Response of Clinical Depression to Desipramine Plasma Levels

Abstract. In 1977, Reisby et al. carried out a study investigating the little-known effects on depression of desipramine, the metabolite of the anti-depressant imiprimamine. Depression was measured using a score from a researcher administered, common scale, and medication was administered for 5 weeks, with 4 plasma measurements taken. In this analysis, the data from that study were examined for longitudinal and cross-sectional effects of the metabolite desipramine (DMI) on depression score. Significant effects were found for individual intercepts, initial plasma DMI level and change in plasma DMI level over time.

About the Study.

Study Design: Controlled clinical trial of drug effect on major depression

Objective: To estimate the clinical response of depression due to plasma levels of tricyclic antidepressant Imipramine and its metabolite, Desipramine (DMI).

Methods: 66 clinically depressed patients in psychiatric hospitals in Sweden and Denmark were given 225mg of Imipramine for 4 weeks after a 7 day placebo wash-out period. The Hamilton Depression Rating Scale (HAM-D) was used to measure patients' depression at the end of each study week beginning at week 2. The score at Day 14, the first measurement of plasma drug level (after one week of administration), was used as the baseline score for comparisons. Depression was classified by the researchers as either reactive to a life event (non-endogenous) or spontaneous (endogenous).

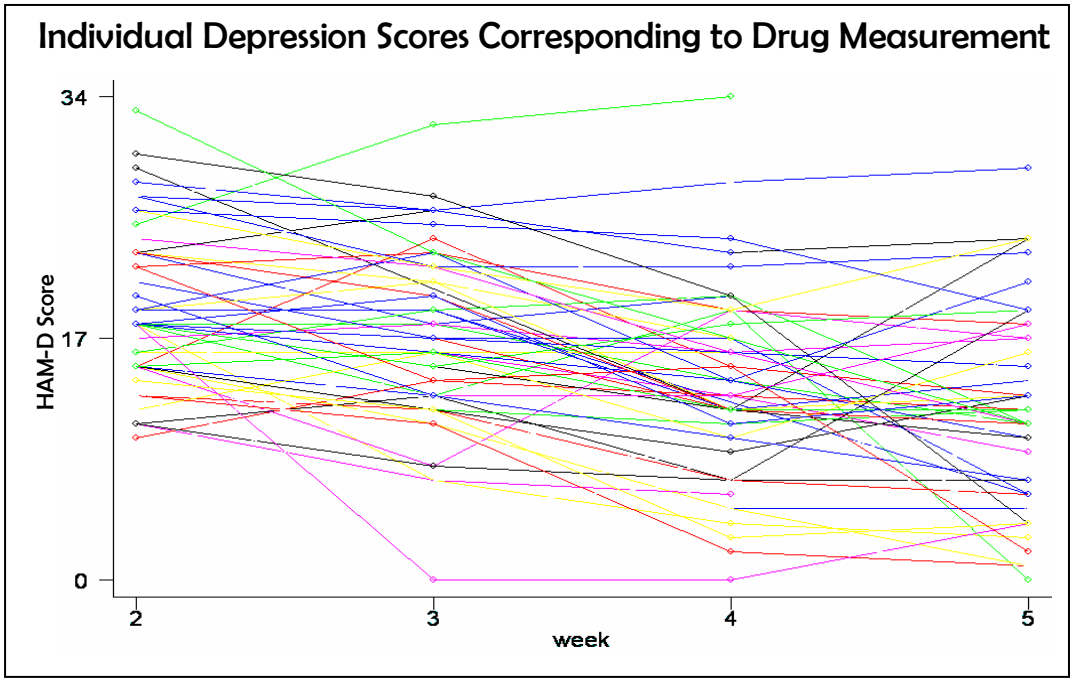
The Data: were obtained from a longitudinal data analysis course website at the University of Chicago. Their original source was the study by Reisby et al., published in *Psychopharmacology* in 1977.

Reference: Reisby, N., G. Lars, P. Bech, A. Nagy, et al. Imipramine: Clinical effects and pharmacokinetic variability. Psychopharmacology: 54, 263-272 (1977).

Research Question

How are the time-varying and initial plasma desipramine levels related to clinical response of depression, as measured by HAM-D score?

Figure 1.
The variation in baseline HAM-D score among the population suggests that the model may not be amiss to allow intercepts to differ by individual.



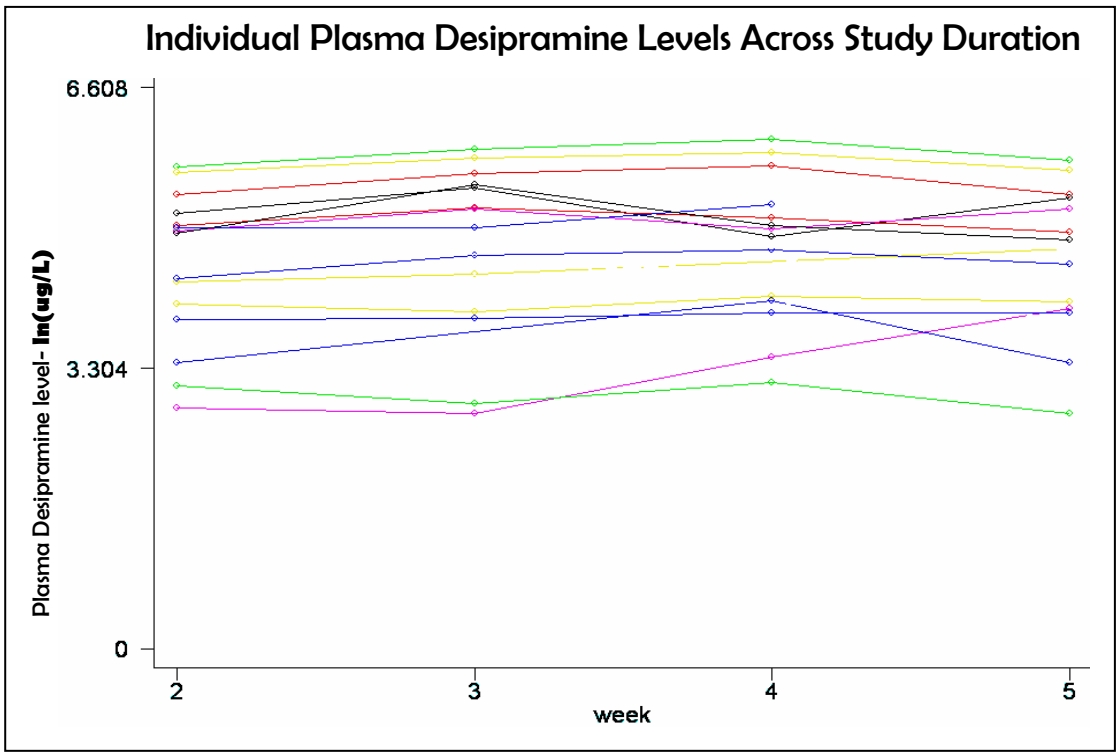


Figure 2.
A sample of 30% of the population shows that a random intercept on the initial DMI level might be a good idea due to the differences in week 2 DMI plasma level, but that a fixed effect on the longitudinal covariate may be appropriate given the roughly parallel slopes over time.

Statistical Translation: Mixed Effects Model

$$E\left(Y_{ij} \mid X_{i11} = x_{i11}, X_{ij1} = x_{ij1}\right) = \beta_0 + \beta_{0i} + \left(\beta_1 + \beta_{1i}\right) X_{i11} + \beta_2 X_{ij1} X_{i11} + e_{ij}$$

Methods to Fit and Compare the Model:

1) GEE – ignoring the possible need for a random intercept and cross-sectional effect estimate, estimate only the marginal effects of initial ln(DMI level) and change in DMI level on HAM-D score.
    - Program Used: STATA, xtgee command

2) Simple Random Effects – allowing for a random intercept but not for a random effect estimate of initial ln(DMI level)
    - Program Used: STATA, xtreg command with the 're' option

3) Mixed Effects – allow for both a random intercept term and a random effect term on the initial ln(DMI level), and estimate the marginal longitudinal effect of DMI level.
    - Program Used: SATA, xtmixed command

Results

Model # 1 (GEE)	**Unweighted OLS Naïve**	**Unweighted OLS Robust**	**Weighted LS Naïve**	**Weighted LS Robust**
β_0 (SE), p	21.275 (2.232), 0.0005	21.275 (2.513), 0.0005	21.482 (3.326), 0.0005	21.482 (2.516), 0.0005
β_1 (SE), p	-1.228 (0.503), 0.015	-1.228 (0.546), 0.015	-1.241 (0.735), 0.091	-1.241 (0.559), 0.026
β_2 (SE), p	-0.017 (0.011), 0.111	-0.017 (0.013), 0.111	-0.02 (0.009), 0.022	-0.02 (0.011), 0.055
Model # 2 (SRE)	**Naïve**	**Robust**		
β_0 (SE), p	21.485 (3.463), 0.0005	21.485 (3.463), 0.0005		
β_1 (SE), p	-1.24 (0.765), 0.105	-1.24 (0.708), 0.080		
β_2 (SE), p	-0.021 (0.009), 0.019	-0.021 (0.009), 0.058		
Model # 3 (Mixed effects)	**Identity V-C Structure**	**Independent V-C Structure (error message)**	**Exchangeable V-C Structure**	**Unstructured V-C (error message)**
β_0 (SE), p	20.925 (2.39), 0.0005	21.301 (3.138), 0.0005	20.94 (2.358), 0.0005	No calculation (not concave)
β_1 (SE), p	-1.111 (0.561), 0.048	-1.197 (0.709), 0.091	-1.115 (0.551), 0.043	No calculation (not concave)
β_2 (SE), p	-0.021 (0.009), 0.019	-0.021 (0.009), 0.019	-0.021 (0.009), 0.019	No calculation (not concave)

$$E\ Y_{ij} | X_{i11} = x_{i11}, X_{ij1} = x_{ij1} =$$
$$\beta_0 + \beta_{0i} + \beta_1 X_{i11} + \beta_2 X_{ij1} X_{i11} + e_{ij}$$

$$E\ Y_{ij} | X_{i11} = x_{i11}, X_{ij1} = x_{ij1} =$$
$$\beta_0 + \beta_{0i} + \beta_1 + \beta_{1i} X_{i11} + \beta_2 X_{ij1} X_{i11} + e_{ij}$$

Discussion

There is very little change in the inference (such as standard error and p-value) between the marginal and random effect estimates. In the marginal (GEE) model, the effect and inference estimates are largley identical between the weighted LS robust and unweighted LS robust models. The simple random effects model is almost exactly the same as the weighted LS naïve marginal model. The effects estimates are equal to those estimated by the robust GEE, but the inferences are higher.

In the mixed effects model, assuming an identity V-C matrix as compared to an exchangeable V-C matrix produced equivalent effect and inference estimates. The differences in the effect estimates of the terms with random coefficients as compared to those withoutare small, but indicate that the offset by individual may be worth noting – particularly because the intial drug level is on the log scale. However, the SEs are nearly the same, and the terms remain significant at an α= 0.05 level.

The very minimal difference in the inference and effect estimates between the models indicates that assuming an exchangeable correlation structure is not a greivous mistake. Intuitively, the final model that makes the most sense is the mixed effects model, allowing for a random intercept and random coefficient on the initial level of desipramine in the blood.
In this model (outlined in blue, above):

- At Day 0 (0.0 plasma DMI level, extrapolated), the mean HAM-D score for the population was 20.94 (clinically depressed). Each individual also contributed a personal effect. (p=.0005)
- The marginal effect of initial desipramine level is that for every 1 ln(ug/L) increase in initial desipramine level, the depression score decreased by -1.12 points. Each individual then contributed a personal effect. (p=.04)
- For every 50 ug/L increase in the desipramine level from the initial level, depression score decreased by 1.05 points. (p=.02)

Conclusion: Initial metabolism of desipramine and subsequent increase in plasma levels are associated with a decreasing clinical response of depression.