MULTI-LEVEL NETWORK META-ANALYSIS TO ACCOUNT FOR DOSE-RESPONSE AND CLASS EFFECTS

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Introduction

Conducting a Network Meta-Analysis (NMA) involves synthesising relative treatment effects from Randomised Controlled Trials (RCTs) comparing several different treatments¹. Grouping and splitting treatments (e.g. by dose) is important both from a methodological and a decision making perspective². An analysis conducted with interventions grouped by the ‘treatment’ or ‘class’ levels will inevitably show more heterogeneity, but a network split too thin will be less powered to detect meaningful differences between interventions and may not actually be connected.

The decision to group or split is often informed by the decision making perspective. Clinicians may favour an approach where interventions are grouped and compared at the class level allowing flexibility to recommend specific treatments to individual prescribing clinicians. Decision makers making recommendations on the basis of cost-effectiveness may prefer a splitting approach since individual treatments and doses are associated with specific costs and outcomes.

While arguments can be made for grouping and splitting, each is associated with disadvantages. If doses are grouped a comparison at the dose level is not possible and therefore a fully informed decision cannot be made between competing doses of the same intervention. Information regarding heterogeneity that arises due to grouping of doses is also lost.

Analyses conducted at the dose level make the assumption that all treatment dosages have distinct effects and therefore may lead to less precision in estimation of effect sizes since doses of the same treatment will not borrow information from each other.

Objectives

The objective of this study was to explore multi-level NMA models where interventions could be compared at the dose, treatment and class levels and the utility of these models in explaining dose-response and improving model fit and increasing precision of treatment effects.

Methods

We used four previously conducted Cochrane reviews⁴ as a basis. Network meta-analysis models were developed to account for ‘dose’, ‘treatment’ and ‘class’ effects simultaneously and applied to the collected data, a schematic of the intervention hierarchy modelled is shown in Figure 1.

Pain free at 2 hours was chosen as the main outcome of interest. The network of RCT evidence is shown in figure 2. 'Pain free at 2 hours' was chosen as the main outcome of interest. The network of RCT evidence is shown in figure 2.'

Conclusions

Careful consideration should be given when making assumptions about dose-response in NMA. Grouping doses together for NMA can cause high amounts of unexplained heterogeneity that could be explained by a more flexible modeling method.

Steps effect sizes at the lowest dose are then assumed exchangeable within each treatment and their treatment level effects are assumed exchangeable within classes in a similar way to the 3-level model. Effect sizes for each treatment and class were estimated by calculating an inverse variance weighted average using post-estimation to avoid the confounding bias associated with taking the simple geometric mean.

Models were fitted using MCMC in OpenBUGS. Flat normal priors were given to all location parameters and uniform or half-normal priors were given to all standard deviation parameters. All models were run for 300,000 iterations with a 100,000 burn-in and convergence was by visual inspection of plots. We compared all fitted models in terms of DIC, posterior residual deviance and heterogeneity.

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Results

Statistics pertaining to model fit can be found in table 1. Treatment effects for different doses of sumatriptan vs placebo with associated credible intervals for 1-level and 3-levelNMA can be seen in figure 3. This is intended to show that using a multi-level structure, i.e. allowing doses of the same intervention to borrow information from each other leads to more precise estimates of treatment effect. Estimated treatment effects from both the models vs placebo for sumatriptan can be seen in figure 4. This is intended to show here models making different assumptions around dose-response will estimate treatment effects at different doses.

3-levelNMA was the best model in terms of DIC and heterogeneity (Table 1). This model also produced the most precise treatment effects (Figure 3). It can be seen from comparing the models that the improvement in model DIC was due to a reduction in effective parameters rather than a substantive improvement in fit as residual deviances are very similar.

3-levelNMA had higher heterogeneity and poorer fit than the 1-level and 3-levelNMA models and failed to capture the monotonic nature of the dose-response. This is due to the fact that imposing exchangeability causes all the effect sizes to be pulled towards the overall mean. In general we expect dose-response to be monotonic and therefore the exchangeability assumption is violated since we know a-priori which effect sizes are likely to be higher. This approach should therefore be used with caution and only if there is strong reason to believe a-priori that the dose-response is flat.

3-levelNMA appeared to underestimate the effect size for sumatriptan 200 mg, which is due to lack of data on the 200 mg dose and that there is no information on intermediate doses (i.e. 100-200 mg).

References

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