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# Comparative Efficacy and Safety of Pharmacological Prophylactic Agents for Migraine in Children and Adolescents: A Systematic Review and Bayesian Network Meta-Analysis

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## Abstract

# Background

Migraine is a leading cause of recurrent disabling headache in children and adolescents, yet most prophylactic agents have failed to outperform placebo, and head-to-head trials are scarce. We conducted a network meta-analysis (NMA) comparing the efficacy and safety of pharmacological migraine prophylaxis in pediatric patients.

# Methods

We searched PubMed, Cochrane CENTRAL, Scopus, and Embase for RCTs of migraine prophylaxis in patients < 18 years. Outcomes were change in frequency, severity, and duration (SMD), ≥ 50% responder rate (OR), and adverse events (OR), analyzed via Bayesian random-effects NMA (gemtc/JAGS) with node-splitting for inconsistency, SUCRA for ranking, and CINeMA for certainty. Risk of bias was assessed with RoB 2.

# Results

52 trials ( 4567 participants, 37 agents) were included. For frequency, riboflavin 200 mg (SMD 1.95), topiramate plus vitamin D (SMD 1.40), and levetiracetam (SMD 0.94) ranked highest, while topiramate, propranolol, and amitriptyline did not separate from placebo. For severity, sodium valproate (SMD 2.04), pregabalin (SMD 1.75), and cinnarizine (SMD 0.87) were superior to placebo. Duration data were sparse and inconsistent. No agent showed a robust responder-rate advantage. Levetiracetam had higher adverse-event odds than placebo (OR 6.54). Risk of bias was high or of some concern in most trials, with moderate-to-high heterogeneity.

# Conclusions

No agent showed consistent superiority across outcomes; efficacy was outcome-specific rather than universal. Riboflavin, topiramate-vitamin D, and levetiracetam showed the most consistent frequency signal, but CINeMA found no comparison reached high or moderate certainty, most rated very low, reflecting sparse, indirect, high-risk-of-bias evidence. Findings are hypothesis-generating pending larger head-to-head trials.

# Registration:

[PROSPERO ID: **CRD420261454779**]

## 1. INTRODUCTION

Migraine affects a substantial proportion of children and adolescents, with pooled prevalence estimates of approximately 11% (95% CI 9–14%) among 8- to 18-year-olds, and overall primary headache prevalence in this age group approaching two-thirds when tension-type and other headache phenotypes are included [1]. Migraine in youth is associated with school absenteeism, reduced quality of life, and a substantial risk of persistence into adulthood, making effective prophylaxis a clinically important goal [2].

Despite this burden, the evidence base guiding pharmacological migraine prophylaxis in children remains markedly weaker than in adults. The 2019 American Academy of Neurology (AAN) and American Headache Society (AHS) practice guideline update concluded that the majority of randomized controlled trials evaluating preventive medications in pediatric migraine, including well-studied agents such as topiramate, amitriptyline, and divalproex, failed to demonstrate superiority over placebo, a finding driven substantially by unexpectedly high placebo response rates in pediatric headache trials and by the pragmatic, multi-arm CHAMP trial that halted early for futility [3]. This guideline was limited to a small number of Class I–III studies and pairwise comparisons, and could not simultaneously rank the large and growing number of agents now used off-label or studied in trials, including anticonvulsants, beta-blockers, calcium-channel blockers, nutraceuticals (riboflavin, coenzyme Q10, magnesium-adjacent

compounds), melatonin, antihistamines, and, more recently, calcitonin gene-related peptide (CGRP) monoclonal antibodies repurposed from adult migraine practice.

Because head-to-head trials directly comparing more than two or three of these agents are rare, conventional pairwise meta-analysis cannot produce a comprehensive comparative ranking. Network meta-analysis (NMA) addresses this limitation by combining direct and indirect evidence across a connected network of trials, under a set of transitivity and consistency assumptions, to estimate the relative effects of every included treatment against every other treatment and to generate a probabilistic ranking of agents for a given outcome [4, 5].

To our knowledge, no network meta-analysis has yet consolidated the full contemporary landscape of pharmacological prophylactic agents evaluated in randomized trials of pediatric migraine, across the primary efficacy domains most relevant to patients and clinicians (headache frequency and severity) alongside duration, treatment response, and safety. We therefore conducted a systematic review and Bayesian network meta-analysis to compare the efficacy and safety of pharmacological prophylactic agents for migraine in children and adolescents, following PRISMA-NMA reporting guidance [6], with the aim of providing a comparative ranking to inform clinical decision-making and to identify priority agents and evidence gaps for future trials.

## 2. METHODS

## 2.1 Protocol and reporting

This systematic review and network meta-analysis was conducted and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [7] and its extension for network meta-analyses (PRISMA-NMA) [6]. The review protocol was registered prospectively with PROSPERO (registration number: **CRD420261454779**) prior to data extraction.

## 2.2 Eligibility criteria

Studies were eligible if they met the following PICOS criteria: Population: Children and adolescents (< 18 years) with a clinical diagnosis of migraine (with or without aura), per International Classification of Headache Disorders criteria or equivalent study-defined criteria. Intervention: Any pharmacological agent (or fixed-dose combination) administered for migraine prophylaxis, at any dose or duration, including but not limited to anticonvulsants (topiramate, sodium valproate, divalproex, levetiracetam, pregabalin), beta-blockers (propranolol), calcium-channel blockers (flunarizine, nimodipine, cinnarizine), tricyclic antidepressants (amitriptyline), nutraceuticals/vitamins (riboflavin, coenzyme Q10, vitamin B-complex, pyridoxine, vitamin D, L-carnitine, omega-3 fatty acids, butterbur extract, 5-hydroxytryptophan), melatonin, antihistamines/serotonergic agents (trazodone, pizotifen), probiotics, and CGRP monoclonal antibodies (fremanezumab). Comparator: Placebo, no treatment, or an alternative active pharmacological agent within the network. Outcomes: At least one of the five outcomes defined in Section 2.5. Study design: Parallel-group or crossover randomized controlled trials (RCTs). Non-randomized studies, observational studies, case series, conference abstracts without extractable arm-level data, and studies restricted to adult (≥ 18 years) populations were excluded.

## 2.3 Information sources and search strategy

We searched PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Embase from database inception to 2026, with no language restriction. Search strategies combined controlled vocabulary and free-text terms for migraine, pediatric/child populations, prophylaxis/prevention, and a pre-specified list of pharmacological agents (**Supplementary Table S1**). The search yielded 537 records from PubMed, 197 from Cochrane CENTRAL, 251 from Scopus, and 532 from Embase (1,517 records before de-duplication). Reference lists of included studies and relevant systematic reviews were hand-searched for additional eligible trials.

## 2.4 Study selection and data extraction

Records were de-duplicated and screened independently by two reviewers at the title/abstract and full-text stages, with disagreements resolved by discussion or a third reviewer. Data were extracted independently in duplicate using a standardized, piloted extraction form, capturing study identifiers, design, population characteristics (age, sex distribution, follow-up duration), intervention and comparator arms (including dose, where fixed-dose regimens were used), and outcome data (means, standard deviations, and sample sizes for continuous outcomes; event counts and sample sizes for dichotomous outcomes). The full study

selection process is summarized in the PRISMA 2020 flow diagram (Fig. 1): of 1517 records identified, 1062 were screened after de-duplication, 140 full-text reports were assessed for eligibility, and 52 studies were included in the qualitative synthesis and quantitative network meta-analysis.

Fifty-two randomized trials were identified as eligible for inclusion based on the baseline characteristics and risk-of-bias extraction tables supplied for this analysis. Table 1. shows the baseline characteristics of included studies. Where trials reported dose-ranging arms (e.g., topiramate 15/25/50/100 mg, riboflavin 50/100/200 mg, melatonin 3/6 mg, divalproex 250 mg/500 mg/1 g, fremanezumab 120/225 mg), each dose was modeled as a distinct node in the treatment network. Where an agent was administered at a weight-adjusted rather than fixed dose, or where dose data were pooled across arms in the source trial, it was modeled as a single, undifferentiated node (e.g., “Topiramate”, “Propranolol”, “Melatonin”); these weight-adjusted/pooled nodes should not be interpreted as equivalent to, or interchangeable with, the fixed-dose nodes of the same agent.

Table 1

**Baseline Characteristics Table of Included Studies** *For studies with a placebo/control arm, that arm is listed under "Control." For head-to-head trials without a placebo arm, the second active arm is listed under "Control" for pairing purposes only. Where a study has more than one intervention arm, values are listed in the same order across cells and separated by "/" (e.g., Intervention "A / B" pairs with Age "x ± y / x ± y"). M-F % values use a hyphen between the male and female percentage (e.g., 60 – 40).*

| Study | Intervention | Control | Age, Intervention (Mean ± SD) | Age, Control (Mean ± SD) | Follow-up | M-F %, Intervention | M-F %, Control |
|---|---|---|---|---|---|---|---|
| Abdi2026 | Cinnarizine | Topiramate | 9.9 ± 2 | 10.1 ± 2.2 | 3 months | 62.5–37.5 | 60.4–39.6 |
| Amanat2019 | Cinnarizine / Sodium Valproate | Placebo | 10.4 ± 2.8 / 11.2 ± 2.9 | 11.2 ± 3.1 | 3 months | 56.6–43.4 / 62.3–37.7 | 51.9–48.1 |
| Amini2021 | L-carnitine | Propranolol | 9.6 ± 1.9 | 9.8 ± 2.4 | 3 months | 59 – 41 | 59 – 41 |
| Apostol2008 | Divalproex sodium ER | Placebo | 14.2 ± 1.7 / 14.1 ± 1.6 / 14.3 ± 1.7 | 14.2 ± 1.5 | 3 months | 36–64 / 46–54 / 53 – 47 | 48–52 |
| Ashrafi2005 | Sodium Valproate | Propranolol | 10 ± 2.3 | 9.7 ± 2.7 | 3 months | 63.2–36.8 | 69 – 31 |
| Ashrafi2014a | Cinnarizine | Placebo | 10.7 ± 2.4 | 8.9 ± 1.9 | 3 months | 53.3–46.7 | 34.5–65.5 |
| Ashrafi2014b | Cinnarizine | Topiramate | 9.3 ± 2.4 | 8.7 ± 3 | 3 months | 60 – 40 | 55 – 45 |
| Bali2015 | Pregabalin | Propranolol | 9.9 ± 2.4 | 9.8 ± 2.7 | 2 months | 74 – 26 | 69 – 31 |
| Battistella1990 | Nimodipine | Placebo | 12.2 ± 3.3 | 12.2 ± 3.3 | 3 months | 53.3–46.7 | |
| Battistella1993 | Trazodone | Placebo | 12.6 ± 3.8 | 12.6 ± 3.8 | 3 months | 55 – 45 | |
| Bazmamoun2024 | Probiotic | Placebo | 8.9 ± 3.1 | 7.9 ± 2.4 | 3 | 61.1 | 43.5 |
| Bidabadi2010 | Propranolol | Sodium Valproate | 9.8 ± 2.8 | 9.9 ± 2.6 | 6 months | 63 – 37 | 70 – 30 |
| Bruijn2010 | Riboflavin | Placebo | 9.91 ± 1.9 | 9.5 ± 1.6 | 10 months | 60 – 40 | 54 – 46 |
| Dalrymple2017 | topiramate / amitriptyline | placebo | 14.2 | 14.2 | ≈ 6 months | 32–68 | 32–68 |
| Fallah2013 | propanolol | topiramate | 10.68 ± 2.35 | 10.11 ± 2.24 | 3 | 54 – 46 | 42–58 |
| Fallah2017 | amitriptyline | melatonin | 10.11 ± 2.13 | 10.57 ± 2.44 | 3 | 52.5–47.5 | 45–55 |
| Fallah2019 | topiramate | topiramate + VitD | 10.67 ± 2.11 | 10.33 ± 2.45 | 2 | 42.9–57.1 | 48.3–51.7 |
| Fayyazi2016 | sodium valporate plus omega 3 | sodium valporate plus placebo | 10.5 ± 3.147 | 10.23 ± 2.74 | 2 | 41.7–58.3 | 46.2–53.8 |
| Fayyazi2022 | propanolol+melatonin | propanolol | 10.28 ± 3.34 | 10.28 ± 3.34 | 4 | 66.7–33.3 | 73.3–26.7 |
| Forsythe1984 | Propranolol | Placebo | | | 1 | 45.45 | 64.7 |

| Study | Intervention | Control | Age, Intervention (Mean ± SD) | Age, Control (Mean ± SD) | Follow-up | M-F %, Intervention | M-F %, Control |
|---|---|---|---|---|---|---|---|
| Gelfand2023 | melatonin | placebo | 15.2 ± 2.1 / 14.3 ± 2.4 | 15.4 ± 1.5 | 2 | 29–71 / 14–86 | 21–79 |
| Ghazavi2019 | Levetiracetam | Amitriptyline | 10.6 ± 2.6 | 9.6 ± 2.6 | 3 | 53.3–46.7 | 70 – 30 |
| Gibler2023 | topiramate / Amitriptyline | placebo | 14.7 ± 2.4 / 14.3 ± 2.3 | 14.6 ± 2 | 6 | 16–84 / 34–66 | 16–83 |
| Gillies1986 | Pizotifen (crossover) | Placebo (crossover) | 10.5 ± 5.69 | 10.5 ± 5.69 | 3 months | 69.2–30.8 | 69.2–30.8 |
| Hershey2026 | fremanezumab | placebo | 13.3 ± 2.7 | 13.4 ± 3 | 3 | 46–54 | 43–57 |
| Jafari2023 | Sodium Valproate | Pregabalin | 10.18 ± 2.56 | 11.25 ± 2.53 | 4 months | 64 – 36 | 51.6–48.4 |
| Katibeh2021 | Propranolol + Cinnarizine | Propranolol + Placebo | 10.17 ± 2.59 | 9.8 ± 2.68 | 2 months | 68.9–31.1 | 53.3–46.7 |
| Keerthana2023 | Propranolol | Placebo | 10 ± 1.48 | 9.5 ± 2.22 | 3 | 66.7–33.3 | 45.5–54.5 |
| KotbElmala2022 | Topiramate + Vitamin D3 | Topiramate + Placebo | 10.12 ± 2.03 | 10.18 ± 2.45 | 4 | 35.7–64.3 | 42.9–57.1 |
| Lakshmi2007 | Topiramate | Placebo | 10.95 ± 1.53 | 10.14 ± 1.35 | 4 | 85.7–14.3 | 52.4–47.6 |
| Lewis2009 | Topiramate | Placebo | 14.2 ± 1.6 / 14.2 ± 1.5 | 14.4 ± 1.7 | 4 | 29–71 / 51 – 49 | 36–64 |
| Ludvigsson1974 | Propranolol | Placebo | | | 3 | | |
| MacLennan2008 | Riboflavin | Placebo | 11.1 ± 2.1 | 11.5 ± 2.5 | 3 | 56 – 44 | 43–57 |
| Montazerlotfelahi2019 | Levetiracetam | Placebo | 10.4 ± 2.42 | 8.8 ± 2.7 | 3 | 44–56 | 62 – 38 |
| OelkersAx2008 | Butterbur root extract / Music therapy | Placebo | 10.6 ± 1.2 / 9.9 ± 1.4 | 10.6 ± 1.5 | 5 | 52.6–47.4 / 85 – 15 | 68.4–31.6 |
| Olfat2024 | Cinnarizine | Amitriptyline | 10.1 ± 2.9 | 11.09 ± 4.43 | 3 | 63.6–36.3 | 61.9–38.1 |
| Powers2017 | Amitriptyline / Topiramate | Placebo | 14.2 ± 2.4 / 14.2 ± 2.5 | 14.2 ± 2.2 | 6 | 33–67 / 30–70 | 32–68 |
| Puliappadamb2023 | Flunarizine + Alpha-Lipoic Acid (test/add-on) | Flunarizine (control) | 16.1 ± 2.7 | 15.3 ± 3.4 | 3 | 46.7–53.3 | 30–70 |
| Sadeghvand2023 | Vitamin B-complex | Placebo (control) | 11.09 ± 2.79 | 10.73 ± 2.53 | 6 | 53.33–46.67 | 55.56–44.44 |
| Santucci1986 | L-5Hydroxytryptophan | Placebo | | | 3 months | | |
| Sezer2013 | Amitriptyline | Topiramate | 15.4 ± 2.1 | 14.9 ± 2.4 | 4 months | 44.8–55.1 | 50–50 |
| Shahnawaz2019 | Melatonin | Amitriptyline | 9.78 ± 2.3 | 9.48 ± 2.7 | 3 months | 55.55–44.4 | 48.8–51.1 |
| Shariatmadari2026 | Pyridoxine | Propranolol | 9.9 ± 2.53 | 9.71 ± 2.41 | | 58.06–41.94 | 61.29–38.71 |

| Study | Intervention | Control | Age, Intervention (Mean ± SD) | Age, Control (Mean ± SD) | Follow-up | M-F %, Intervention | M-F %, Control |
|---|---|---|---|---|---|---|---|
| Slater2011 | Coenzyme Q10 | Placebo | 13.3 ± 3 | 14 ± 2.6 | 7.36 months | 33.33–66.67 | 37.04–62.96 |
| Sorge1985 | Flunarizine | Placebo | 10.58 ± 3.25 | 10.7 ± 3.29 | 3 months | 41.66–58.33 | 45.83–54.16 |
| Talebian2018 | High dose ribolavin / Low dose riboflavin | Placebo | 8.97 ± 2.21 / 8.47 ± 2.06 | 7.9 ± 2.19 | 3 months | 56.7–43.3 | 50–50 |
| Togha2012 | Cinnarizine | Propranolol | 9.8 ± 2.3 | 8.9 ± 2.7 | 3 months | 66.7–33.3 | 67.9–32.1 |
| Tonekaboni2013 | Topiramate | Propranolol | 8.5 ± 2.9 | 8.3 ± 2.8 | 4 months | 50–50 | 52.5–47.5 |
| Vaswani2024 | Flunarizine | Propranolol | 10.2 ± 2.21 | 9.6 ± 1.93 | 3 months | 45–55 | 45–55 |
| Winner2005 | Topiramate | Placebo | 11.3 ± 2.5 | 10.7 ± 2.6 | 4.2 months | 50.9–49.1 | 53.1–46.9 |
| Yaghini2022 | Amitriptyline | Coenzyme Q10 | 9.56 ± 2.76 | 8.58 ± 2.82 | 3 months | 69.44–30.55 | 58.33–41.66 |

## 2.5 Outcomes

Five outcomes were pre-specified, each analyzed as a separate network: Change in migraine frequency: the change in headache/migraine attack or day frequency from baseline to end of follow-up, expressed as a standardized mean difference (SMD, Hedges' g) versus placebo, with higher (positive) values indicating greater improvement (reduction in frequency). Change in migraine severity: the change in headache pain intensity (as measured by study-specific instruments, e.g., visual analogue scale, numeric rating scale, or comparable severity index), expressed as SMD, with higher values indicating greater improvement. Change in migraine duration: the change in the duration of individual migraine attacks, expressed as SMD, with higher values indicating greater improvement. Secondary/responder outcome: ≥50% reduction in headache frequency: the proportion of participants achieving a clinically meaningful (≥ 50%) reduction in headache frequency from baseline, a standard responder threshold in migraine prophylaxis trials, expressed as an odds ratio (OR) versus placebo, with OR < 1 favoring the active/comparator treatment. Overall adverse events: the proportion of participants experiencing at least one adverse event of any severity during the trial period, expressed as an OR versus placebo, with OR < 1 favoring the treatment (fewer adverse events). Because included trials used non-uniform instruments and scales to measure frequency, severity, and duration, all continuous outcomes were harmonized on the SMD (Hedges' g, small-sample corrected) scale rather than pooling raw mean differences, consistent with standard practice for outcome harmonization across heterogeneous scales in network meta-analysis of headache disorders.

## 2.6 Risk of bias assessment

Risk of bias in individual RCTs was assessed independently in duplicate using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [8], across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result, with each domain and an overall judgment classified as "low risk," "some concerns," or "high risk" **(Supplementary Figs. 1 and 2)**

## 2.7 Statistical analysis (network meta-analysis)

We conducted a Bayesian random-effects network meta-analysis separately for each of the five outcomes, using the gemtc R package (which automates generation of Markov chain Monte Carlo network meta-analysis models) interfaced with JAGS via rjags, with placebo as the reference treatment for all networks [9].

For continuous outcomes (frequency, severity, duration), arm-level means, standard deviations, and sample sizes were first converted to study-specific contrasts against each trial's own baseline (control/reference) arm using Hedges' g standardized mean

difference (metafor::escalc, measure = “SMD”), producing a contrast-based dataset appropriate for the gemtc random-effects consistency model with a normal likelihood and identity link. For the dichotomous outcomes (≥ 50% responder rate, overall adverse events), arm-level responder/event counts and sample sizes were modeled directly in an arm-based framework with a binomial likelihood and logit link.

All models used a random-effects (exchangeable) structure to account for between-study heterogeneity, four independent Markov chains, a half-normal prior on the between-study heterogeneity standard deviation (mean 0, scale 0.5), and a vague normal prior on treatment effects (outcome-measure scale parameter = 2). Each model was run with 10,000 adaptation iterations, 50,000 sampling iterations, and a thinning interval of 10. Convergence was assessed using the Gelman–Rubin potential scale reduction statistic (target $\hat{R} < 1.05$) and effective sample size (target > 400) for all monitored parameters, supplemented by visual inspection of trace, density, and autocorrelation plots.

Heterogeneity was summarized by the posterior mean, median, and 95% credible interval (CrI) of the between-study standard deviation ($\tau$) on the relevant effect scale. Relative treatment effects for each outcome are reported as SMDs (continuous outcomes) or ORs (dichotomous outcomes) versus placebo, with 95% credible intervals, in forest plots, and as all pairwise comparisons in league tables.

Local inconsistency between direct and indirect evidence was evaluated for every closed loop in each network using the node-splitting method of Dias et al., [10] with a Bayesian p-value < 0.10 taken to indicate possible inconsistency and $p < 0.05$ taken as more substantial evidence against the consistency assumption, in line with conventional thresholds used in this method.

Treatment ranking was estimated for each outcome using rank probabilities and the surface under the cumulative ranking curve (SUCRA), where a SUCRA of 100% indicates a treatment that is certain to be ranked best and 0% indicates certainty of being ranked worst [11]. Cumulative ranking probability curves and ranking probability heatmaps are reported alongside SUCRA bar charts for each outcome.

The overall certainty of evidence for each network estimate was evaluated using the Confidence in Network Meta-Analysis (CINeMA) framework [12, 13], which considers six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence, yielding an overall rating of high, moderate, low, or very low confidence for each treatment-versus-placebo comparison.

All analyses were conducted in R (version [to be inserted]) using the gemtc, netmeta, metafor, coda, igraph, and ggplot2 packages. Statistical significance for pairwise comparisons was inferred from 95% credible intervals excluding the null value (SMD = 0 or OR = 1).

## 3. RESULTS

# 3.1 Study selection and characteristics

Fifty-two RCTs met inclusion criteria [14–62], enrolling participants across a wide age range (individual study mean ages approximately 7.9 to 16.1 years), with follow-up durations ranging from 1 month to approximately 10 months (most commonly 2–6 months). Trials were conducted predominantly as two- or three-arm parallel-group designs, with a minority of head-to-head (non-placebo-controlled) comparisons (e.g., cinnarizine vs. topiramate [Abdi 2026, Ashrafi 2014b], propranolol vs. sodium valproate [Bidabadi 2010], flunarizine plus alpha-lipoic acid vs. flunarizine alone [Puliappadamb 2023], topiramate plus vitamin D vs. topiramate alone [Fallah 2019, KotbElmala 2022]).

# 3.2 Risk of bias

Across the five RoB 2 domains, risk of bias was most frequently rated “low” for bias arising from the randomization process (approximately half of trials) and least favorable for bias in measurement of the outcome, where roughly a third of trials were rated low risk and approximately a quarter rated high risk, reflecting the difficulty of blinding outcome assessment (headache diaries, patient-reported severity) in many pediatric prophylaxis trials. Overall risk of bias was judged low in approximately one-fifth of trials, some concerns in approximately one-third, and high in approximately two-fifths, with a small proportion rated as having insufficient information to judge. Study-level judgments across all five domains are displayed in the traffic-light plot. The predominance of

“some concerns” and “high risk” ratings, concentrated in domains D2 (deviations from intended interventions) and D4 (outcome measurement), should be borne in mind when interpreting network estimates, particularly for smaller or single-study-informed nodes.

## 3.3 Network geometry

All five treatment networks were placebo-anchored and star-shaped, with the substantial majority of direct evidence deriving from two-arm, active-versus-placebo trials, and a comparatively small number of closed loops available to evaluate consistency (Table 1). The frequency and adverse-event networks were the largest and best connected (37 and 33 nodes, respectively), while the duration network was markedly smaller and sparser (15 nodes, 4 closed loops). Figure 2. shows the entire treatment network.

## 3.4 Change in migraine frequency

Twenty-three closed loops permitted node-splitting; six showed possible inconsistency ($p < 0.10$), clustered around the topiramate/amitriptyline/coenzyme Q10/placebo evidence loop (Amitriptyline:Placebo, Propranolol:Topiramate_100mg, Topiramate_100mg:Placebo, Topiramate:Placebo, Amitriptyline:CoenzymeQ10, CoenzymeQ10:Placebo). Elsewhere the network was locally consistent **(Supplementary Fig. 33)**.

Relative to placebo, riboflavin 200 mg (SMD 1.95, 95% CrI 1.06–2.85), topiramate plus vitamin D (SMD 1.40, 95% CrI 0.76–2.04), flunarizine plus lipoic acid (SMD 1.29, 95% CrI 0.22–2.37), and levetiracetam (SMD 0.94, 95% CrI 0.10–1.75) were the only agents whose credible intervals excluded the null in the direction of benefit. Conventional first-line prophylactic agents, namely topiramate (unspecified/weight-adjusted dosing; SMD 0.32, 95% CrI − 0.09 to 0.74), propranolol (SMD 0.27, 95% CrI − 0.19 to 0.73), and amitriptyline (SMD 0.37, 95% CrI − 0.05 to 0.79), did not separate from placebo. A single node, topiramate 25 mg, showed an implausibly large negative (harmful) effect (SMD − 5.95, 95% CrI − 7.44 to − 4.46) **(**Fig. 3a**)**, inconsistent with all other topiramate-dose nodes and with clinical plausibility; this estimate is very likely driven by a single small, outlying study arm and should not be interpreted as a genuine treatment effect.

SUCRA rankings placed riboflavin 200 mg (98.5%), topiramate plus vitamin D (94.2%), flunarizine plus lipoic acid (90.3%), and levetiracetam (83.4%) at the top of the hierarchy, with placebo ranked mid-to-low (32.4%) and topiramate 25 mg ranked last (0%, reflecting the outlier estimate above).

## 3.5 Change in migraine severity

Only nine closed loops were available; two showed borderline possible inconsistency (Propranolol:Placebo, Propranolol:Topiramate; both $p \approx 0.06–0.07$), otherwise the network was locally consistent (**Supplementary Fig. 34)**.

Three agents showed a statistically robust advantage over placebo: sodium valproate (SMD 2.04, 95% CrI 0.84–3.21), pregabalin (SMD 1.75, 95% CrI 0.57–2.92) (Fig. 3b**)**, and cinnarizine (SMD 0.87, 95% CrI 0.06–1.74). Several of the top-ranked agents for migraine frequency (riboflavin 200 mg, levetiracetam, topiramate plus vitamin D) did not reach statistical significance for severity, and sodium valproate, the top-ranked agent for severity (SUCRA 96.6%), ranked poorly for frequency (SUCRA 22.0%), a discordance discussed further in Section 4.

## 3.6 Change in migraine duration

Evidence for this outcome was markedly sparser (15 nodes) and displayed very high heterogeneity (τ mean 2.784, 95% CrI 1.699–4.249) ) (Fig. 3c**)**, approximately an order of magnitude greater than the frequency and severity networks. Of eight node-split comparisons, six showed statistically significant inconsistency ($p < 0.05$), including Propranolol:Placebo (direct SMD ≈ − 12 vs. indirect SMD ≈ − 1.5), Propranolol:Topiramate, Amitriptyline:Topiramate, Amitriptyline:Placebo, Topiramate:Placebo, and Propranolol:Topiramate_100mg. Only the topiramate/topiramate-plus-vitamin-D loops were locally consistent ) (**Supplementary Fig. 35)**. Given this pervasive inconsistency, network estimates for migraine duration are reported descriptively only and should not be used to rank treatments with confidence: propranolol was the only agent with a credible interval excluding the null, and in the unfavorable direction (SMD − 5.76, 95% CrI − 10.06 to − 1.69), a finding that conflicts with propranolol’s neutral profile in the frequency and severity networks and most plausibly reflects the underlying inconsistency and sparse-data instability of this network rather than a genuine adverse effect on attack duration.

## 3.7 ≥ 50% reduction in headache frequency

Nineteen closed loops were evaluable; three showed possible inconsistency ($p < 0.10$), most notably within the riboflavin dose-ladder (Riboflavin_100mg:Riboflavin_200mg and Riboflavin_100mg:Placebo, both $p < 0.05$), suggesting that riboflavin dose-response data may not be fully transitively poolable across trials, alongside a borderline Amitriptyline:Placebo loop ) (**Supplementary Fig. 36)**.

No agent retained a robust, interval-excluding advantage over placebo once extreme-uncertainty nodes were accounted for. Flunarizine plus lipoic acid showed the numerically largest effect (OR 36.79, 95% CrI 1.78–859.85) ) (Fig. 4a **)**and the highest SUCRA (94.0%), but its 95% credible interval spans nearly three orders of magnitude, indicating this estimate is driven by very sparse event data (most likely a single small trial) and should be interpreted with substantial caution rather than as a robust clinical finding. Riboflavin 200 mg (OR 5.54, 95% CrI 0.94–30.65; SUCRA 74.1%) and pregabalin (OR 6.93, 95% CrI 0.72–62.48; SUCRA 77.9%) showed directionally consistent, borderline signals.

# 3.8 Overall adverse events

Seventeen closed loops were evaluable, and no loop reached statistical significance for inconsistency at $p < 0.05$ (lowest $p \approx 0.11$–0.14 for several loops) ) (**Supplementary Fig. 37)**, indicating the adverse-event network was the most internally consistent of the five.

Levetiracetam was associated with significantly greater odds of experiencing an adverse event than placebo (OR 6.54, 95% CrI 1.19–41.31) ) (Fig. 4b**)**, consistent with its established tolerability profile in pediatric use, and ranked poorly for safety (SUCRA 17.9%, third-worst). L-carnitine showed a numerically large but statistically imprecise signal (OR 14.63, 95% CrI 0.80–542.93). No other agent differed significantly from placebo on this outcome. Agents combining a favorable efficacy signal (Section 3.4) with a comparatively favorable safety ranking included topiramate plus vitamin D (adverse-event SUCRA 63.4%) and riboflavin 200 mg (adverse-event SUCRA 59.6%), whereas levetiracetam's frequency benefit was accompanied by the least favorable safety ranking among the top efficacy performers.

Reported adverse events varied by agent and were not coded to a common taxonomy across trials, precluding a single pooled percentage breakdown by event type. Among the most consistently named events, topiramate was associated with upper respiratory tract infection, anorexia, weight decrease, paresthesia, dizziness, somnolence, and reduced concentration [43, 44, 58]; amitriptyline with fatigue, dry mouth, and daytime sleepiness [27, 30]; levetiracetam with irritability, daytime sedation, and mild tics [46]; flunarizine with drowsiness, gastrointestinal complaints, and fatigue, which led to discontinuation in a minority of patients [53, 57]; and cinnarizine with appetite reduction and sedation, generally at lower rates than comparator agents [14, 15, 55]. Injection-site erythema was the leading adverse event with fremanezumab (9.8% vs. 5.4% with placebo) [38]. Discontinuation due to adverse events was generally low (e.g., 6.5% vs. 4.0% for topiramate vs. placebo [58]), and several trials, including those of nimodipine, trazodone, and probiotic add-on therapy, reported no adverse events beyond mild, transient complaints, or none at all [22, 23, 24].

# 3.9 Certainty of evidence (CINeMA)

Confidence in the network estimates was evaluated across the six CINeMA domains (within-study bias, reporting bias, indirectness, imprecision, heterogeneity, incoherence) for each treatment-versus-placebo comparison (full domain-level ratings for 35 frequency comparisons, 25 severity comparisons, and the flagged/key comparisons from the duration, responder-rate, and adverse-event networks are reported in **Supplementary Table 2**). No comparison in any of the five networks reached high or moderate overall confidence. For migraine frequency, 31 of 35 comparisons (89%) and for migraine severity 20 of 25 comparisons (80%) were rated very low confidence, driven principally by three recurring problems: (i) roughly one-third of nodes per network have no direct placebo-controlled trial and are connected to placebo only through one or more active-comparator "chain" trials; (ii) point estimates for many nodes derive from only one or two small trials, several with high or unclear risk of bias; and (iii) credible intervals were wide relative to a minimally important effect threshold for the majority of comparisons. A small number of comparisons were rated low rather than very low confidence: fremanezumab 120 mg and 225 mg, riboflavin 50 mg, 5-hydroxytryptophan (frequency and/or severity), and amitriptyline (severity only). These reflected single low-risk-of-bias source trials with no detected local inconsistency, though still limited by imprecision and network sparsity. All assessed comparisons in the duration, ≥ 50% responder-rate, and adverse-event networks were rated very low confidence, for the duration network because of pervasive local inconsistency (Section 3.6), and for the two flagged outlier nodes (topiramate 25 mg for frequency; flunarizine plus lipoic acid for responder rate) because of extreme, implausible effect sizes with correspondingly major indirectness/imprecision concerns.

## DISCUSSION

In this network meta-analysis evaluated data from 4567 patients across 52 randomized trials spanning up to 37 pharmacological agents and regimens, no single prophylactic agent demonstrated consistent superiority across all efficacy domains. Riboflavin 200 mg, topiramate combined with vitamin D, and levetiracetam showed the most consistent signal for reducing migraine frequency, while sodium valproate, pregabalin, and cinnarizine were the only agents to show a statistically robust benefit for migraine severity, a largely non-overlapping set of "top" agents depending on which outcome is prioritized. Consistent with the 2019 AAN/AHS guideline finding that most pediatric migraine prophylaxis trials fail to separate from placebo [3], several of the most widely used first-line agents in clinical practice, topiramate, propranolol, and amitriptyline, did not show a statistically robust advantage over placebo for frequency reduction in this network, reinforcing that established clinical use of these agents in children rests more on adult extrapolation and open-label experience than on a robust pediatric randomized-evidence base.

The discordance between the frequency and severity hierarchies, most strikingly sodium valproate's ranking best for severity (SUCRA 96.6%) but poorly for frequency (SUCRA 22.0%), may reflect genuine differences in drug mechanism (e.g., an agent that blunts attack intensity without altering attack frequency), differences in which outcome individual trials were adequately powered to detect, or simply the instability inherent in sparse, largely single-study-informed network nodes. This discordance argues against selecting a single "best" prophylactic agent from ranking metrics alone, and in favor of matching agent selection to the outcome domain of greatest concern for an individual patient (e.g., attack frequency versus attack severity versus school/functional impact).

Two findings recurred as extreme statistical outliers across outcomes and warrant particular caution rather than being presented as headline results: topiramate 25 mg's implausible frequency effect (SMD − 5.95), which is inconsistent with the effects observed at every other topiramate dose and most likely reflects a single small, atypical study arm; and flunarizine plus lipoic acid's extreme responder-rate odds ratio (OR 36.79, 95% CrI spanning 1.78–859.85), whose enormous imprecision signals near-zero-event, single-trial-driven instability rather than a robust treatment effect. Both nodes dominate their respective SUCRA rankings despite this fragility. We recommend that any clinical or policy conclusions drawn from this NMA explicitly exclude, or heavily caveat, these two findings, and that a leave-one-study-out sensitivity analysis be performed and reported for both prior to journal submission.

The adverse-event network was the most internally consistent of the five, lending relatively greater confidence to its findings. Levetiracetam's significantly elevated odds of adverse events, despite its favorable frequency-reduction ranking, illustrates a benefit–risk trade-off that should be weighed explicitly in practice and reflects known behavioral and neuropsychiatric tolerability concerns with levetiracetam in pediatric populations. By contrast, riboflavin 200 mg and topiramate plus vitamin D combined a favorable efficacy signal with a comparatively reassuring safety ranking, making them plausible candidates for prioritization in future confirmatory trials.

Our findings are broadly consistent with, and extend, the conclusions of the 2019 AAN/AHS pediatric migraine prevention guideline [3], which, based on a much smaller set of Class I–III studies analyzed pairwise, likewise found limited evidence of superiority over placebo for the most commonly prescribed agents (topiramate, amitriptyline) and highlighted high placebo response as a major contributor. Our network extends this picture by incorporating a substantially larger and more contemporary evidence base (including nutraceuticals, melatonin, and monoclonal antibody data not available at the time of the 2019 guideline) and by providing, for the first time to our knowledge, a simultaneous probabilistic ranking across this full agent landscape.

This review has several strengths: a comprehensive, multi-database search; simultaneous synthesis of five clinically relevant outcomes; use of a Bayesian random-effects framework with formal evaluation of local inconsistency via node-splitting for every evaluable comparison; and reporting of both point-estimate rankings (SUCRA) and full uncertainty (credible intervals, rank probability distributions) rather than ranking alone.

Several important limitations must be acknowledged. First, all five networks were placebo-anchored and star-shaped, with direct head-to-head trials between active agents comprising a minority of the evidence base; this limits the ability to fully evaluate the transitivity assumption underlying indirect comparisons, and findings for agents connected to the network only through a single small trial should be regarded as preliminary. Second, heterogeneity was moderate for frequency, severity, and adverse events, but very high for duration, and the duration network showed pervasive local inconsistency (6 of 8 loops), such that duration findings are reported descriptively only and should not inform clinical ranking. Third, several headline findings (topiramate 25 mg for frequency; flunarizine plus lipoic acid for responder rate) are driven by extreme, single-study-level statistical outliers and require independent

replication before being considered robust. Fourth, overall risk of bias was low in only a minority of included trials, with the largest concerns in blinding of outcome assessment and deviations from intended intervention, both plausible contributors to the unusually large effect sizes observed in select small trials. Fifth, dosing was heterogeneous: several nodes represent fixed doses while others (e.g., unlabeled "Topiramate," "Propranolol," "Melatonin") represent pooled or weight-adjusted dosing across constituent trials, and these should not be treated as interchangeable with same-named fixed-dose nodes. Sixth, formal certainty-of-evidence assessment using the CINeMA framework **(Supplementary table 2)** found that no treatment-versus-placebo comparison in any of the five outcome networks reached high or moderate confidence; the large majority were rated very low, and even the small number of "low"-confidence comparisons were limited by network sparsity and imprecision. This finding should temper the interpretive weight placed on every SUCRA ranking reported in this manuscript: rankings describe relative ordering of point estimates under the model's assumptions, not certainty, and here that certainty is uniformly low. We recommend this manuscript's abstract and conclusions explicitly foreground the CINeMA findings rather than reporting SUCRA rankings in isolation, to avoid over-stating what this evidence base can support.

For clinicians, these findings suggest that no currently available agent can be recommended as a uniformly superior first-line prophylactic choice for pediatric migraine on frequency, severity, duration, and safety simultaneously; agent selection may reasonably be individualized to the outcome domain of greatest clinical concern, with riboflavin (200 mg), topiramate–vitamin D co-therapy, and levetiracetam meriting consideration for frequency-predominant presentations (balancing levetiracetam's tolerability signal), and sodium valproate, pregabalin, or cinnarizine for severity-predominant presentations, pending confirmatory head-to-head evidence. For researchers, this analysis highlights a persistent need for adequately powered, low-risk-of-bias, head-to-head trials directly comparing the top-ranked agents identified here (rather than further single-agent-versus-placebo trials), harmonized outcome reporting (standardized frequency, severity, and duration instruments) to reduce reliance on SMD harmonization, and dedicated evaluation of newer agents such as CGRP monoclonal antibodies in pediatric populations, for which the current evidence base remains minimal.

## CONCLUSION

In this network meta-analysis of pharmacological prophylaxis for pediatric migraine, riboflavin 200 mg, topiramate–vitamin D combination therapy, and levetiracetam showed the most consistent efficacy signal for reducing migraine frequency, while sodium valproate, pregabalin, and cinnarizine were most effective for reducing severity; commonly used first-line agents (topiramate, propranolol, amitriptyline) did not clearly outperform placebo. Given sparse, placebo-anchored, and heterogeneous evidence, several outlier findings requiring cautious interpretation, and predominantly low-to-moderate trial quality, these results should be viewed as hypothesis-generating and used to prioritize future confirmatory head-to-head trials rather than to mandate a single preferred agent in clinical practice.

## Declarations

**Ethics Approval and Consent to Participate:**

Not applicable

**Consent for Publication:**

Not applicable

**Competing Interest:**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.


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# Author Contribution

HWS and TK contributed the most and equally in conceptualization, literature review, project administration, analysis and manuscript writing. AB supervised and reviewed the study and contributed in manuscript writing and analysis. HAZ, RB and RA participated in data extraction and validation. MO and SRK participated in quality assessment and literature review. MSK and FuN screened the studies, MFI participated in reviewing and project administration.

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None

# Data Availability

Attached as electronic supplementary table

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## Figures

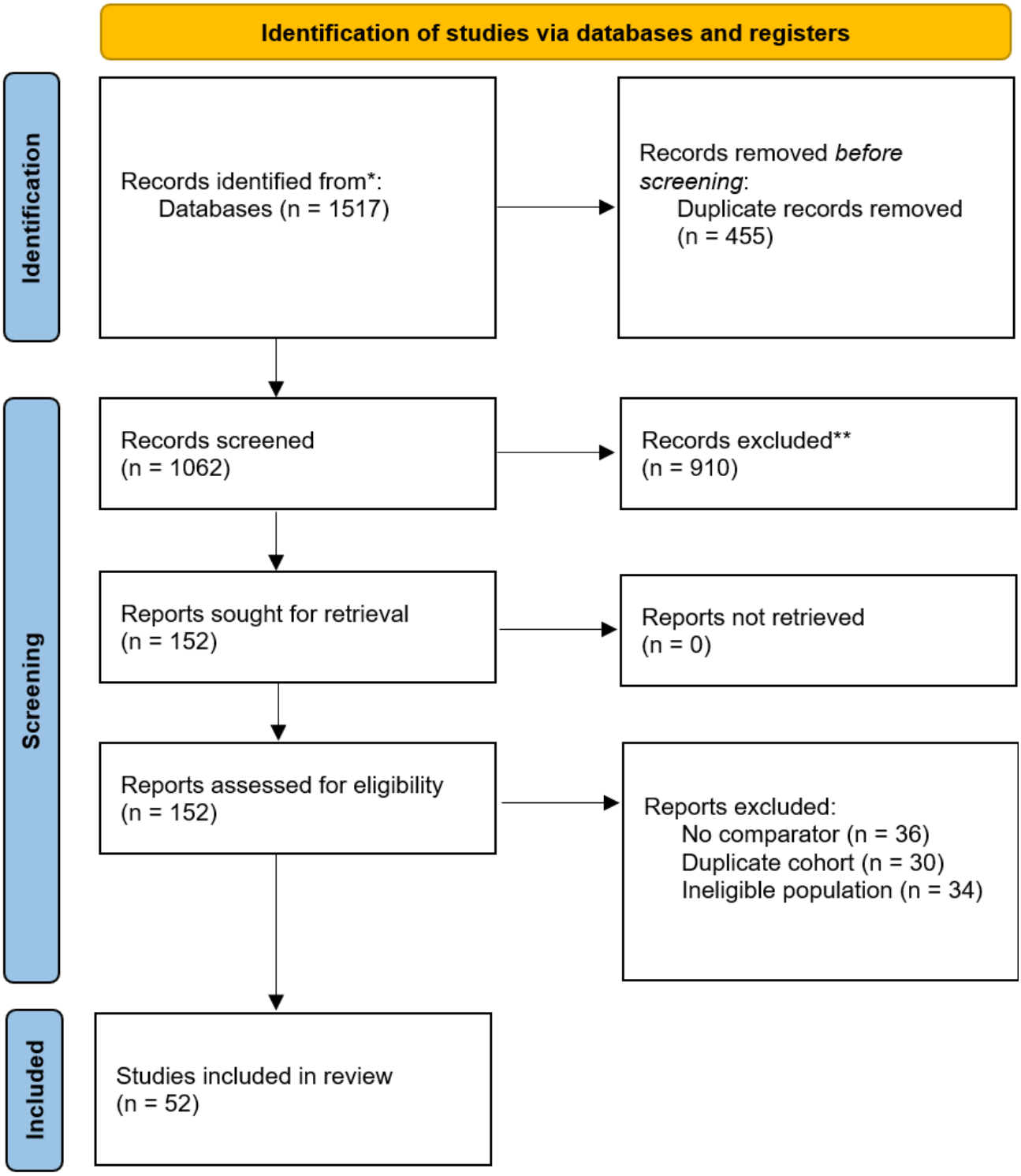



**Figure 1**

**Figure 1. Prisma Flow Chart**

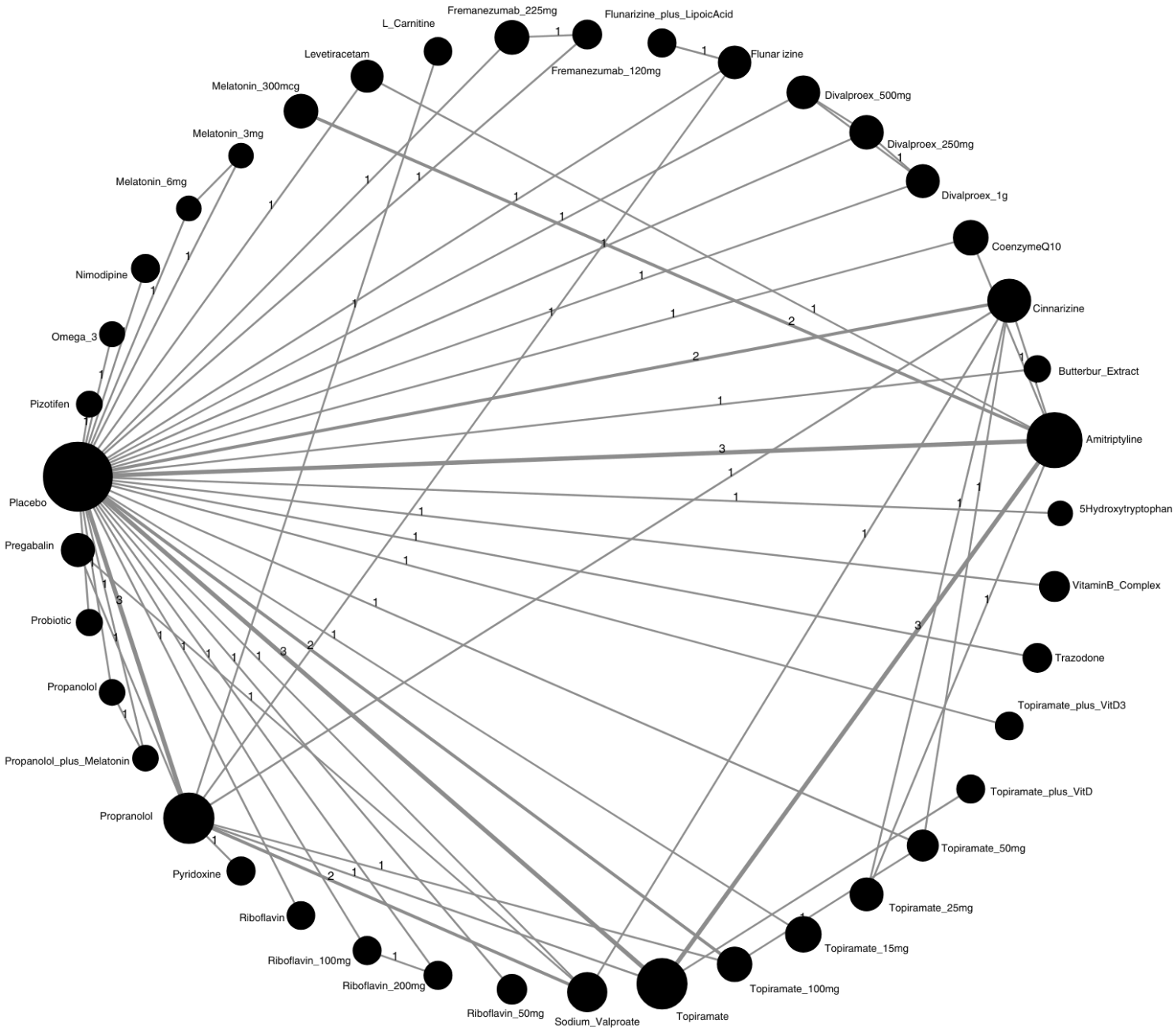
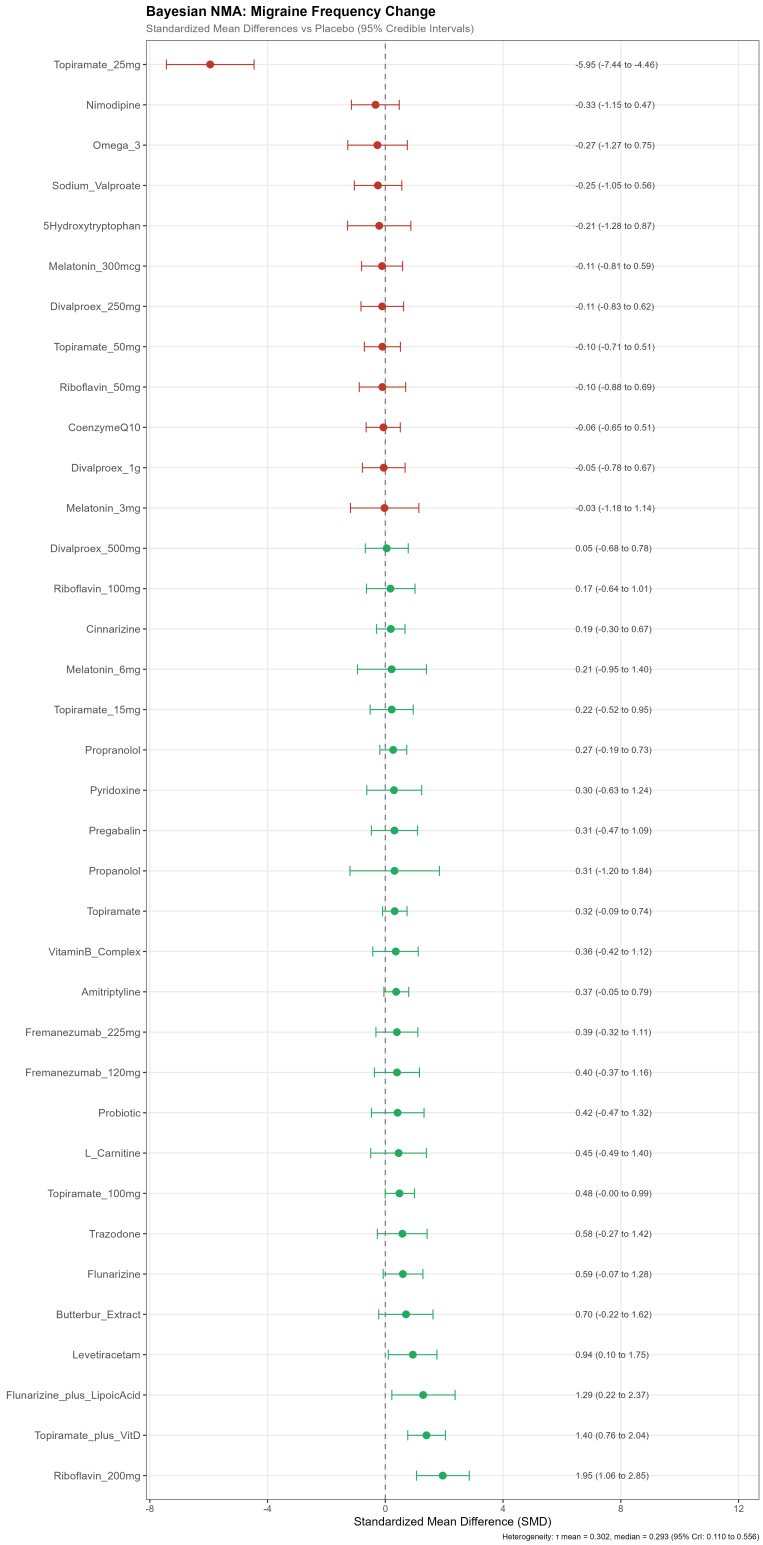



**Figure 2**

**Figure 2 Treatment Network**




## Figure 3

## Figure 3a. Forest Plot for Change in Migraine Frequency

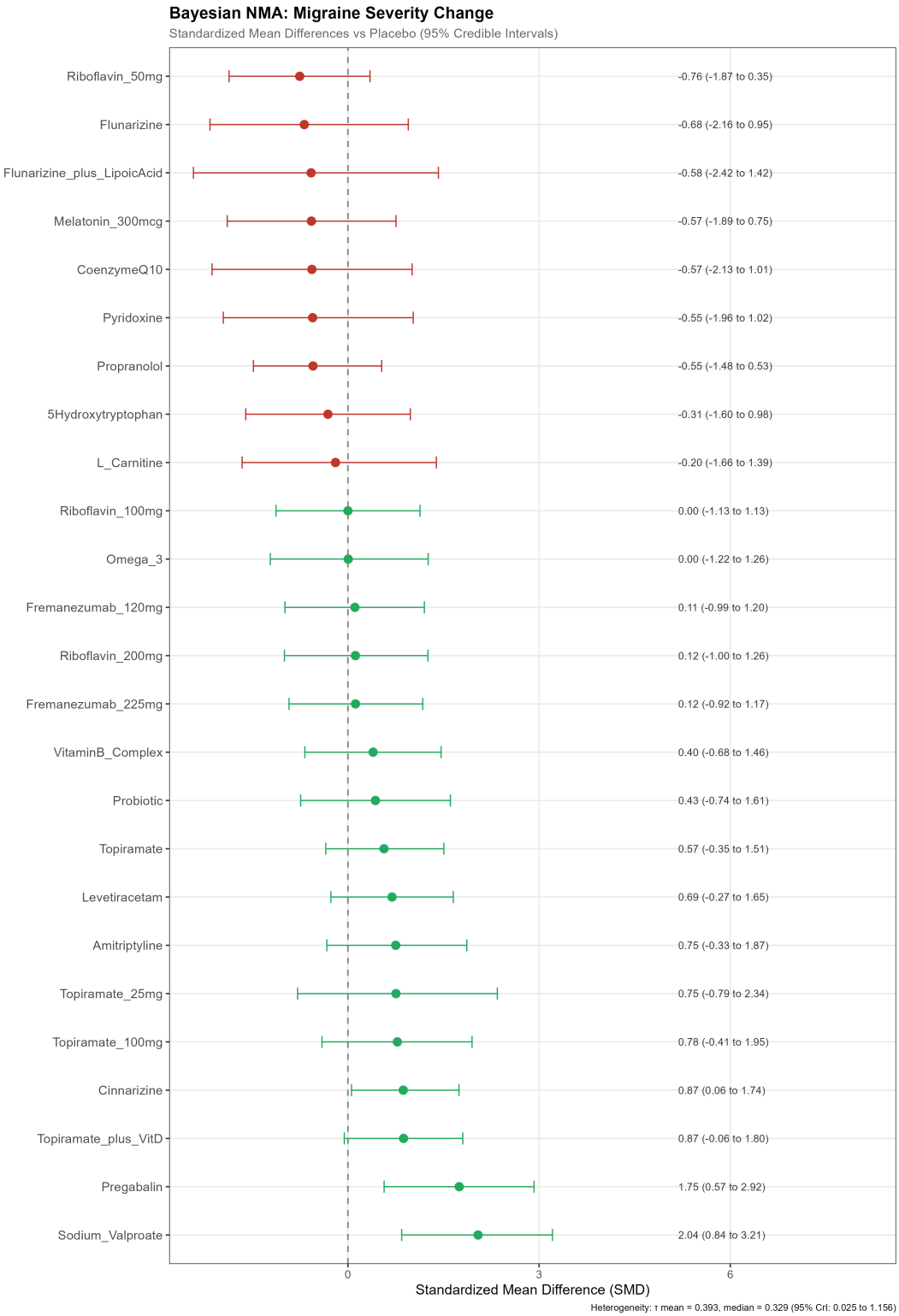



**Figure 4**

**Figure 3b. Forest Plot for Change in Migraine Severity**

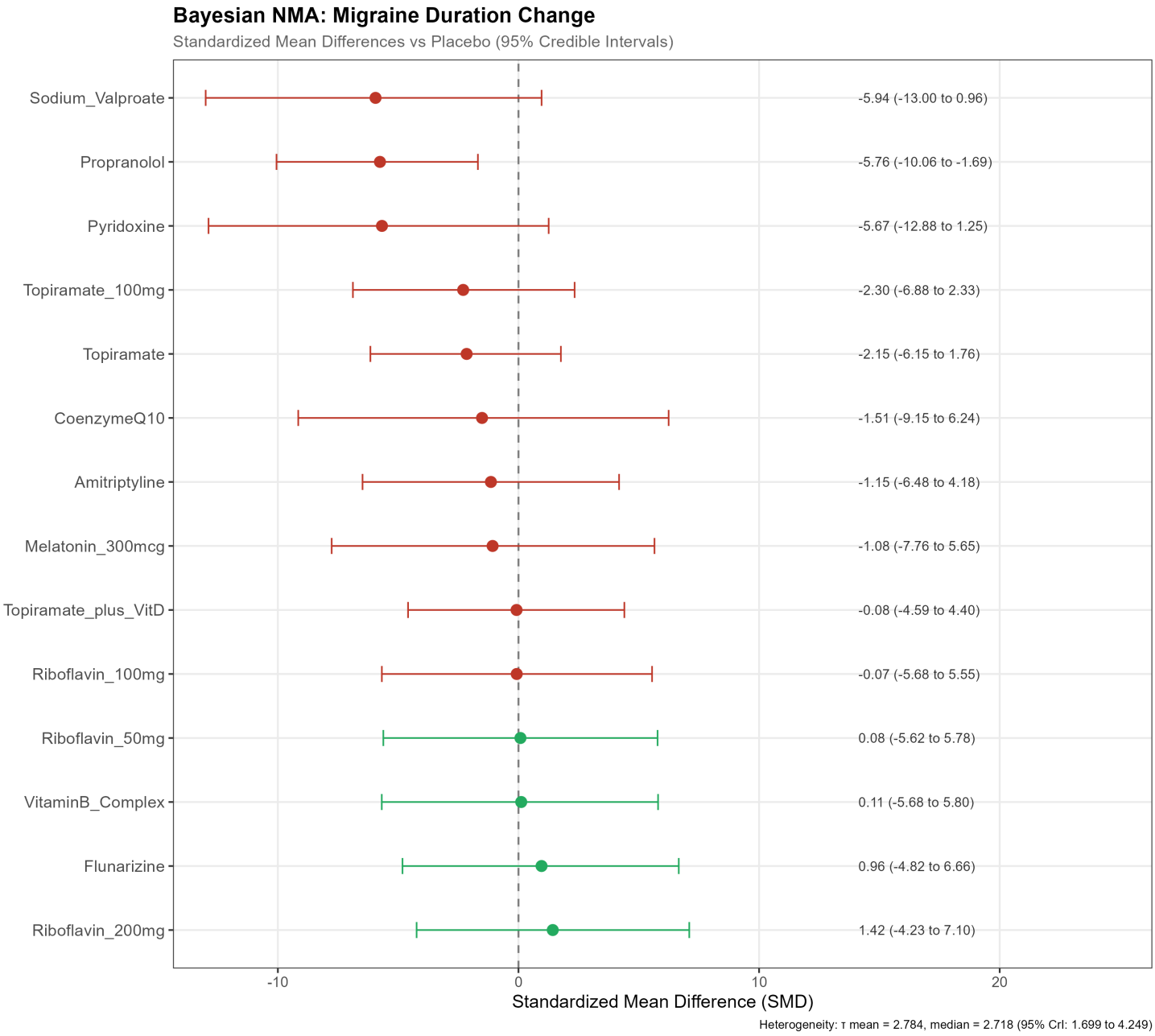



**Figure 5**

**Figure 3c. Forest Plot for Change in Migraine Duration**

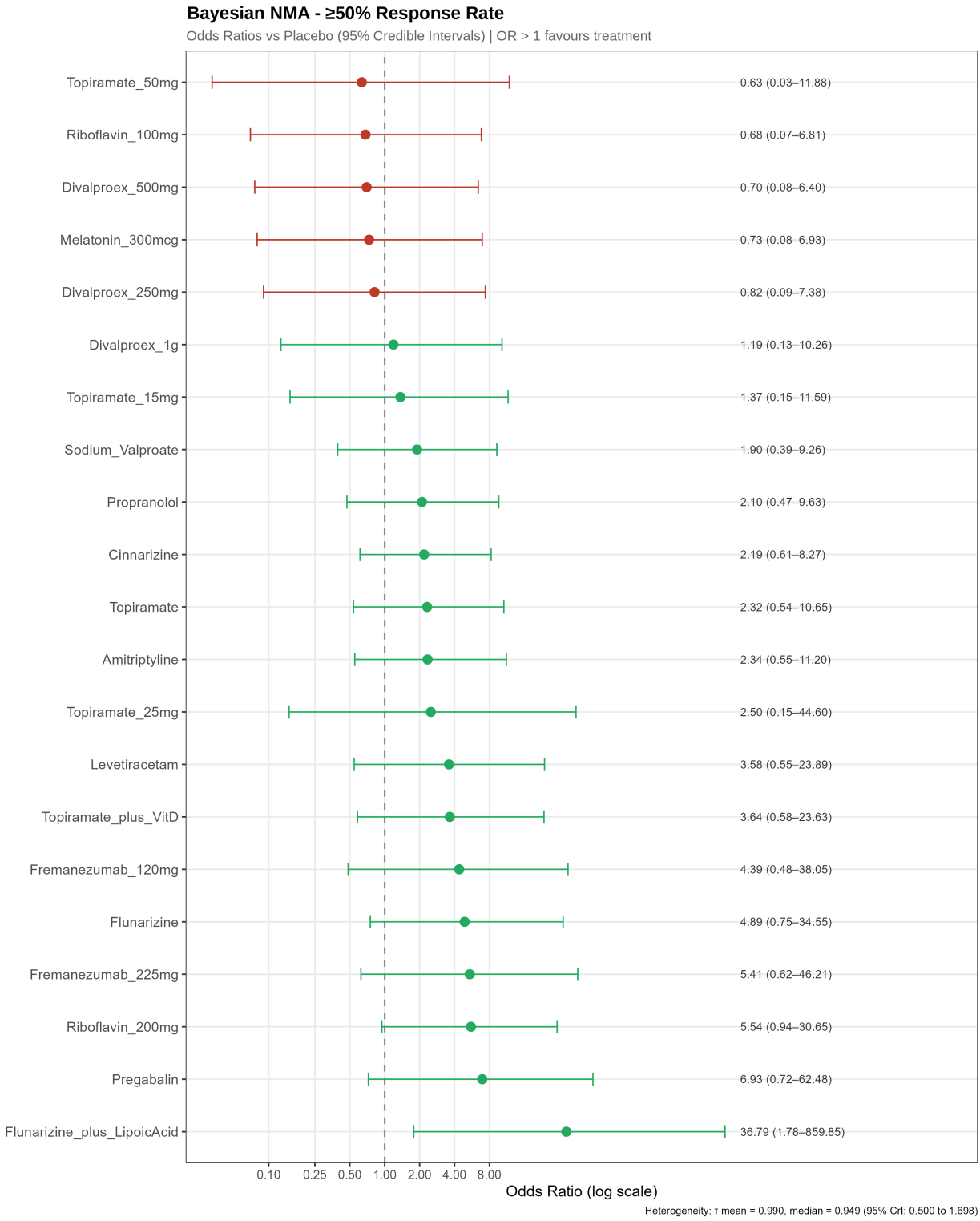



**Figure 6**

**Figure 4a. Forest Plot for ≥50% Reduction in Headache Frequency**

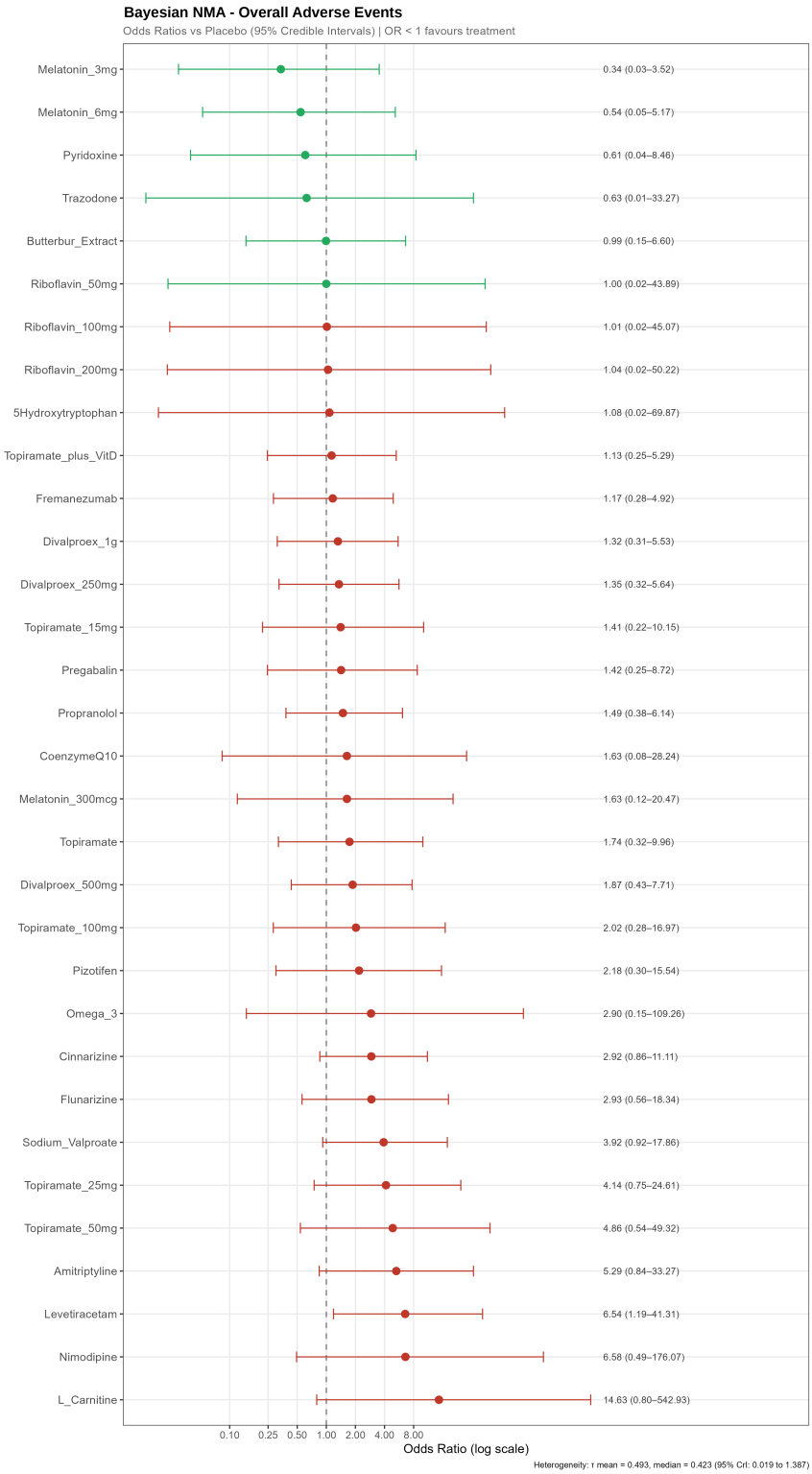



**Figure 7**

**Figure 4b. Forest Plot for Overall Adverse Events**

# Supplementary Files

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- Supplementaryfile.docx