Model Based Network Meta-Analysis for Pharmacometrics and Drug-Development: a 3 year Research Collaboration between Pfizer and the University of Bristol.

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Objectives

Meta-analysis is a well-established methodology for combining the results of randomised controlled trials (RCTs) that compare the same treatments and outcomes. Network meta-analysis (NMA) allows the simultaneous comparison of multiple treatments [1,2] and provides a framework for model comparison and to assess evidence consistency [3]. Multiple doses and end-points can be compared in NMA by "lumping" similar doses and end-points, or by regarding them as separate treatments. "Lumping" introduces the potential of inconsistency between evidence sources. Separating treatments can lead to a sparse or unconnected network of evidence. Both approaches ignore the structural relationships for dose response and time-course that is a feature of model based meta-analysis (MBMA); a technique which uses non-linear pharmacokinetic-pharmacodynamic type models to allow dose-response and time-course effects to be modelled [4, 5], making using of all trial data. Although MBMA can be used to assess the relative effect of >2 treatments [6], to date there has been little attention paid to model fit and evidence consistency. This project aims to integrate the two approaches into a model based network meta-analysis (MBNMA) to model dose and time course information across multiple treatments incorporating an assessment of model fit and evidence consistency.

Methods

We illustrate the two approaches using time-course information for a comparison of 15 active treatments in 31 trials for the relief of pain due to osteoarthritis, measured on a standardised WOMAC scale [7]. Only trials using the most common total daily dose (TDD) for each treatment were included in the analysis. Trials were between 6 and 26 weeks long (median 12 weeks), with between 2 and 9 (median 4) pain score readings per trial.

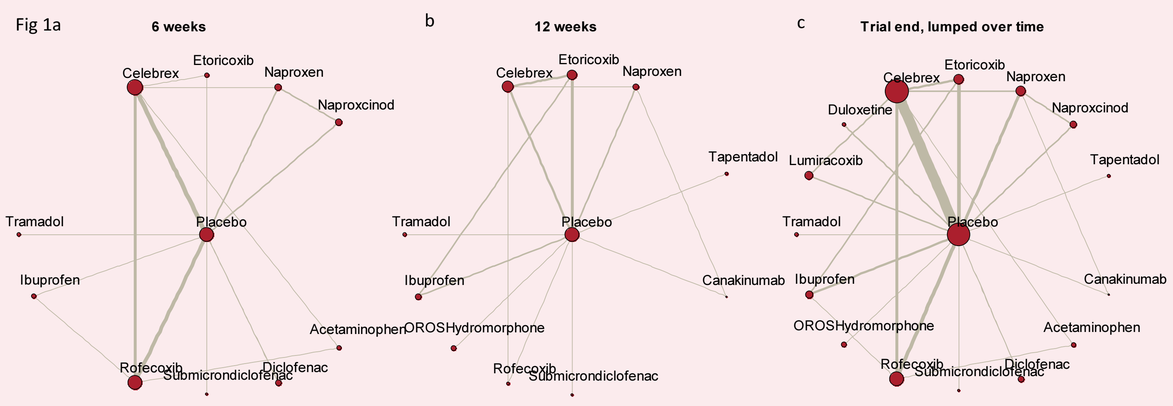
Network meta-analysis

We explored the effect of lumping on evidence consistency and available comparisons by considering three different NMAs: reported pain at 6 weeks, 12 weeks and the commonly used strategy of reported pain at final follow-up (i.e. lumping over time).

NMAs were modelled using gemtc [8] for R. Evidence consistency was assessed using node splitting [3], which compares the direct, indirect and network evidence.

The amount of included data and possible treatment comparisons are limited by the time point chosen (Fig 1a,b), compared to the final follow-up measurement, which allows the greatest number of comparisons (Fig 1c).

Fig 1a

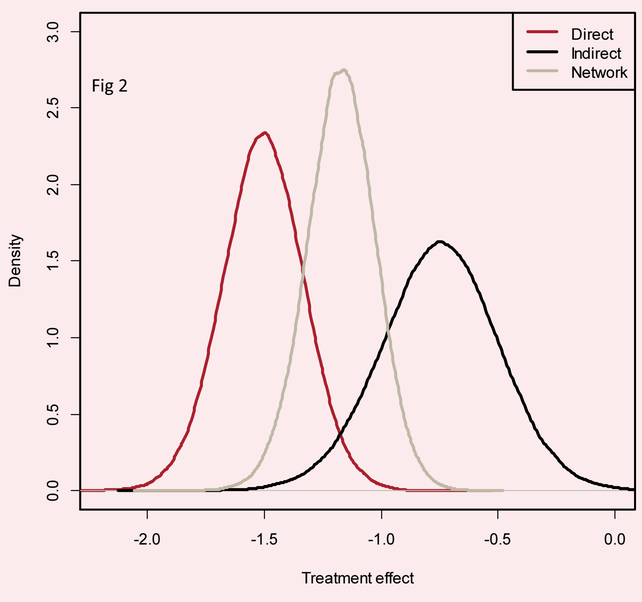


b

c

Neither the 6 or 12 week NMAs show any evidence of inconsistency ($p>0.05$ for all comparisons). For the trial end NMA we observe inconsistency between the posterior distributions for the direct and indirect evidence for the Rofecoxib vs placebo comparison ($p=0.017$) (Fig 2). The direct evidence suggests a much greater treatment effect, which is inconsistent with the weaker treatment effect predicted by the indirect evidence

Fig 2



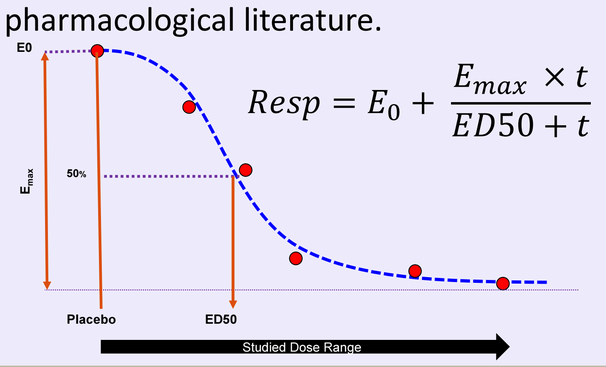
Model based meta-analysis

As a simple example of a pairwise MBMA we modelled the time course of WOMAC change from baseline for Etoricoxib vs placebo trials assuming the Emax model. This model makes use of all time-course information from the trials for the most common TDD; the model could be extended to include the effects of dose. We simultaneously modelled placebo and treatment effects [9], to produce 95% prediction intervals for a typical trial (i.e. assuming a trial specific random effect of zero [10]) (Fig 3).

A more complex model could simultaneously model all the direct comparisons in our example data-set (Fig 4), making use of complete dose and time-course information from each trail. The model could then be used to make indirect comparisons in the absence of a head-to-head trials. In such models where direct and indirect evidence exists the consistency of evidence has not previously been assessed.

The Emax model

The Emax model is widely used to model dose or time response in the pharmacological literature.



$$Resp = E_0 + \frac{E_{max} \times t}{ED50 + t}$$

Fig 3

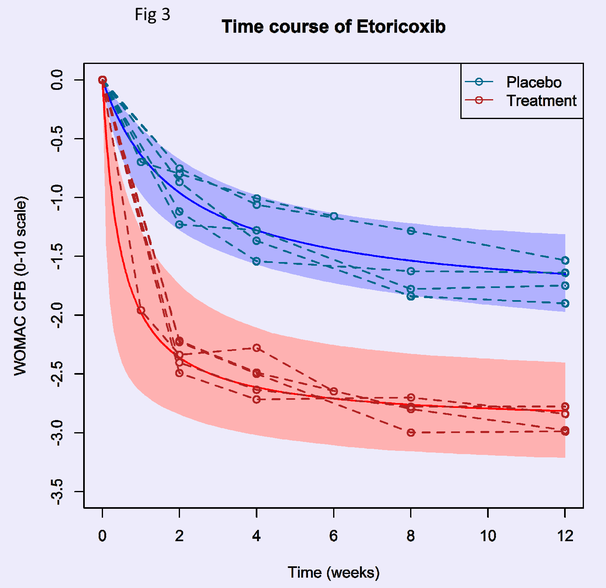
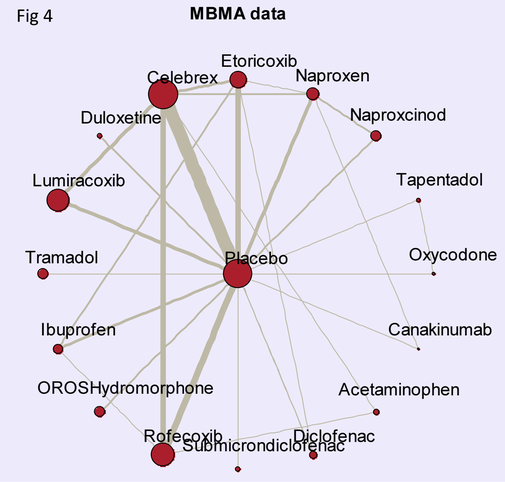


Fig 4



Discussion/Conclusions

NMA allows us compare treatment efficacy for a single endpoint even when we lack direct evidence for the comparison. Where both direct and indirect evidence exist we can use this to assess evidence consistency. We have shown that "lumping" data by time (i.e. using the trial end) in this example NMA leads to evidence inconsistency. If we wish to avoid lumping, the number of possible treatment comparisons is limited.

NMA uses a single measurement from each trial. In contrast, the MBMA methodology can make use of all trial data but there are no formal methods for the assessment of evidence consistency.

This project will combine MBMA and NMA methodologies, to make use of all the available data, allowing model consistency to be assessed and allowing treatments to be compared even where there are no head to head trials comparing them.

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