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Network Meta-Analysis: Development of a Three-Level Hierarchical Modeling Approach Incorporating Dose-Related Constraints

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ABSTRACT

Background: Network meta-analysis (NMA) is commonly used in evidence synthesis; however, in situations in which there are a large number of treatment options, which may be subdivided into classes, and relatively few trials, NMAs produce considerable uncertainty in the estimated treatment effects, and consequently, identification of the most beneficial intervention remains inconclusive. **Objective:** To develop and demonstrate the use of evidence synthesis methods to evaluate extensive treatment networks with a limited number of trials, making use of classes. **Methods:** Using Bayesian Markov chain Monte Carlo methods, we build on the existing work of a random effects NMA to develop a three-level hierarchical NMA model that accounts for the exchangeability between treatments within the same class as well as for the residual between-study heterogeneity. We demonstrate the application of these methods to a continuous and binary outcome, using a motivating example of overactive bladder. We illustrate methods for incorporating ordering constraints in increasing doses, model selection, and assessing inconsistency between the direct and indirect evidence. **Results:** The methods were applied to a data set obtained from a systematic literature review of trials for overactive bladder, evaluating the mean reduction in incontinence episodes from baseline and the number of patients reporting one or more adverse events. The data set involved 72 trials comparing 34 interventions that were categorized into nine classes of interventions, including placebo. **Conclusions:** Bayesian three-level hierarchical NMAs have the potential to increase the precision in the effect estimates while maintaining the interpretability of the individual interventions for decision making.

Keywords: network meta-analysis, statistical methods, mixed treatment comparisons, overactive bladder.

Introduction

Network meta-analyses (NMA) are widely used in an evidence synthesis setting due to the attractive nature of utilizing all relevant information from both direct and indirect evidence [1–4]. Nevertheless, in situations in which there are a large number of interventions of interest and relatively few trials, there is a potential issue with the sparsity of data in the treatment networks, which can lead to parameter uncertainty. Collapsing the intervention arms into their respective treatment classes increases the evidence base and precision in the effect estimates, but with such a class-based approach, the direct interpretation of individual intervention effects is lost, which makes decision making difficult. To overcome this issue, a three-level hierarchical NMA can be applied [5–7]. This approach incorporates the exchangeability between interventions of the same class to predict an effect estimate for each of the interventions individually [8]. Thus, this approach allows strength to be borrowed within the classes of interventions, strengthening inferences and potentially reducing the uncertainty around the individual intervention effects, and consequently increasing the ability to rank these and inform decision-making frameworks. To further increase the precision in the effect estimates, constraints can be applied on increasing doses of the same intervention, making the assumption that higher doses have an effect greater or equal to that of lower doses [9,10].

To illustrate the use of the hierarchical framework, we applied the proposed methods to a real clinical question in overactive

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bladder (OAB) syndrome. To manage the OAB syndrome, the National Institute for Health and Care Excellence in the United Kingdom [11] currently recommends a course of supervised pelvic floor muscle training, behavioral therapy, anticholinergic medication, sacral nerve stimulation, and more recently, botulinum toxin type A (BoNTA). Given the availability of numerous interventions and emerging alternative treatments such as BoNTA, there is an increasing need to identify the most beneficial intervention. However, given the large number of interventions and the limited evidence base, in terms of both the number of trials and the number of direct comparisons between active interventions, the estimated intervention effects from a standard NMA will have a considerable level of uncertainty associated with them. In situations in which there are a limited number of trials in a meta-analysis, estimating the heterogeneity between trials may also be problematic. One approach to overcome this issue, and increase precision in the treatment effects, involves incorporating external information from similar studies relevant to the treatment of interest [12]. In an NMA that includes all available trials in a specific field, however, such external information may be limited. The aim of this article was to develop and apply hierarchical NMAs to evaluate the clinical effectiveness of interventions for the OAB syndrome by borrowing strength between interventions of the same class and applying ordering constraints on increasing doses of BoNTA, thus increasing the precision that we have in our effect estimates but maintaining the interpretability of results at the individual intervention level. For illustration purposes, we focus on two outcomes associated with intervention effectiveness (mean change in incontinence episodes from baseline) and treatment tolerability (number of patients reporting one or more adverse events).

In this article, we demonstrate the individual treatment, class-based, and three-level hierarchical random effects model approaches, and where applicable we demonstrate the use of extending hierarchical NMAs to incorporate ordering constraints. We apply these models to a motivating clinical example in the OAB syndrome. Furthermore, we demonstrate a comprehensive technique to assess inconsistency between the direct and indirect estimates of an extensive network using the method of node-splitting [13] and assess model fit using residual deviance [14] and the deviance information criterion (DIC) [15].

Methods

Illustrative Data Set

Almost all published articles reporting data on interventions for the OAB syndrome compare the intervention against placebo, which makes comparison across active interventions difficult without using indirect comparisons or NMA. This is particularly evident for trials evaluating anticholinergic drugs. Only three meta-analyses have been undertaken in the field of the OAB syndrome [16–18]. The interventions were assessed on a head-to-head basis, where studies comparing the interventions directly were pooled in a pairwise meta-analysis. Chapple et al. [16] focused on the evaluation of the clinical effectiveness of anticholinergic drugs compared with placebo, while Novara et al. [17] compared the efficacy of increased doses of each anticholinergic drug with that of their respective lower dose. Anger et al. [18] evaluated the effect of BoNTA against that of a placebo intervention. In the current literature, there is no coherent comparison between all the available interventions, and consequently, there is little information of a superior treatment for the OAB syndrome.

Figure 1A,B illustrates the network diagrams of direct comparisons for the individual intervention and classes of

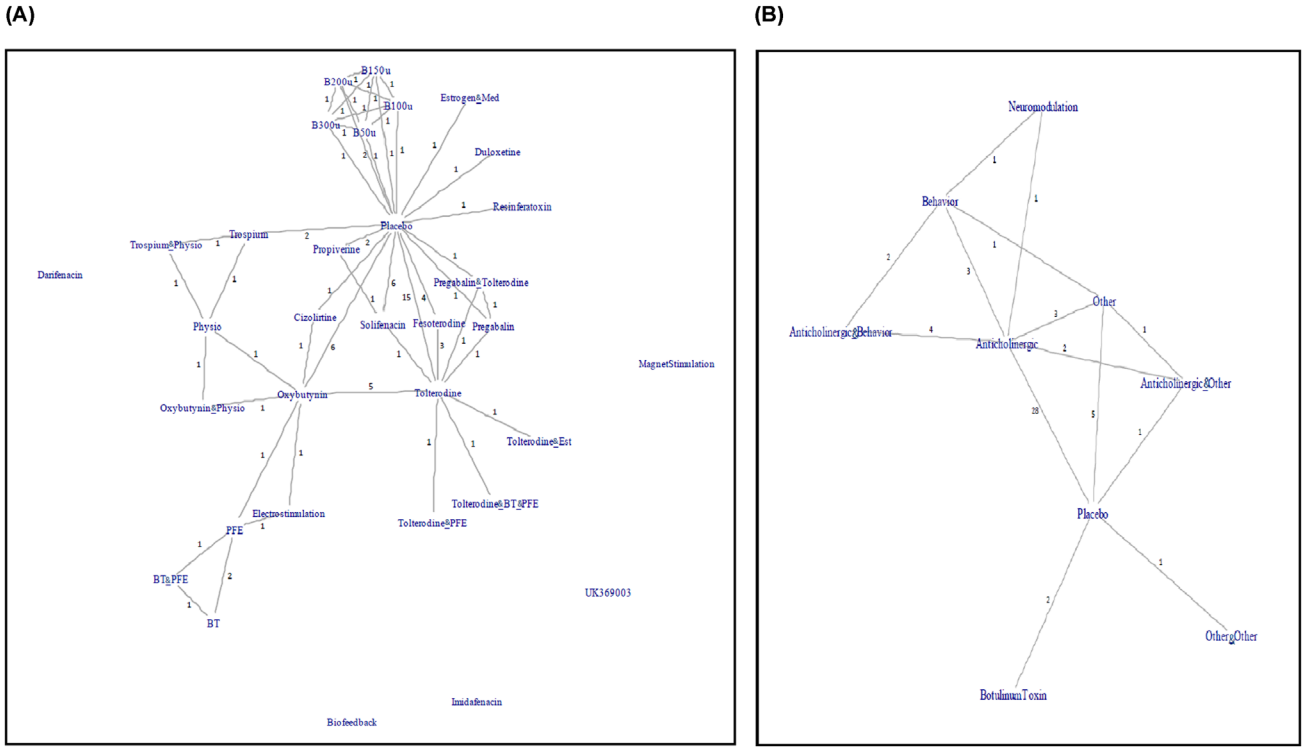

Fig. 1 – Network diagrams for urinary incontinence. (A) Individual and hierarchical network diagram. (B) Classified network diagram. B50u, Botulinum toxin type A 50 units; B100u, Botulinum toxin type A 100 units; B150u, Botulinum toxin type A 150 units; B200u, Botulinum toxin type A 200 units; B300u, Botulinum toxin type A 300 units; BT, Bladder training; Est, Estrogen; Med, Medroxyprogesterone; PFE, Pelvic floor exercises; Physio, Physiotherapy.