A Bayesian Meta-Analysis of Longitudinal Data in Placebo Controlled Studies with Naproxen

Martin Boucher[1] [1] Pfizer, Sandwich, United Kingdom

Introduction

- Naproxen is an NSAID used in the treatment of pain.
- We want to understand the time profile response for Naproxen versus placebo for the WOMAC pain endpoint in subjects with osteoarthritis (OA) pain.
- Aim to incorporate all available, relevant data into a meta-database.
- A comprehensive systematic literature search was carried out to identify suitable studies.
- Total of 15 references identified with 5 external and 10 internal studies.
- Different teams interested in responses at different time points so makes sense to apply a longitudinal model from which the relevant contrasts can be pulled.
- Using summary level (mean) data.
- Ninety four summary observations corresponding to a total of 4121 subjects (sample size range: 41-280 per group) across the 15 studies.
- A Bayesian approach is applied to meta-analysis using non-informative priors to enable probabilistic statements to be made about contrasts and parameters of interest.

Model and Methods

A Bayesian E_{max} model was applied to the 15 studies with the basic structure given below:

$$\overline{Response}_i = E0 - \frac{(Emax * time_i)}{(te50 + time_i)}$$

$Response_i$ = Womac pain score (0-20) for observation i.
E_{max} = E_{maxp} + I(naproxen)*E_{maxn} + β (bsl – mean(bsl)).
te_{50} = te_{50p} + I(naproxen)*te_{50n}.
E_0 = Base + η(j), where j is the study number (1-15).

Where I(Naproxen) = 1 for naproxen and 0 for placebo.
bsl - observed baseline WOMAC pain score.

A random effect, η(j), was fitted to baseline such that η(j) is normally distributed mean 0, variance Tau^2.

Modelling was carried out using WinBUGS. A burn-in of 10000 iterations was used and a subsequent update of 50000 to get posterior distributions.

In addition to diagnostic plots, the WinBUGS DIC tool was used to compare 2 models for model selection by assessing the difference in Dbar for each model. This is equivalent to the difference in residual deviance.

Priors

•All prior knowledge of naproxen/placebo response is effectively contained within the dataset being modelled.
•Expert prior knowledge would inevitably be a function of some of these data hence non-informative priors were used for the parameters (Table 1).

Results

Table 1 also presents the posterior medians of each parameter of interest from the Emax model and also gives the corresponding classical parameter estimates based on the same model. Note that posterior distributions are available for each η (not listed here for brevity reasons as there are 15 η's).

Figure 1 shows a plot of each posterior median versus the observed value which gives an overall good fit.

Figure 2 presents model predictions over time for naproxen and placebo. The bands represent the 2.5 and 97.5 percentiles.

Table 1 – Prior Distributions and Posterior Medians with Classical parameter estimates for comparison

Parameter	Prior	Bayesian Posterior Median (95% CRI*)	Classical parameter estimates (95% CI)
Base	Uniform(0, 20)	10.8 (10.3, 11.4)	10.8 (10.3, 11.3)
E_{maxp}	Uniform(-20, 20)	-2.6 (-2.9, -2.3)	-2.5 (-3.2, -1.8)
E_{maxn}	Uniform(-20, 20)	-1.6 (-1.9, -1.3)	-1.5 (-2.1, -0.9)
te_{50p}	Uniform(0, 24)	0.54 (0.25, 0.92)	0.67 (0.39, 0.94)
te_{50n}	Uniform(-te50p, 24) *	-0.39 (-0.76, -0.09)	-0.51 (-0.82, -0.20)
β	Normal (0, 1600)	-1.0 (-1.2, -0.8)	-0.8 (-1.5, -0.1)
tau	Uniform(0, l0)	1.02 (0.70,1.62)	0.72 (?)

*ensures an overall positive te50

Figure 1: Posterior Median versus Observed WOMAC Pain Score

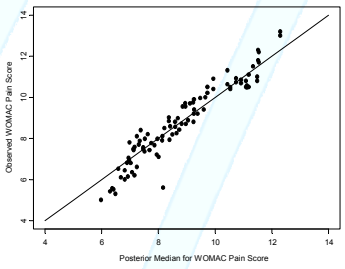
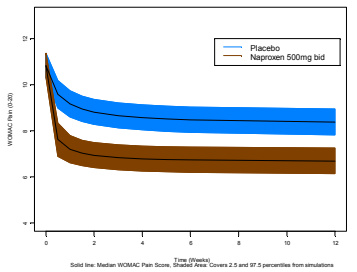


Figure 2: Predicted WOMAC Pain Score incorporating Parameter Uncertainty



- We are interested in the expected week 12, baseline adjusted, contrast for naproxen versus placebo for say 100 subjects per treatment group.
- This predictive distribution will include between study variation (tau) but will also take into account the uncertainty in tau.
- The probabilities of naproxen beating placebo by at least 1, 1.5 and 2 points are summarised in Table 2.

Table 2: Probabilistic statements around the contrast (naproxen – placebo)

Difference to detect (δ)	-1	-1.5	-2
P(N-P)<δ	0.999	0.838	0.052

Conclusions

- A Bayesian approach to a longitudinal model gave a good fit to the data and comparable parameter estimates to the classical approach.
- Direct probabilistic statements were made from the resultant posterior distributions. This was done simultaneously to the modelling itself rather than by post modelling simulation.
- Based on the posterior distribution, the median difference between naproxen and placebo at week 12 is approximately 1.7 points on a 0-20 scale with 95% credible interval (1.2, 2.2).

Discussion

This poster covers the very first steps in developing a Bayesian Emax model and further work might focus on looking at:

- Subjectively weighting the evidence (e.g. giving more weight to internal studies than external ones, or weighting according to age of study).
- Internal database includes patient level data. We could combine individual and summary level data to get a better idea about covariates.
- A Bayesian approach allows for indirect treatment comparisons so could look at other studies with either placebo and naproxen where there is some other positive comparator in common.
- Assessing literature bias.