Serotonin receptor agonists and the risk of paresthesia in migraine patients: network meta-analysis and dose–response meta-analysis

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Abstract

This meta-analysis investigated the relationship between 8 serotonin receptor agonists and the risk of paresthesia for migraine patients. This analysis aims to answer two questions: 1) which treatment has a higher relative risk or absolute risk; 2) is there any dose-response relationship that exists. Hence, both contrast/arm-based network meta-analysis and dose-response meta-analysis methods were used to answer the questions of interest. The results show agent Lasmiditan (LAN) with a dose of 400mg has the highest absolute risk (0.27, 95%CI [0.17, 0.41]), and agent Zolmitriptan (ZTN) with a dose of 10mg has the highest relative risk (12.3, 95%CI [3.05, 49.52]). Besides, the risk of paresthesia for agent FRN increases significantly while increasing the dose and the risk of paresthesia increases by 12.98% when five more unit dose of FRN is taken.

Keywords: Network meta-analysis, dose-response, serotonin receptor agonists

1 Introduction

Network meta-analysis (NMA) is a statistical technique to compare multiple treatments simultaneously. In medical research, the use of NMA has become increasingly popular in recent years [1]. Two widely used approaches in NMA are contrast-based and arm-based. The former focuses on modeling relative treatment effects while the latter provides estimation for each treatment arm's population-averaged absolute effect sizes [8]. Currently, the R package *netmeta* and *pcnetmeta* implementing the two methods are available [4,5].

Migraine is a primary headache disorder, often accompanied by nausea, vomiting, and sensitivity to light, sound, or smell. The serotonin receptor subtype agonists (triptans) are

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See Github link for R codes.

nowadays common therapy for migraine [9]. However, though most people do well on triptans, triptans have several serious adverse side effects, including paresthesias. Thus, comparing the risk of paresthesias between different triptans treatments can help patients choose one treatment out of all potential therapies.

I compared the risk of paresthesia between any serotonin-receptor agonists with different doses and placebo treatment in this meta-analysis. Furthermore, I wanted to know which treatment has a significantly higher absolute risk (AR) than placebo. Besides, for agonist FRN, I fitted a linear dose-response model to investigate the relationship between dose and paresthesia risk.

2 Background

Included randomized-control trials recruited migraine patients, provided participants with triptans or placebo, and recorded whether they have a side effect of paresthesia within 24 hours after taking the given drug.

All trials were assessed using the risk-of-bias assessment tool as outlined in the Cochrane Handbook, and most of the trials were assessed as low or unclear risk of bias.

The utilized database consisted of 25 published trials with 22755 patients and was searched from PubMed, Embase, and Cochrane Library databases. All trials are placebo-controlled clinical trials with at least two arms. In total, eight triptans with different doses (30 treatment combinations) were collected.

This final database included publication characteristics (author and year of publication) and summary statistics: number of events, number of participants, kind of agent, and dose per arm. (see figure 6 in appendix B for truncated database)

Abbreviation explanation: ZTN: Zolmitriptan, LAN: Lasmiditan, ATN: Almotriptan, ETN: Eletriptan, FRN: Frovatriptan, NTN: Naratriptan, RNT: Rizatroptan, STM: Sumatriptan.

3 Method

Since this analysis aims not only to find out better treatments (compared with placebo) with the highest risk of paresthesia, but also to compare the absolute effect size of each treatment, both the contrast-based and arm-based models were fitted to answer the two questions. Besides, for the agent FRN, which was taken in 2 trials (11 arms, which is the highest frequency among all agents), I wonder how this agonist dose is associated with the risk of paresthesia. Hence, a dose-response meta-analysis was also conducted.

3.1 Network Meta Analysis (NMA)

Notation:

Assume there are I studies/trials in the network and studies are labeled as $i = 1, 2, \ldots, I$. For each study, K is the treatment index. In study i, when n_{ik} refers to the total number of participants for treatment group k, the observed number of events y_{ik} arisen from a binomial process: $y_{ik} \sim Bin(n_{ik}, p_{ik})$ where p_{ik} is the probability of the event.

Contrast-based (CB) model

As mentioned above, contrast-based NMA focuses on estimating trial-specific relative effects under consistency assumption. In general, there are two contrast-synthesis approaches: modeling the estimates of the probability of the event of interest and modeling the estimates of treatment contrasts [1].

In this analysis, I used the second approach in a frequentist framework.

Setting baseline treatment/placebo as b for each study and using logit link function, the random effect of treatment k versus b in the ith trial can be written as δ_{ibk} and μ_1 is expected value of placebo treatment b in ith trial. The log odds ratio for treatment k relative to placebo b, δ_{ibk}, can be expressed as:

$$\delta_{ibk} = log(OR_{ibk}) = log(\frac{p_{ik}/(1-p_{ik})}{p_{ib}/(1-p_{ib})}) = logit(p_{ik}) - logit(p_{ib}) = \eta_{ik} - \mu_i.$$

Hence, the contrast-base model is:

$$\eta_{ik} = \mu_i + \delta_{ibk}.$$

Assume δ_{ibk} follows a normal distribution with mean b_{bk} and variance σ^2_{bk} in a random effect model: $\delta_{ibk} \sim N(d_{bk}, \sigma^2_{bk})$, where d_{bk} is mean effect of treatment k versus b and σ^2_{bk} is between-trial variance in treatment effects [1] (see appendix A for a simple example of estimation process for CB model).

The contrast-based model assumes relative effects are exchangeable across studies: three parameters are inter-related as follows $d_{AB} = d_{CB} - d_{CA}$ [8]. Inconsistency was diagnosed with Cochran's Q statistics which can be decomposed into two parts: coming from each design (within design) and coming from each study (between designs), where a design is each combination treatments within a study in an NMA (e.g., for three treatments, the possible designs are A:B, A:C, B:C, A:B:C).

Ranking treatments are performed by P-score, which can be interpreted as the average extent of certainty that one treatment is better than other treatments. Besides, this P-score is an analog to the surface under the cumulative ranking curve (SUCRA) in the Bayesian framework [1].

R package *netmeta* was used to fit a contrast-synthesis model in a frequentist framework, and a weighted least squares estimation approach was utilized in this package.

Arm-based (AB) model

Arm-based NMA intends to estimate population-averaged absolute effect sizes for each treatment arm. One assumption of arm-based model is that absolute effects are exchangeable [8].

The arm-based model is:

$$\eta_{ik} = \beta_i + \alpha_k + u_{ik},$$

where β_i is the fixed main-effect of the ith trial, α_k is the main-effect of the kth treatment, and u_{ik} is the random effect associated with η_{ik}. Vector of random effect u_{ik} for the ith trial is u_i, which has zero mean and covariance matrix Σ_i: $E(u_i) = 0$, $var(u_i) = \Sigma_i$ [1]. The AB model can also be viewed as a classical two-way ANOVA model with random effects for trial and fixed effect for treatments [11] and is similar to incomplete block designs [13].

R package *pcnetmeta* was used to implement this model in a Bayesian framework. This package applies Markov Chain Monte Carlo (MCMC) algorithms to obtain Bayesian estimates for parameters. Note: this estimation might not converge well when some treatments are only included in less than three studies. In our cases, only 5 treatments out of 30 are included in more than three studies. Thus, the estimation might be biased and need further investigation.

Relationship between AB and CB model:

Under Bayesian estimation with flat priors for μ_i and β_i, the CB and AB model are identical [12].

$$\begin{aligned}\eta_{ik} &= \beta_i + \alpha_k + u_{ik} \\ &= (\beta_i + \alpha_b + u_{ib}) + (\alpha_k - \alpha_b + u_{ik} - u_{ib}) \\ &= \mu_i + \delta_{ibk}\end{aligned}$$

3.2 Dose response meta analysis

Dose-response meta-analysis (DRMA) is to investigate the relationship between exposure dose and the outcome of interest.

Dose-response meta-analysis model:

Let i be study index and j be dose index within each study. $y_{ij} \sim Bin(n_{ij}, p_{ij})$ and p_{ij} is the probabilities of having the event of interest in dose j within study i, and y_{ij} is the dose-specific number of events.

The linear dose-response meta-analysis model for log relative risk:

$$\delta_{ij} = \beta_i(X_{ij} - X_{ib}) + \epsilon_{ij},$$

where δ_{ij} are the underlying log relative effects of dose X_{ij} relative to placebo dose X_{ib} in ith trial and $\delta_{ij} = \lambda(p_{ij}) = log(\frac{p_{ij}}{p_{ib}})$. The random dose-response coefficients model assumes that the trial-specific regression coefficients follow a normal distribution: $\beta_i \sim MVN(B, \Sigma)$, where mean is B and variance-covariance matrix is Σ [7].

R package *dosersmeta* was utilized to analyze the dose-response relationship between doses of agent "FRN" and the risk of having an adverse effect - paresthesia [2,6].

4 Results

4.1 Network plot

Network plot assigns different colors to each agent and a thicker line indicates more direct comparisons between two treatments, where a node denotes a treatment.

From figure 1, we can see all treatments are directly compared with placebo, but only agents "FRN" and "LAN" have several direct comparisons between different doses. Based on this network plot, we can compare all of those treatments directly or indirectly.

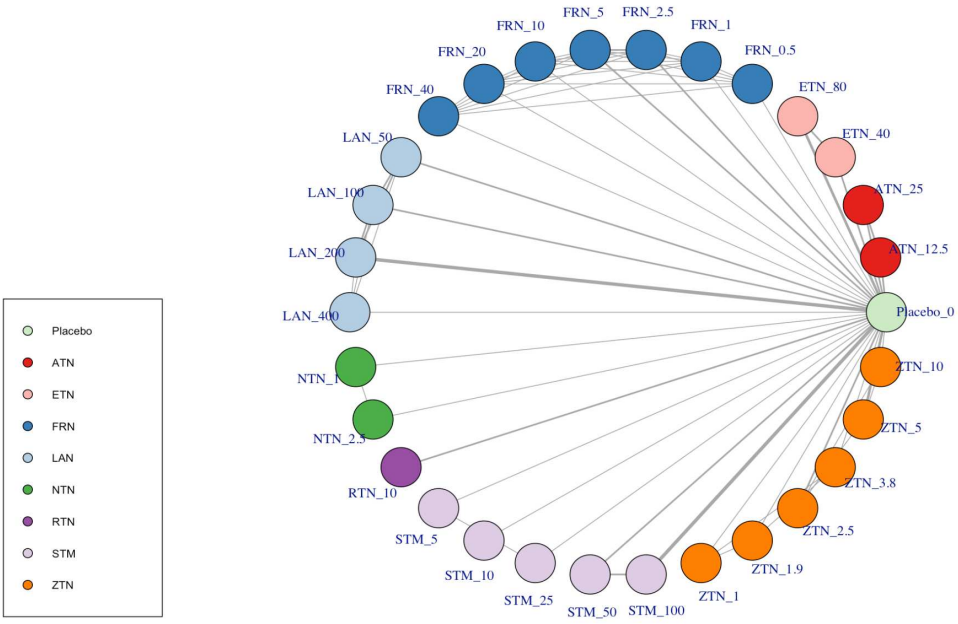

FIGURE 1: Network Plot for 30 treatments (combination of 8 triptans and different doses)

4.2 Construct-based NMA

A random-effects model was fitted using relative risk/risk ratio (RR) as the underlying summary measure, and the Inverse Variance method was used to pool estimates from different trials.

Based on the fixed-effect model's heterogeneity test, we have Cochren's Q statistic with a value of 37.83 and a p-value of 0.009, which shows considerable heterogeneity in the network and indicates a random-effects model would be more suitable. With a random-effects model, though the overall test gives a Q value 33.05 with a p-value less than 0.05 (p-value=0.03), the consistency (Q=15.83, p-value=0.105) and homogeneity (Q=17.22, p-value=0.07) assumptions seem hold.

Figure 2 is the forest plot for each treatment compared with placebo. Predicted relative risk (compared to placebo) and its 95% confidence intervals were draw for each treatment. We can see nine treatment's 95% confidence intervals of relative risk do not cross with a

vertical line at 1 (e.g., LAN with dose 100mg, 200mg, 400mg; FRN with dose 10mg, 40mg; STM with dose 100mg, ZTN with dose 2.5mg, 5mg, 10 mg). Since those nine intervals are greater than 1, we can say those nine treatments have higher RR versus placebo.

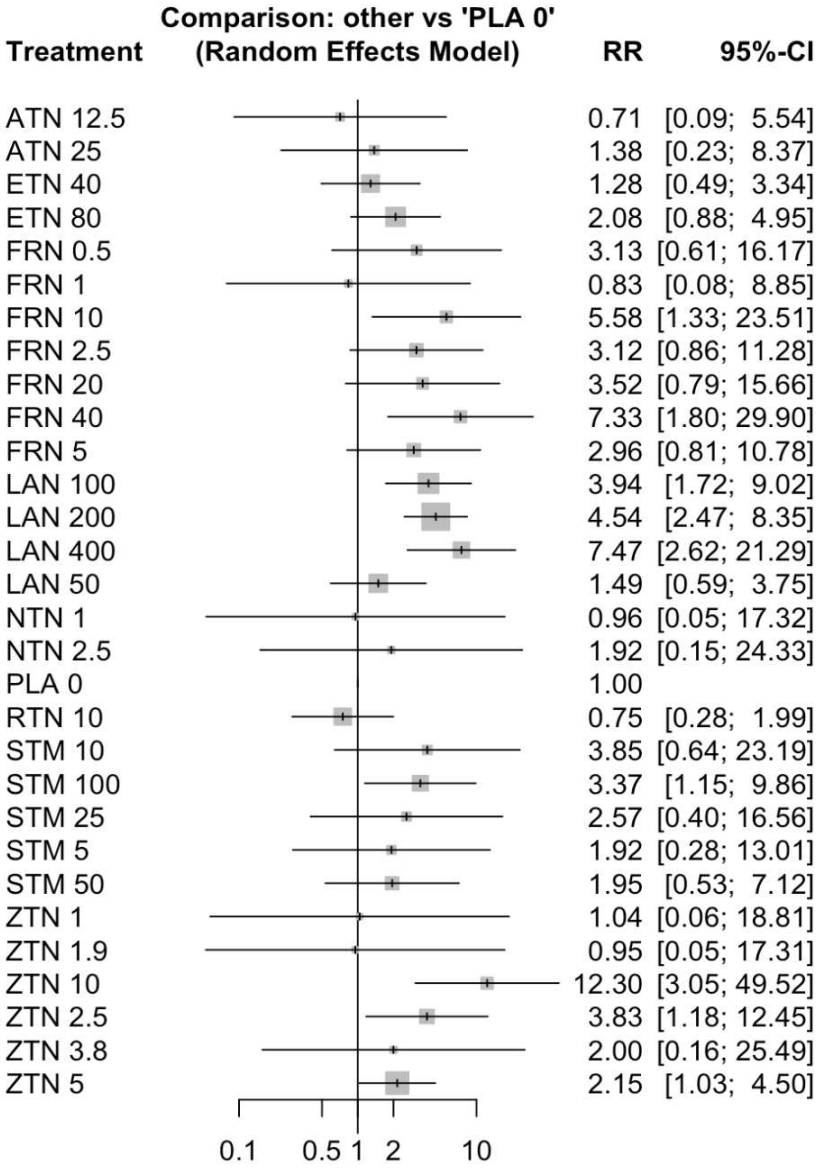

FIGURE 2: Forest plot of relative risk versus placebo and 95% confidence intervals based on contrast-based model

Table 1 shows point estimation of relative risks, P-score for the contrast-based model, and RR, AR for the arm-based model. A large P-score indicates a better treatment (e.g., RTN 10mg has the highest P-score and is the overall best treatment with the lowest risk of

paresthesia). In general, we can see treatments having large P-scores have relatively low relative risk.

After decomposing the Cochran's Q into between and within designs and detaching one design at a time, we can see that two designs (Placebo: ETN 80 and Placebo: ETN 40: ETN 80) have the lowest Q statistics with a value of 6.59, which indicates that those two designs contributed to between-design inconsistency (see figure 10 in appendix B).

4.3 Arm-based NMA

We already learned that several treatments have a significantly higher relative risk for paresthesia than placebo. It is natural to wonder what is the absolute treatment effect size for each treatment.

Assigning inverse-Wishart prior to unstructured covariance matrix Σ_k and using logit function as link function, we can obtain estimations of both absolute treatment effects and relative effects in an arm-based model.

Figure 3 shows the treatment-specific 95% CI plot for the absolute risk of paresthesia: Clearly, ENT with a dose of 80mg and LAN with a dose of 400mg do not overlap with other CIs, indicating a significant difference between those two treatments and others. Their absolute risks are higher than placebo (median absolute risk 0.02, 95%CI [0.014, 0.020]). Besides, one thing that deserves notice is that only one out of nine treatments, which we discovered has significantly higher relative risk than placebo, has an absolute risk higher than 0.1. (LAN with 400mg: median absolute risk 0.27, 95%CI [0.17, 0.41]).

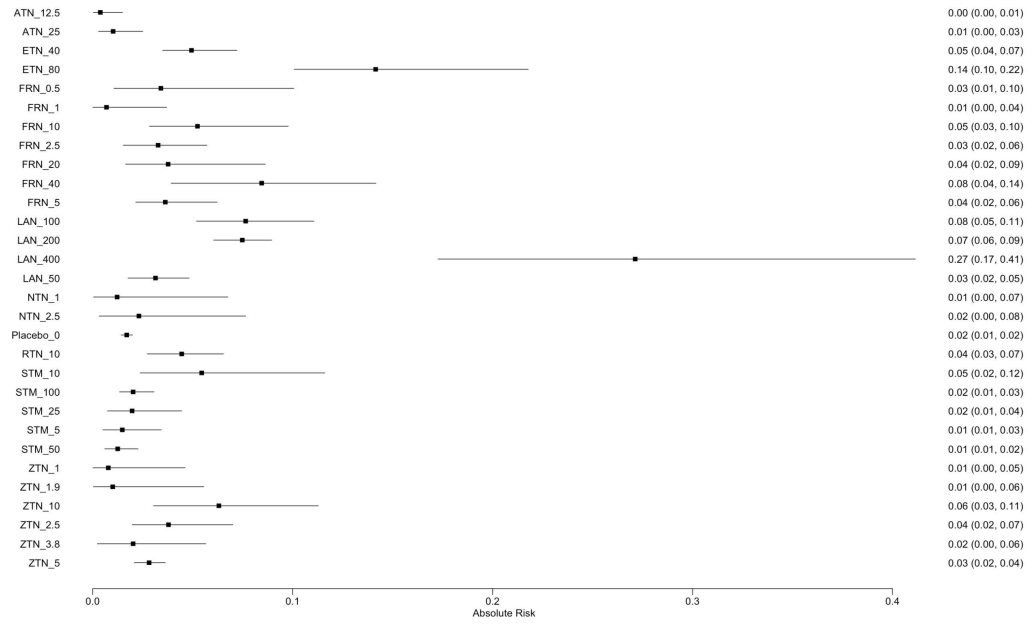

FIGURE 3: Forest plot of treatment-specific absolute risk and 95% credible intervals via arm-based model

TABLE 1: Summary of Relative risk (RR) and P-score for contrast-based model; RR and Absolute risk (AR) for arm-based model

	RR-contrast	P-score	RR-arm	AR-arm
Placebo	.	0.80	.	0.02
RTN 10	0.75	0.84	2.60	0.04
ATN 12.5	0.71	0.80	0.22	0.00
FRN 1	0.84	0.75	0.39	0.01
ETN 40	1.28	0.71	2.90	0.05
ZTN 1.9	0.95	0.70	0.59	0.01
NTN 1	0.96	0.70	0.73	0.01
ZTN 1	1.04	0.68	0.45	0.01
LAN 50	1.49	0.66	1.83	0.03
ATN 25	1.38	0.65	0.61	0.01
STM 50	1.95	0.57	0.72	0.01
STM 5	1.92	0.56	0.86	0.01
NTN 2.5	1.92	0.55	1.37	0.02
ETN 80	2.08	0.55	8.39	0.14
ZTN 5	2.15	0.54	1.66	0.03
ZTN 3.8	2.00	0.53	1.18	0.02
STM 25	2.57	0.47	1.15	0.02
FRN 5	2.96	0.44	2.11	0.04
FRN 0.5	3.13	0.42	2.04	0.03
FRN 2.5	3.12	0.42	1.87	0.03
FRN 20	3.52	0.38	2.22	0.04
STM 100	3.37	0.38	1.17	0.02
STM 10	3.85	0.37	3.24	0.05
ZTN 2.5	3.83	0.34	2.21	0.04
LAN 100	3.94	0.33	4.50	0.08
LAN 200	4.54	0.27	4.38	0.07
FRN 10	5.58	0.23	3.06	0.05
FRN 40	7.33	0.16	5.00	0.08
LAN 400	7.47	0.15	15.61	0.27
ZTN 10	12.30	0.08	3.73	0.06

Figure 4 is the 95% CI plot of RR comparing the placebo and other treatments. Besides ENT with a dose of 80mg and LAN with a dose of 400mg, twelve more CIs do not intersect with the vertical line at RR=1. Fourteen treatment effects are significantly different from placebo, and eight of them were also identified from the above contrast-based model. Hence, we can see those two models give us relatively similar results, but the different magnitude of RR. Hence, further investigations are required when deciding between those two approaches.

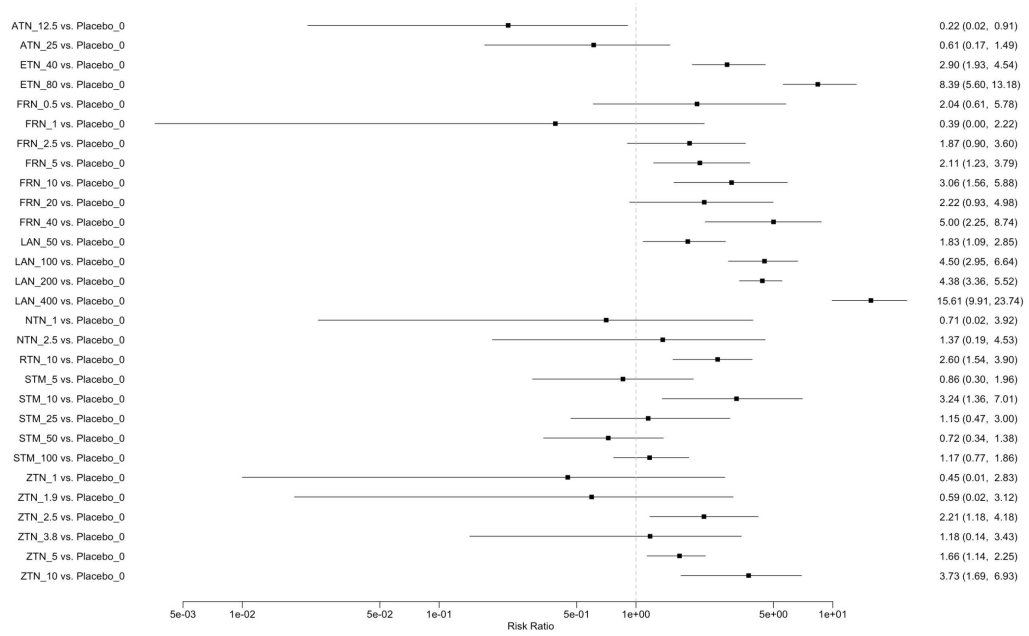

FIGURE 4: Forest plot of treatment-specific relative risk versus placebo and 95% credible intervals via arm-based model

From the output of the treatment rank plot (figure 7), treatment LAN with a dose of 400mg has the lightest vertical bar overall, which means it is the worst treatment and has the highest probability of having paresthesia (median absolute risk 33.5%). This finding is consistent with what we found before (LAN with a dose of 400mg: the second-lowest P-score 0.149).

In conclusion, based on both contrast-based and arm-based NMA, we can conclude that the below treatments have a higher risk of paresthesia than placebo: LAN with dose 100mg, 200mg, 400mg; FRN with dose 10mg, 40mg; ZTN with a dose of 2.5mg, 5mg, 10mg. As for absolute risk, I believe there are two treatments that need additional attention: LAN with a dose of 400mg and ETN with a dose of 80mg.

4.4 Dose response relationship

There are two trials (including 11 doses) using agent FRN. Hence, we can fit a linear dose-response model to evaluate the effect of the dose of FRN on the risk of paresthesia.

In the scatter plot (see figure 8 in appendix B), the horizontal axis is the dose of FRN, and the vertical axis is the log risk ratio. Besides, the size of the circle is the inverse number of the standard error. Thus, a larger circle indicates a more accurate study. From the plot, we can see an increasing pattern in general: log RR increases when the dose of FRN increases.

Linear model

The estimated regression coefficient is 0.024 which is statistically significant (p-value=0.03) at level 0.05. Cochran Q-test shows homogeneity between different doses (Q=0.15, df=1, p-value=0.69). After the exponential transformation, the pooled risk of paresthesia increases by 12.98% (exp(0.122) = 1.298) when five more mg dose of agonist - FRN is taken (95%CI [1.042, 1.225]) (see figure 9 in appendix B for more details).

Figure 5 shows the predicted relative risk of paresthesia corresponding to the dose of FRN, and dotted lines indicate the 95% upper and lower confidence interval bounds. The linear model's regression coefficient increases along with the dose, and the solid line seem linear with a constant slope.

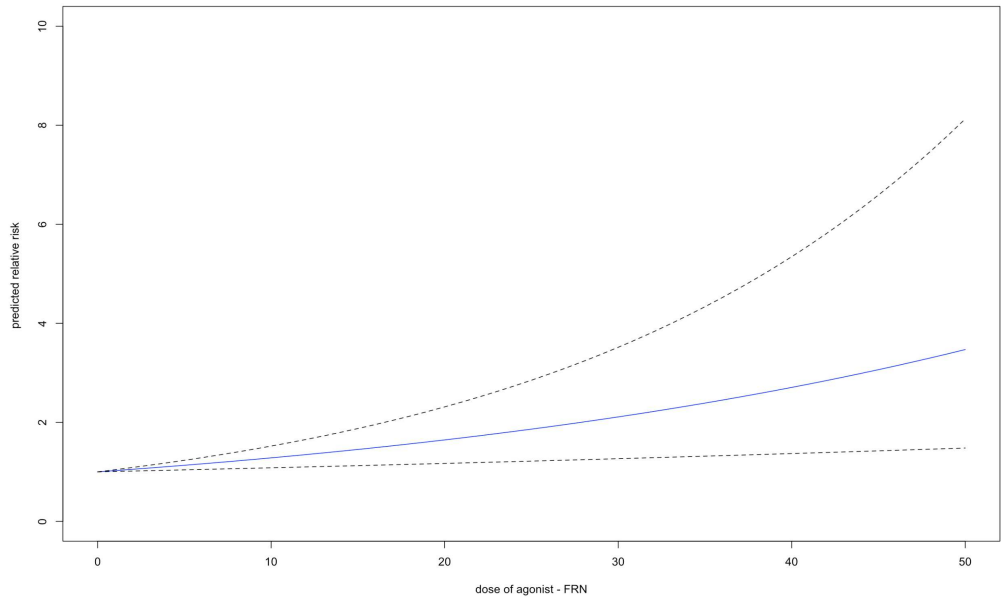

FIGURE 5: Predicted relative risks against dose for agent FRN via a linear dose-response meta-analysis model

5 Discussion

This analysis compared 30 treatments of triptans regarding the risk of paresthesia. Both contrast-based and arm-based Network meta-analysis models were constructed to estimate relative and absolute treatment effects, respectively. Besides, for triptan FRN, a dose-response meta-analysis linear model was fitted to quantify the effect of dose on the risk.

Hugo et al. proposed a method to perform model-based network meta-analysis while considering the dose-response relationship [10]. Nevertheless, I was unable to use the package provided by Hugo. If possible, I would like to try this model and compare the results with the above results.

Based on the above results, we can see that paresthesia risks for eight treatments are significantly higher than for placebo. I believe scientists need to conduct more experiments with the two treatments - LAN with a dose of 400mg and ETN with a dose of 80mg - to further thoroughly investigate the adverse drug effects (especially regarding paresthesia).

The estimated relative treatment effects for the contrast-based and arm-based models are similar but have relatively different magnitudes. However, it is hard to conclude which model is more reliable since the contrast-based models' overall extent of heterogeneity exists and the arm-based models' prior distributions were arbitrarily assigned. Hence, further researchers can provide a practical guideline that discusses under what conditions one model is more appropriate.

Lastly, as we can see from figure 5, the upper CI bound slope seems to increase along with the dose. Hence, a quadratic model might be more suitable than a linear model. The problem with fitting this quadratic model is that the number of arms of one trial is too small to estimate coefficients in a non-linear model. However, I fitted a quadratic and restricted cubic spline model with only one trial (8 doses), and the linearity test shows the slope of the regression lines for each dose level are similar. Thus, the linear model we obtained might be more appropriate than we expected.

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Appendix A

Assume relative risk vector $\hat{\theta} = X\theta + \epsilon$, $\epsilon \sim N(0, \Sigma)$.

Graph-theoretical methods to solve problem regarding X is not full-rank for weighted least square: 1) Laplacian matrix $L = X^T W X$, where $W = \{diag(\frac{1}{s_i^2})\}$ and s_i^2 are standard errors. 2) Moore-Penrose pseudoinverse $L^+ = (L - J/n)^{-1} + \frac{J}{n}$, J is matrix with elements are all 1.

The network estimates $\tilde{\theta}$ are linear combinations of the observed estimate $\hat{\theta}$: $\tilde{\theta} = XL^+X^TW\hat{\theta} = H\hat{\theta}$.

Q statistic measures the extent of heterogeneity within the network: $Q = (\hat{\theta} - \tilde{\theta})^T W(\hat{\theta} - \tilde{\theta})$.

Appendix B

studyID	AuthorYear	N	r	dose	agent
1	Dowson et al 2002	184	1	12.5	ATN
1	Dowson et al 2002	99	1	0	PLA
1	Dowson et al 2002	191	2	25	ATN
2	Linder et al 2008	181	1	12.5	ATN
2	Linder et al 2008	170	1	0	PLA
2	Linder et al 2008	186	2	25	ATN
3	Goadsby et al 2000	129	7	10	STM
3	Goadsby et al 2000	142	2	0	PLA
4	Landy et al 2018	111	3	100	STM
4	Landy et al 2018	119	1	0	PLA
5	Marcus et al 2014	100	2	100	STM
5	Marcus et al 2014	209	2	0	PLA

FIGURE 6: A plot of truncated database

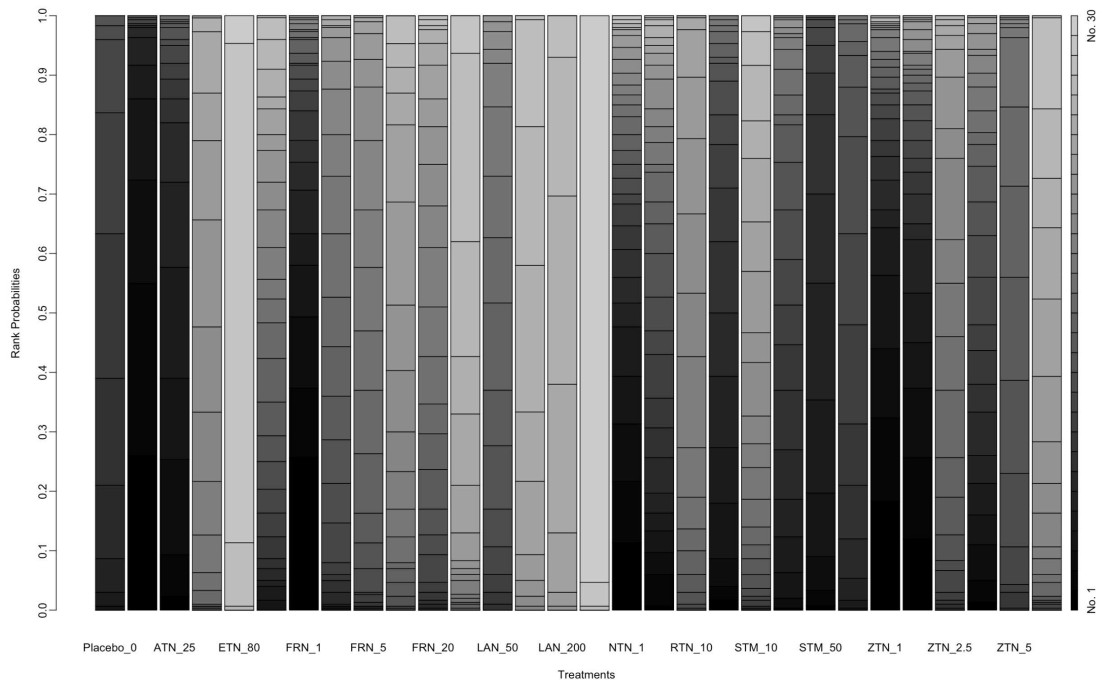

FIGURE 7: Plot for treatment rank probabilities - arm-based model

In the plot, each vertical bar represents probabilities that one treatment has different possible ranks for each Markov Chain Monte Carlo run. A lighter color indicates a larger rank and a higher risk.

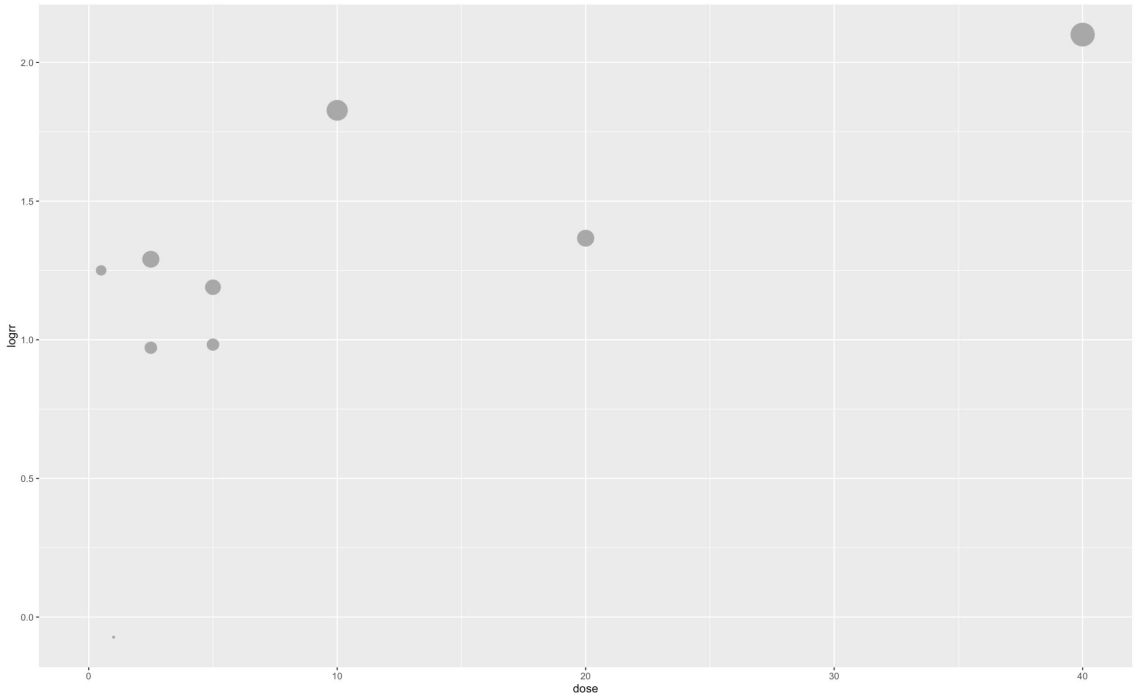

FIGURE 8: Scatter plot of log relative risks against doses for agent FRN

```
Call:  dosresmeta(formula = logrr ~ dose, id = studyID, type = type,
    cases = r, n = N, data = data2, se = se)

Two-stage random-effects meta-analysis
Estimation method: REML
Covariance approximation: Greenland & Longnecker

Chi2 model: X2 = 8.2067 (df = 1), p-value = 0.0042

Fixed-effects coefficients
             Estimate  Std. Error       z  Pr(>|z|)  95%ci.lb  95%ci.ub
(Intercept)    0.0249      0.0087  2.8647    0.0042    0.0079    0.0419  **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Between-study random-effects (co)variance components
  Std. Dev
    0.0000

Univariate Cochran Q-test for residual heterogeneity:
Q = 0.1588 (df = 1), p-value = 0.6902
I-square statistic = 0.0%

2 studies, 2 values, 1 fixed and 1 random-effects parameters
 logLik      AIC      BIC
 0.4499   3.1001  -0.8999
```

FIGURE 9: Summary of results of linear dose-response meta-analysis for agent FRN

```
Q statistics to assess homogeneity / consistency

                    Q df p-value
Total           33.05 20  0.0333
Within designs  17.22 10  0.0696
Between designs 15.83 10  0.1045

Design-specific decomposition of within-designs Q statistic

                Design    Q df p-value
         PLA 0:LAN 200 0.53  1  0.4676
          PLA 0:RTN 10 3.61  1  0.0574
         PLA 0:STM 100 0.08  1  0.7763
           PLA 0:ZTN 5 4.84  1  0.0279
 PLA 0:ATN 12.5:ATN 25 0.12  2  0.9416
   PLA 0:ETN 40:ETN 80 4.78  2  0.0917
  PLA 0:STM 100:STM 50 3.27  2  0.1953

Between-designs Q statistic after detaching of single designs

                                          Detached design     Q df p-value
                                             PLA 0:ETN 80  6.59  9  0.6800
                                            PLA 0:LAN 200 11.61  9  0.2363
                                            PLA 0:STM 100 15.58  9  0.0762
                                            PLA 0:ZTN 2.5 15.73  9  0.0728
                                              PLA 0:ZTN 5 15.80  9  0.0713
                                    PLA 0:ETN 40:ETN 80  6.59  9  0.6800
 PLA 0:FRN 0.5:FRN 1:FRN 10:FRN 2.5:FRN 20:FRN 40:FRN 5 15.75  8  0.0461
                                    PLA 0:FRN 2.5:FRN 5 15.75  8  0.0461
                  PLA 0:LAN 100:LAN 200:LAN 400:LAN 50 12.39  7  0.0884
                           PLA 0:LAN 100:LAN 200:LAN 50 11.77  7  0.1082
                                  PLA 0:STM 100:STM 50 15.58  9  0.0762
                             PLA 0:ZTN 10:ZTN 2.5:ZTN 5 15.73  8  0.0465

Q statistic to assess consistency under the assumption of
a full design-by-treatment interaction random effects model

                   Q df p-value tau.within tau2.within
Between designs 8.69 10  0.5619     0.4995      0.2495
```

FIGURE 10: Summary of decomposition the Cochran's Q statistics for contrast-based model