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Review Article

Overview of Network Meta-analysis for a Rheumatologist

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The need to combine direct and indirect evidence is increasing in clinical fields, and this is especially true when direct evidence is inconclusive. Thus, in recent years, network meta-analysis has been utilized increasingly in medicine. Network meta-analysis is a statistical method that enables comparison of multiple treatments simultaneously—by combining direct and indirect evidence of the relative treatment effects—to assess the comparative effectiveness of multiple interventions even if there are no head-to-head comparisons. Network meta-analysis has some advantages in addressing all treatments for a specific condition, comparing interventions and ranking the efficacy and safety of multiple treatments, and increasing the certainty of evidence by pooling direct and indirect evidence to generate overall estimates. The major assumption in network meta-analysis is exchangeability of the studies, and other key assumptions include similarity, consistency, and transitivity. The Bayesian approach is used most commonly in network meta-analysis because it provides greater flexibility that allows for the use of more complex models and can produce estimates of rank probabilities. Bayesian network meta-analysis produces treatment rankings according to the probability of being the best treatment, the second best, third best, and so forth. Network meta-analysis is an interesting method that provides useful information for use in by rheumatologists in decision-making. **(J Rheum Dis 2016;23:4-10)**

Key Words. Meta-analysis, Bayesian analysis

INTRODUCTION

Meta-analysis is a statistical tool for combining results from different studies on the same topic, and it has been a popular method for resolving discrepancies. Meta-analysis pools weighted estimates of studies of head-to-head treatments to answer questions about the same topic, with weights based on study precision or sample size [1]. A limitation of this pairwise meta-analysis is that it includes comparisons between only two treatments at a time and does not allow comparison of relative effectiveness of several interventions. A pairwise meta-analysis cannot be applied when there are no head-to-head studies, or when more than two treatments need to be compared with each other simultaneously [2]. For instance, real-world direct evidence from head-to-head trials of several available interventions for specific diseases often is lacking or insufficient, and yet it may be important for physicians to identify the most effective treatment or comparative efficacy and safety of all of the different interventions [3].

Network meta-analysis, also called multiple-treatments meta-analysis, is a statistical method that permits comparison of multiple treatments simultaneously by combining direct and indirect evidence of the relative treatment effects [4]. Network meta-analysis assesses the comparative effectiveness of multiple interventions and combines evidence across a network of randomized controlled trials (RCTs), even if there are no head-to-head comparisons [2]. Network meta-analysis has been proposed as a generalization and an extension of pairwise meta-analysis [5]. If there are direct comparisons of A vs. C and B vs. C, indirect estimates of comparison of A vs. B can be obtained through the common comparator C in the network [6]. Network meta-analysis has advantages over traditional meta-analysis, because the technique borrows

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strength from indirect evidence to gain certainty about all treatment comparisons [2]. Among the advantages of network meta-analysis [3] are its ability to address all treatments for a specific condition, compare interventions and rank the efficacy and safety of multiple treatments, and to increase certainty of the evidence by pooling direct and indirect evidences to generate overall estimates [3,7]. Thus, it has been utilized increasingly in medical research areas in recent years [8]. Even when a trial comparing hypothetical A and B treatment interventions exists, combining the direct estimates with the results of indirect comparisons can result in refined estimates [3]. When the results of a direct comparison between two treatments are inconclusive, the direct and indirect evidences are combined to strengthen the result of the direct comparison [4].

MAIN SUBJECTS

Basic concept and assumptions

If there are three interventions (i.e., A, B, and C) and direct comparisons (i.e., A vs. C and B vs. C trials), the relative effectiveness between A and B can be estimated indirectly via the common comparator C in the network [6]. Network meta-analysis uses only relative effects, not absolute differences, of two treatments through the common comparator in order not to break randomization of trials [6].

The major assumption in network meta-analysis is exchangeability of the studies [9]. There are important assumptions for network meta-analysis. First, there is an assumption of similarity; studies included in network meta-analysis should be comparable in terms of effect modifiers that are studied and patient characteristics that can affect the treatment effect [10]. Second, there is an assumption of consistency; it is assumed that direct and indirect estimates are consistent. Inconsistency refers to the extent of disagreement between direct and indirect evidence [11]. Inconsistency between the direct and indirect comparisons may be explained by chance and heterogeneity [12]. Imbalanced distribution of effect modifiers between trials results in heterogeneity and inconsistency, thus leading to a biased indirect estimate. Third, there is an assumption of transitivity; if treatment A is better than B, and B is better than C, it is assumed that A is better than C [7]. For the transitivity, there should be no differences in the distribution of effect modifiers among the trials [10]. Transitivity and consistency require similarity, which means that studies are sufficiently alike in terms of effect modifiers [10]. Violation of assumptions of similarity or consistency disturbs transitivity assumption, such that we cannot know that A is better than C from trial results that have already proven that A is better than B and B is better than C. However, these key assumptions for network meta-analysis are subject to substantial uncertainty and are unlikely to be statistically verifiable [2]. It is likely to depend on clinical and epidemiological judgment in context and can be verified conceptually and epidemiologically. Researchers must assess the appropriateness of the assumptions from clinical and methodological viewpoints [11].

Bayesian approach

Network meta-analysis can be conducted using a frequentist or a Bayesian approach [11]. However, the most commonly used method in network meta-analysis is the Bayesian approach, because it provides greater flexibility to use more complex models and can produce estimates of rank probabilities [13]. The Bayesian method uses both results of studies and prior knowledge, while the frequentist analysis uses only results of studies. A Bayesian analysis combines two data of information about the parameters. The first one is the sample data, and the second is the prior distribution, which represents available additional information. The data on the prior distribution is used only in the Bayesian approach. A Bayesian analysis computes a probability distribution of unknown parameters by synthesizing data and the previous knowledge about the parameters [14]. In other words, Bayesian method combines a prior probability distribution, which reflects a prior belief of the possible values of the pooled effect, with a likelihood distribution of the pooled effect based on the observed data to obtain a posterior probability distribution [14]. In order not to influence the observed results by the prior distribution, a non-informative or vague prior distribution often is used for the pooled effect [15]. A non-informative prior distribution represents the equal probability of all possible parameter values within a certain range [16]. In this case, posterior results are not influenced by the prior distribution but are affected by the observed data as in a frequentist meta-analysis [15]. Although frequentists use the sampling distribution as the basis of statistical inference, the posterior distribution obtained with the Bayesian approach permits calculating the probability that each treatment can produce better outcomes than those produced by competing

interventions [14]. The treatment effects in Bayesian network meta-analysis are presented with 95% credible intervals (CrIs), which are the Bayesian equivalent of confidence intervals (CI) [14]. Another advantage of the Bayesian method is that it provides information that is directly relevant to clinicians. Bayesian network meta-analysis produces treatment rankings according to the probability of being the best treatment, second best, third best, and so forth [14]. These values often are summarized by the surface under the cumulative ranking curve (SUCRA) [17]. However, there is a risk of over-interpreting this probability of ranking treatments [18]. These values only provide an estimate of the probability of a treatment being the best and do not show anything about the effect size of this difference [7]. Also, treatment rankings may exaggerate small differences in benefits [19]. Thus, clinicians need to consider these rankings with relative and absolute effect measures.

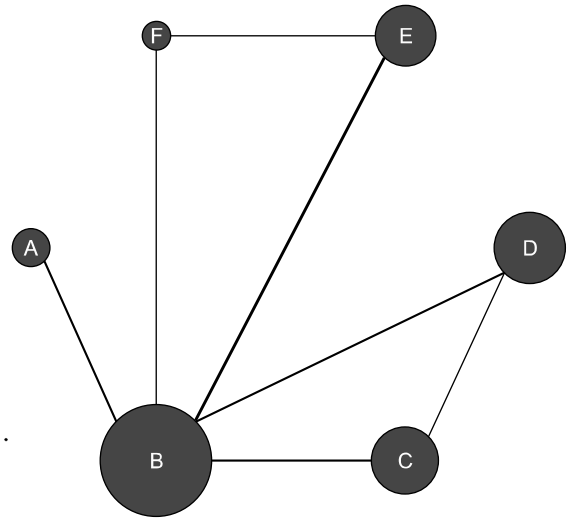

Figure 1. Evidence network diagram of network meta-analysis comparisons. The width of each edge is proportional to the number of randomized controlled trials comparing each pair of treatments, and the size of each treatment node is proportional to the number of randomized participants (sample size). (A) Duloxetine 60 mg, (B) placebo, (C) milnacipran 200 mg, (D) milnacipran 100 mg, (E) pregabalin 300 mg, (F) pregabalin 150 mg.

Method of network meta-analysis

1) Network plot

Network plot or diagram depicts the shape of the network by nodes and uses lines to connect those interventions that have been compared directly in an RCT, thus showing which treatments have been compared directly in RCTs and the contribution of treatment comparisons in the network (Figure 1) [20]. The size of the node is used to represent the number of participants who have been randomized to this intervention, and the width of the lines is used to denote the number of studies for comparisons [21]. The network plot reveals how strong the evidence is for the network as a whole and for the individual comparisons [21].

2) Statistical analysis for network meta-analysis

Most network meta-analysis uses WinBUGS statistical analysis program version 1.4.3 (MRC Biostatistics Unit, Institute of Public Health, Cambridge, United Kingdom), and NetMetaXL program [13] is commonly used to conduct a Bayesian network meta-analysis. The Markov Chain Monte Carlo method is used to obtain the pooled effect sizes in the network meta-analysis [2]. Network meta-analysis uses fixed-effect or random-effect models like a pairwise meta-analysis. The fixed-effect model assumes that genetic factors have similar effects on disease susceptibility in all the studies, and that the observed variations between studies are caused by chance alone [22]. The random-effects model assumes that different studies exhibit substantial diversity and assesses both intra-study sampling errors and inter-study variances [23]. The choice of meta-analysis model depends on the presence or absence of heterogeneity. In the absence of heterogeneity, a fixed-effects model is used for meta-analysis. When a significant heterogeneity exists in the studies, a random-effects model is utilized for meta-analysis [24]. Information of relative effects was converted to a probability that a treatment is best, second best, and so on, or the ranking of each treatment, called the SUCRA [17], which is expressed as a percentage—the SUCRA would be 100% when a treatment is certain to be the best and 0% when a treatment is certain to be the worst. The league table arranges the presentation of summary estimates by ranking the treatments in order of the most pronounced impact on the outcome under consideration based on SUCRA [17]. CI in a frequentist analysis cannot be interpreted in terms of probabilities, but a Bayesian inference method presents probabilities. The pairwise odds ratio (OR) and 95% CrI (adjusted for multiple-arm trials) are calculated, and pooled results are considered statistically significant if the 95% CrI does not contain the value 1.

3) Inconsistency test

Consistency is a key assumption for network meta-anal-

ysis and needs to be checked in network meta-analysis. Assessment of inconsistency is important for conducting a network meta-analysis [25]. NetMetaXL allows users to assess inconsistency in fitted consistency and inconsistency models [2]. One can plot the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to assess the network inconsistency between direct and indirect estimates in each loop [26]. Although it is important to perform tests for inconsistency, this should not be considered only in a statistical way [11].

Example: Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia

This network meta-analysis was performed to assess the relative efficacy of duloxetine, pregabalin, and milnacipran at the recommended doses in patients with fibromyalgia. RCTs examining the efficacy of duloxetine 60 mg, pregabalin 300 mg, pregabalin 150 mg, milnacipran 200 mg, and milnacipran 100 mg compared to placebo in patients with fibromyalgia were included in this Bayesian network meta-analysis.

A Bayesian random-effects model for network meta-analysis using NetMetaXL [13] and WinBUGS statistical analysis program version 1.4.3 using the Markov Chain Monte Carlo simulation were conducted. A random effect model was chosen because it incorporates between-study variations and is a conservative method. The information on relative effects was converted to a probability of treatment effectiveness (e.g., best treatment, second best, third best) in the ranking of each treatment, called the SUCRA [17], which is expressed as a percentage. The league table arranges the presentation of summary estimates by ranking the treatments [17]. The posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model was plotted to assess the network inconsistency between direct and indirect estimates in each loop [26].

Nine RCTs, which included 5,140 patients, met the inclusion criteria. The evidence network diagram shows the data related to the number of studies performed comparing the different treatments and the number of patients in each treatment (Figure 1). The proportion of patients with >30% improvement from baseline in pain was significantly higher in the duloxetine 60 mg, pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg groups than in the placebo group (pairwise OR 2.33, 95% CrI 1.50 to 3.67; OR 1.68, 95% CrI 1.25 to 2.28; OR 1.62, 95% CrI 1.16 to 2.25; and OR 1.61, 95% CrI 1.15 to 2.24, respectively) (Figures 2 and 3). Ranking probability based on the surface under the SUCRA indicated that duloxetine 60 mg had the highest probability of being the best treatment for achieving the response level (SUCRA=0.9431), followed by pregabalin 300 mg (SUCRA=0.6300), milnacipran 100 mg (SUCRA=0.5680), milnacipran 200 mg (SUCRA=0.5617), pregabalin 150 mg (SUCRA=0.2392), and placebo (SUCRA=0.0580) (Table 1). Inconsistency plots assessing network inconsistencies between direct and indirect estimates showed a low possibility that inconsistencies may significantly affect the network meta-analysis results (Figure 4). This network meta-analysis demonstrates that duloxetine 60 mg, pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg are more efficacious than placebo. However, there was no significant difference in efficacy between the medications at the recommended doses. Long-term studies are needed to determine the relative efficacy and safety of

Duloxetine 60 mg					
1.39 (0.80~2.40)	Pregabalin 300 mg				
1.45 (0.84~2.53)	1.04 (0.67~1.64)	Milnacipran 100 mg			
1.46 (0.84~2.55)	1.04 (0.68~1.65)	1.00 (0.68~1.49)	Milnacipran 200 mg		
1.98 (0.92~4.19)	1.41 (0.80~2.51)	1.35 (0.69~2.63)	1.35 (0.68~2.63)	Pregabalin 150 mg	
2.33 (1.50~3.67)	1.68 (1.25~2.28)	1.62 (1.16~2.25)	1.61 (1.15~2.24)	1.19 (0.67~2.13)	Placebo

Figure 2. League tables showing the results of the network meta-analyses comparing the effects of all drugs including odds ratios (OR) and 95% credible intervals. OR >1 means the top-left treatment is better.

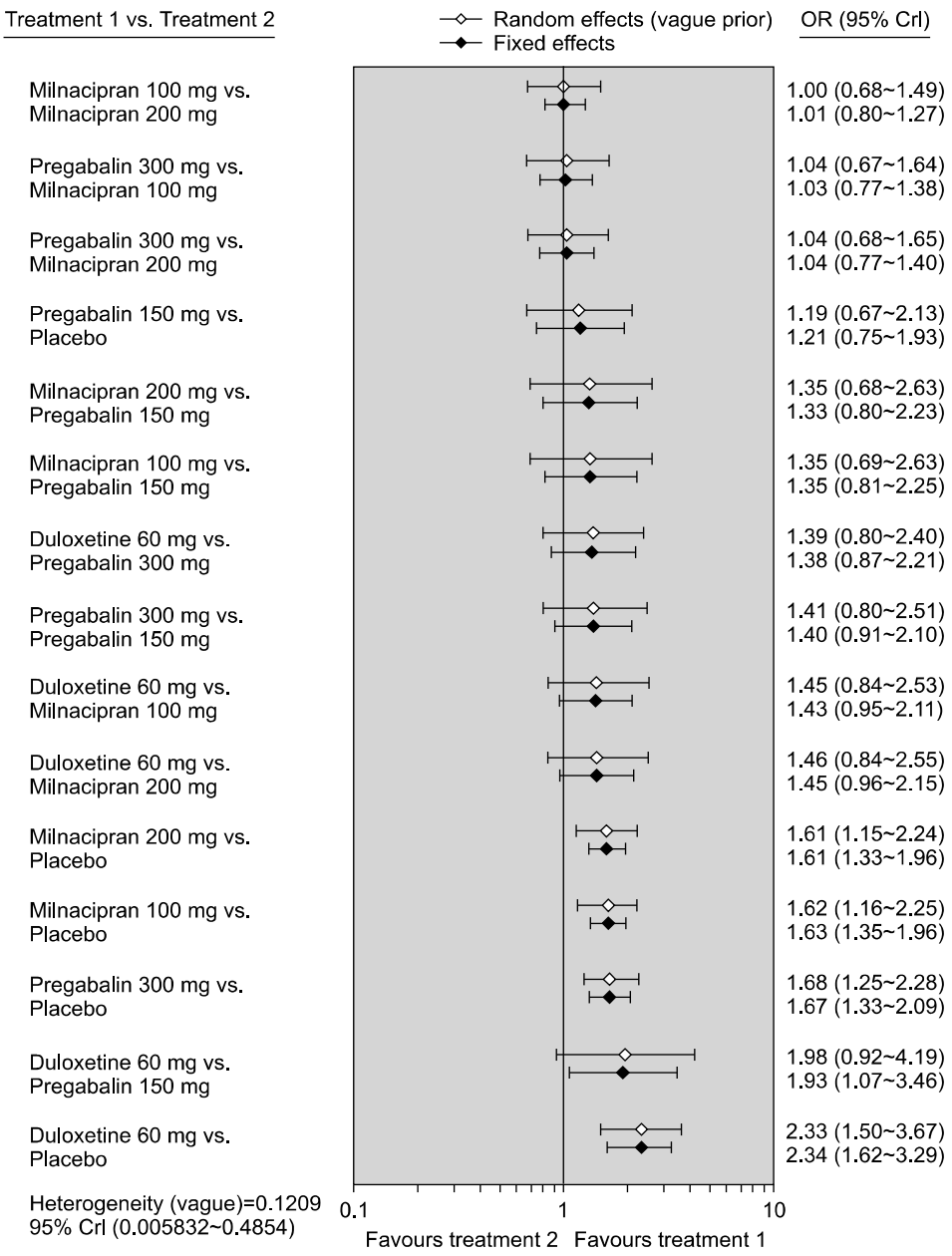

Figure 3. Bayesian network meta-analysis results of randomized controlled studies on the relative efficacy of duloxetine, pregabalin, milnacipran, and placebo, respectively. CrI: credible interval, OR: odds ratio.

Table 1. Rank probability of duloxetine, pregabalin, milnacipran, and placebo*

Treatment	SUCRA
Duloxetine 60 mg	0.9431
Pregabalin 300 mg	0.6300
Milnacipran 100 mg	0.5680
Milnacipran 200 mg	0.5617
Pregabalin 150 mg	0.2392
Placebo	0.0580

SUCRA, surface under the cumulative ranking curve. *Efficacy based on the number of patients achieving at least 30% improvement in pain.

duloxetine, pregabalin, and milnacipran in a large number of patients with fibromyalgia.

CONCLUSION

Network meta-analysis is an interesting method that combines all available data in the same topic and permits simultaneous analysis. Network meta-analysis is a new statistical tool that incorporates evidence from both direct and indirect treatment comparisons and in a network of trials to assess the benefits and risks of numerous interventions. The advantage of network meta-analysis is that it allows for the identification of which drug is best in

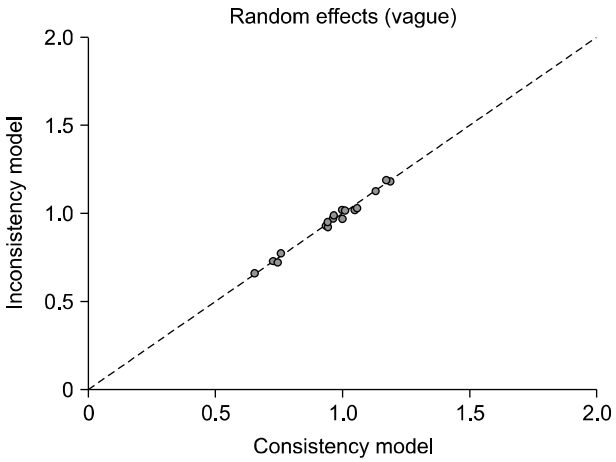

Figure 4. Inconsistency plots for efficacy of duloxetine, pregabalin, milnacipran, and placebo. Plot of the posterior mean deviance contribution of individual data points for the consistency model (horizontal axis) and the unrelated mean effects model (vertical axis), along with the line of equality.

terms of safety and effectiveness with regard to the chosen outcome, based on rank order, and for the determination that one drug is better than another, and it provides a more precise pooled effect estimate by combining direct and indirect evidences. Thus, network meta-analysis is helpful in comparing the relative effectiveness and safety of competing treatments even if there are no head-to-head trials. Network meta-analysis can help a rheumatologists' decision-making by providing useful information on the relative efficacy and safety of interventions for a specific condition.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533-7.
2. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331:897-900.
3. Jansen JP, Crawford B, Bergman G, Stam W. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value Health 2008;11:956-64.
4. Catalá-López F, Tobías A, Cameron C, Moher D, Hutton B. Network meta-analysis for comparing treatment effects of multiple interventions: an introduction. Rheumatol Int 2014;34:1489-96.
5. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23: 3105-24.
6. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50:683-91.
7. Mavridis D, Giannatsi M, Cipriani A, Salanti G. A primer on network meta-analysis with emphasis on mental health. Evid Based Ment Health 2015;18:40-6.
8. Nikolakopoulou A, Chaimani A, Veroniki AA, Vasiliadis HS, Schmid CH, Salanti G. Characteristics of networks of interventions: a description of a database of 186 published networks. PLoS One 2014;9:e86754.
9. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;33:607-17.
10. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. BMC Med 2013;11:159.
11. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making 2013;33:641-56.
12. Song F, Xiong T, Parekh-Bhurke S, Loke YK, Sutton AJ, Eastwood AJ, et al. Inconsistency between direct and indirect comparisons of competing interventions: meta-epidemiological study. BMJ 2011;343:d4909.
13. Brown S, Hutton B, Clifford T, Coyle D, Grima D, Wells G, et al. A Microsoft-Excel-based tool for running and critically appraising network meta-analyses: an overview and application of NetMetaXL. Syst Rev 2014;3:110.
14. Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. Stat Methods Med Res 2001;10: 277-303.
15. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 2012;41:818-27.
16. Koning A. Bayesian monte carlo method for nuclear data evaluation. Nuclear Data Sheets 2015;123:207-13.
17. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163-71.
18. Bhatnagar N, Lakshmi PV, Jeyashree K. Multiple treatment and indirect treatment comparisons: an overview of network meta-analysis. Perspect Clin Res 2014;5:154-8.
19. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162:777-84.
20. König J, Krahn U, Binder H. Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. Stat Med 2013;32:5414-29.
21. Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. PLoS One 2013;8:e76654.
22. Davey Smith G, Egger M. Meta-analyses of randomised con-

trolled trials. Lancet 1997;350:1182.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
24. Ried K. Interpreting and understanding meta-analysis graphs: a practical guide. Aust Fam Physician 2006;35:635-8.
25. Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. Res Synth Methods 2012;3:98-110.
26. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res Synth Methods 2012;3:285-99.