overall response to treatment
- Quantitative models are helpful for understanding active and inactive treatment responses

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Disease Progress, Placebo/Nocebo, Termination Event

```

SPK
IF (MINUM.EQ.1) THEN ; Nocebo
  PPMAX=-PPOSPPMAX*FPOSET
ELSE
  PPMAX=1 ; Placebo
ENDIF
; Peak response
  PPMAX=POP_PMAX*PPMAX*EXP(PPV_PMAX)
; nominal placebo 'dose'
  BPLA=PPMAX*(Kab-Kel)/(Kab*(EXP(-
  LOG(Kab/Kel)*Kel/(Kab-Kel))) - EXP(-
  LOG(Kab/Kel)*Kab/(Kab-Kel)))
; Baseline disease status
  A_0(1)=S0
SDS
;Disease status (UPDRS)
  DDFRG=A(2) ; linear progression status
  DPLA= (BPLA*Kab)/(Kab-Kel)*(EXP(-
  Kel*T)-EXP(-Kab*T))
  DSTAT=DDFRG+DPLA ; progression +
  placebo
;Termination event hazard
  DADT(1)=BASDRP*EXP(SUPD*DSTAT)
;Disease progression
  DADT(2)=AL ; linear progression slope

SERROR
  CUMHAZ=A(1)
  NH=A(2)
  SRVT=EXP(-CUMHAZ); S(t)
  IF (DVID.EQ.1) THEN
    F_FLAG=0 ; Continuous ELS
    Y = NH * PLA + ERSSD
  ENDIF
  IF (DVID.EQ.2.AND.DV.EQ.0) THEN ;
  Censored
    F_FLAG=1 ; Likelihood
    Y=SRVT
  ENDIF
  IF (DVID.EQ.2.AND.DV.EQ.1) THEN ; Event
    F_FLAG=1 ; Likelihood
    Y=SRVZ-SRVT
  ENDIF
  IF (DVID.EQ.3) THEN
    SRVZ=SRVT ;Save S(t) for start of
    censor interval
  ELSE
    SRVZ=SRVZ ; Keep NM-TRAN happy
  ENDIF

```