A BAYESIAN NETWORK META-ANALYSIS WITH RANDOM INCONSISTENCY EFFECTS FOR MULTI-ARM STUDIES

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Extended Abstract

Introduction: The design-by-treatment interaction model, an inconsistency model for network meta-analysis with random inconsistency effects can also be applied whenever arm-level binary outcome data are available. Arm-based analyses facilitate using binomial distributions. Random-effects formulation of the model allows us to estimate average treatment effects across all designs. This study aims to investigate the ranking of treatments under random inconsistency effects within a Bayesian framework.

Materials & Methods: The dataset consists of 45 randomized controlled trials (RCTs) comparing the effect of 11 pharmacological drugs for acute bipolar mania in adults. The drugs includes mood stabilizers, anti-psychotics, antidepressants, combinations of the above and other agents, were compared against each other as well as with placebo either as monotherapy or add on agents. The drugs considered for the analysis were placebo, aripiprazole, haloperidol, quetiapine, ziprasidone, olanzapine, divalproex, paliperidone, carbamazepine, lithium; and lamotrigine. The outcome of interest was response to treatment (efficacy), which was defined as the number of patients who responded to the treatment for the period of first 3 weeks of treatment. Here, a response is defined as more than equal to 50 per cent reduction in maniac symptoms from the baseline to 3 weeks.

For binary data, a binomial distribution has been adopted for the number of events and the *logit* scale to model the probability of event occurrence. A Bayesian network meta-analysis with random inconsistency effects was performed for treatment efficacy. Further, we used two sensitivity analyses to see how sensitive the conclusions are (1) to different fixed values of the inconsistency variance parameter; and (2) on the ranking of treatments with respect to the

selection of the non-informative prior distributions of heterogeneity (τ_β) and inconsistency (τ_ω) standard deviations.

All results pertain to 10,00,000 Markov Chain Monte Carlo (MCMC) iterations and thinning of 100 to reduce the autocorrelation in the sample. Very large burn-in period of 3,00,000 was used to ensure convergence, which was checked by running three chains at different starting values and using Gelman-Rubin convergence statistics. The proportion of MCMC iterations in which treatments are the most effective gives the probabilities which are then used to rank the treatments. All the analyses have been carried out in WinBUGS.

Results: The impact of including inconsistency in the random-effects model is 14.05%. The probability of Carbamazepine being the best decreases from 0.41 to 0.27 as the level of inconsistency increases from 0 to 0.3 (Table 1); whereas it varies from 0.38 to 0.40 (Table 2) for the various selected prior distributions. Gelman-Rubin convergence statistics were stable and all Monte Carlo errors were around 0.005.

Conclusion: Carbamazepine was found to have the largest probability of being the best in both the sensitivity analyses; and thereby, ranked as the most efficacious drug.

Keywords: Bayesian Network meta-analysis; Markov Chain Monte Carlo; design-by-treatment interaction model; Random inconsistency.

Table 1. Sensitivity analysis at various fixed values of the inconsistency standard deviation τ_ω

	$\tau_\omega = 0$			$\tau_\omega = 0.1$			$\tau_\omega = 0.2$			$\tau_\omega = 0.3$		
Treatment	**Estimate**	**SD**	**P(best)**	**Estimate**	**SD**	**P(best)**	**Estimate**	**SD**	**P(best)**	**Estimate**	**SD**	**P(best)**
A_PBO	-	-	0.00	-	-	0.00	-	-	0.00	-	-	0.00
B_ARI	0.69	0.14	0.03	0.70	0.16	0.04	0.71	0.18	0.06	0.72	0.21	0.07
C_HAL	0.81	0.14	0.13	0.81	0.15	0.13	0.82	0.16	0.14	0.83	0.18	0.14
D_QTP	0.70	0.15	0.04	0.70	0.16	0.05	0.71	0.18	0.05	0.72	0.20	0.06
E_ZIP	0.32	0.17	0.00	0.33	0.20	0.00	0.33	0.23	0.00	0.35	0.28	0.01
F_OLZ	0.74	0.13	0.05	0.75	0.14	0.06	0.75	0.16	0.06	0.76	0.18	0.07
G_VAL	0.68	0.17	0.04	0.67	0.18	0.04	0.66	0.20	0.04	0.65	0.22	0.04
H_PAL	0.75	0.14	0.08	0.76	0.16	0.08	0.76	0.18	0.09	0.76	0.21	0.10
I_CBZ	0.89	0.32	0.41	0.88	0.33	0.38	0.85	0.35	0.33	0.81	0.39	0.27
J_LIT	0.59	0.18	0.02	0.60	0.19	0.02	0.60	0.20	0.02	0.62	0.23	0.03
K_LAM	0.30	0.84	0.19	0.30	0.85	0.20	0.31	0.87	0.20	0.33	0.90	0.21
Quantifying the impact of inconsistency												
R-statistic	Reference			1.0787			1.1769			1.330		
$\boldsymbol{I^2}$ **(%)**	Reference			14.05			27.80			43.47		

NOTE: Estimates (in log scale) are given by posterior means; P(best) is the probability that each treatment is best; SD – Standard Deviation

Abbreviations: Placebo (A_PBO), Aripiprazole (B_ARI), Haloperidol (C_HAL), Quetipaine (D_QTP), Ziprasidone (E_ZIP), Olanzapine (F_OLZ), Divalproex (G_VAL), Paliperidone (H_PAL), Carbamazpine (I_CBZ), Lithium (J_LIT); and Lamotrigine (K_LAM).

Table 2. Sensitivity analysis for the Prior Distributions of τ_β and τ_ω

Distributions →	$\tau_\beta \backsim U(0,1)$ $\tau_\omega \backsim U(0,1)$			$\tau_\beta \backsim U(0,5)$ $\tau_\omega \backsim U(0,5)$			$\tau_\beta \backsim U(0,10)$ $\tau_\omega \backsim U(0,10)$			$\tau_\beta \backsim Beta(0.5,0.5)$ $\tau_\omega \backsim Beta(0.5,0.5)$		
Treatment	**Estimate**	**SD**	**P(best)**	**Estimate**	**SD**	**P(best)**	**Estimate**	**SD**	**P(best)**	**Estimate**	**SD**	**P(best)**
A_PBO	-	-	0.00	-	-	0.00	-	-	0.00	-	-	0.00
B_ARI	0.70	0.16	0.04	0.70	0.16	0.04	0.70	0.16	0.04	0.70	0.15	0.04
C_HAL	0.81	0.15	0.13	0.81	0.15	0.13	0.81	0.15	0.13	0.81	0.15	0.13
D_QTP	0.70	0.16	0.05	0.70	0.16	0.05	0.70	0.16	0.05	0.70	0.15	0.04
E_ZIP	0.33	0.20	0.00	0.33	0.20	0.00	0.33	0.20	0.00	0.32	0.18	0.00
F_OLZ	0.75	0.14	0.06	0.75	0.14	0.06	0.75	0.14	0.06	0.74	0.14	0.05
G_VAL	0.67	0.18	0.04	0.67	0.18	0.04	0.67	0.18	0.04	0.67	0.17	0.04
H_PAL	0.76	0.16	0.08	0.76	0.16	0.08	0.76	0.16	0.08	0.75	0.15	0.08
I_CBZ	0.88	0.33	0.38	0.88	0.33	0.38	0.88	0.33	0.38	0.89	0.32	0.40
J_LIT	0.60	0.19	0.02	0.60	0.19	0.02	0.60	0.19	0.02	0.59	0.19	0.02
K_LAM	0.30	0.85	0.20	0.30	0.85	0.20	0.31	0.85	0.20	0.30	0.85	0.19
Heterogeneity and Inconsistency Estimation												
Est. Heterogeneity mean, τ_β (SD)	0.2863 (0.0710)			0.2863 (0.0708)			0.2864 (0.0710)			0.2821 (0.0715)		
Median (95% CrI)	0.2838 (0.1532, 0.4331)			0.2839 (0.1535, 0.4327)			0.2840 (0.1531, 0.4334)			0.2801 (0.1467, 0.4286)		
Est. Inconsistency mean, τ_ω(SD)	0.104 (0.0802)			0.1032 (0.0802)			0.1036 (0.0803)			0.0649 (0.0710)		
Median (95% CrI)	0.0870 (0.0041, 0.2984)			0.0861 (0.0038, 0.2975)			0.0863 (0.0044, 0.2986)			0.0403 (0.00, 0.2522)		

'*' Estimates (in log scale) are given by posterior means; P(best) is the probability that each treatment is best; SD – Standard Deviation; Crl – Credible Interval

Abbreviations: Placebo (A_PBO), Aripiprazole (B_ARI), Haloperidol (C_HAL), Quetipaine (D_QTP), Ziprasidone (E_ZIP), Olanzapine (F_OLZ), Divalproex (G_VAL), Paliperidone (H_PAL), Carbamazpine (I_CBZ), Lithium (J_LIT); and Lamotrigine (K_LAM).