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Considerations for understanding systematic reviews and network meta-analyses in neurological applications: a review and critique in chronic migraine

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Network meta-analysis (NMA) is an evidence synthesis approach that combines direct and indirect evidence to estimate the relative effects of multiple treatments, including comparisons for which head-to-head clinical trial evidence is unavailable. Although methodological and reporting guidelines for NMAs and their accompanying systematic reviews are well established, we posit that such guidelines are not always followed in practice. In this narrative perspective, we provide a concise overview of key guidelines for conducting and reporting systematic reviews and NMAs and critically appraise two recent NMAs in chronic migraine that deviate from these recommendations. While a broader systematic review was not undertaken and the identified shortcomings of these two NMAs may not be representative of the wider NMA landscape in the neurology literature, we nevertheless encourage readers of published systematic reviews and NMAs to carefully evaluate the underlying data and methods used in evidence synthesis and to interpret findings with appropriate caution, favoring analyses conducted in accordance with rigorous best practice standards.

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Network meta-analysis (NMA) is a quantitative evidence synthesis methodology that is increasingly used to make comprehensive treatment comparisons across randomized clinical trials. NMA has thus become an important component of clinical decision-making, especially for comparing treatments that have not been directly studied, helping to address evidence gaps in areas where head-to-head trials are limited [1]. As well-documented, open-source statistical packages capable of conducting NMAs become more widely available, it is easier for researchers to use this methodology to draw comparisons [2–5]. Indeed, there has been a proliferation in the number of NMA publications in clinical literature. A search of PubMed from 1 January 2010 to 1 January 2026 for 'network meta-analysis' in titles and abstracts produced over 14,000 results, approximately 70% of which were published in the last 5 years.

However, the quality of a NMA, like traditional meta-analysis, is dependent on the quality of the systematic literature review and the exchangeability of the clinical trials which inform the analysis [1]. Lack of transparency in systematic review and inadequate exchangeability across synthesized trials can negatively impact the reproducibility, robustness and validity of NMA results [6]. Although guidelines outline practical recommendations for transparent systematic reviews and methodological standards for robust clinical trial synthesis in NMA, adherence to these recommendations has been inconsistent in practice. This could have serious repercussions for clinical decision-making informed by NMA. Given the recent proliferation of NMA publications, readers of these publications should be aware that analyses conducted without adherence to best-practice guidelines may yield comparisons and conclusions of questionable reliability. To this end, we present an overview of relevant guidelines and principles underlying rigorous, methodologically robust and transparently reported systematic reviews and NMAs.

Table 1. Questions for critically appraising review articles.

- Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs (PICOS)?
- Was the search strategy adequate and appropriate? Were there any restrictions on language, publication status or publication date?
- Were preventative steps taken to minimize bias and errors in the study selection process?
- Were appropriate criteria used to assess the quality of the primary studies, and were preventative steps taken to minimize bias and errors in the quality assessment process?
- Were preventative steps taken to minimize bias and errors in the data extraction process?
- Were adequate details presented for each of the primary studies?
- Were appropriate methods used for data synthesis? Were differences between studies assessed? Were the studies pooled, and if so was it appropriate and meaningful to do so?
- Do the authors' conclusions accurately reflect the evidence that was reviewed?

Reproduced with permission from Centre for Reviews and Dissemination, *Systematic Reviews: CRD's Guidance for Undertaking Reviews in HealthCare*, 3rd ed., University of York, 2009, Box 1.1, p. 3. Centre for Reviews and Dissemination, University of York, 2008.

We also provide a narrative critical commentary on two NMAs in chronic migraine (CM) as they relate to these outlined principles. Several US FDA pharmacotherapies are recommended by the International Headache Society guidelines for first-line preventative treatment of CM, namely onabotulinumtoxinA (onabotA), topiramate and calcitonin gene-related peptide (CGRP) monoclonal antibodies [7]. However, comprehensive head-to-head clinical trials comparing the efficacy and safety of these therapies are lacking [7]. NMAs conducted in accordance with best practice guidelines are thus valuable in this disease area. Narrowing the previously discussed PubMed search to include 'chronic migraine' in titles and abstracts returned 19 records. Of these 19 records, four records presented NMAs of onabotA, topiramate and CGRP agents as first-line treatments of CM. Two of the records were components of robust health technology assessment submissions. The two remaining records are thus the focus of this narrative critical commentary; multiple discrepancies in the associated evidence syntheses were identified during review [8,9]. This article uses these two NMAs as case studies to demonstrate how deviations from best practice guidelines may impact NMA findings.

Best practices for transparent reporting of systematic reviews synthesized in & core assumptions of NMA

Although several methodological guidelines address best practices for conducting systematic reviews, the Cochrane Handbook for Systematic Reviews of Interventions and the Centre for Reviews and Dissemination (CRD)'s Guidance for Undertaking Reviews in Healthcare remain among the most widely recognized [10,11]. Serving as the methodological basis of Cochrane Reviews and many health technology appraisal organizations such as the National Institute for Health and Care Excellence, these guidelines are robust resources for systematic review and evidence synthesis. Though a detailed review of the Cochrane and CRD guidelines is beyond the scope of this article, both emphasize the importance of transparency in systematic reviews, including agreement between search strategy and prespecified Population Intervention Comparator Outcome and Study design (PICOS) criteria, documentation of the rationale for trial inclusion or exclusion and procedures to detect and minimize data extraction errors. The CRD's Guidance for Undertaking Review in Healthcare also provides a useful framework for critically appraising systematic reviews, which is reproduced in Table 1 for reference. Prospective registration of systematic review protocols in registries such as PROSPERO is also increasingly common and promotes transparency throughout the review process [12].

For systematic reviews informing NMA, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) NMA extension provides a checklist of critical items for researchers to include in manuscripts to ensure transparency in NMA methods and results [6]. Given the checklist nature of the PRISMA NMA extension guidance (e.g., researchers note on a checklist where each applicable guideline item appears in their manuscript), it has become common for journals to require submission of a completed PRISMA NMA extension checklist along with the main systematic review and NMA manuscript. While there is notable overlap between the PRISMA NMA extension and the prior discussed systematic review guidelines as they relate to the transparent reporting of data synthesized, such as disclosure of the actual values identified in the systematic review and synthesized in the NMA, the extension includes a number of NMA-specific evidence synthesis guidelines regarding the underlying assumption of NMA.

The core assumption of NMA has previously been described as exchangeability, meaning "[. . .] no important differences between the trials making different comparisons, other than the treatments being compared" [13]. Though 'important differences' may seem like a vague term at first glance, it may be best understood by considering

Table 2. Overarching identified shortcomings and related suggested best practices by area of review.

Area of review	Yang *et al.* overarching shortcoming	Zhao *et al.* overarching shortcoming	Suggested best practices
PICOS criteria and search strategy	Misalignment between stated SLR search terms and identified trials.	Misalignment between stated a priori PICOS and the trials identified in the SLR as well as trials included in the NMA.	Trials identified by an SLR should align with the associated search terms as well as align with the PICOS inclusion and exclusion criteria developed *a priori* to the search; while a subset of the SLR identified trials may be synthesized in NMA, the rationale for such a subset should be clearly stated (e.g., a feasibility assessment identified a notable population heterogeneity in a trial warranting exclusion).
Data transparency	Lack of reported NMA inputs.	Potential disconnects between cited trials and NMA inputs.	All values utilized in the NMA should be reported; care should be taken to ensure the values synthesized in the NMA align with those reported in the cited trials; inputs which do not align with cited trials for methodological reasons (e.g., imputations, continuity corrections, etc.) should be clearly denoted.
NMA assumptions	Heterogeneities in trial populations and outcomes without discussion of potential NMA impacts.		In addition to identifying any heterogeneities in synthesized trials, potential consequences to NMA results from said heterogeneities should be openly discussed as well as sensitivities analyses conducted to mitigate and/or explore impacts from these heterogeneities.

NMA: Network meta-analysis; PICOS: Population Intervention Comparator Outcome Study design; SLR: Systematic literature review.

it to consist of three constituent components: homogeneity, which assumes populations and trial designs are sufficiently similar across synthesized trials; network connectivity, which assumes true common comparators such as placebo or active control arms exist across synthesized trials from which evidence nodes can be interconnected; and consistency/transitivity, which assumes that indirect treatment effect estimates are equivalent to those of direct estimates. NMAs which synthesize clinical trials not aligning to these assumptions, such as those which are heterogeneous in disease state, outcome definition and/or timeframe of assessment, are subject to potential bias.

Beyond the reporting standards of the PRISMA NMA extension, standardized frameworks to assess the quality and certainty of NMA evidence, such as Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Confidence in Network Meta-Analysis (CINeMA), exist as well [14,15].

In summary, adherence to these guidelines encourages transparency in systematic reviews supporting NMAs as well as helps to ensure NMA methodological assumptions are met, thus decreasing the potential risk of bias in evidence synthesis. Conversely, deviation from such guidelines introduces potential risk of bias into evidence synthesis and may call the findings of evidence synthesis into question. Through the lens of the broad recommendations presented within these guidelines, we present a narrative critical commentary of Zhao *et al.* and Yang *et al.* as case studies. The commentary is presented below in detail; the overarching identified shortcomings by area of review as well as related suggested best practices are presented in Table 2.

Reporting in the NMA literature: a critical commentary

PICOS criteria & search strategy disagreement

Alignment between the specified PICOS criteria and the search strategy, including search terminology, as well as between the PICOS criteria and the included trials, is a hallmark of a robust systematic review. Both Zhao *et al.* and Yang *et al.*, however, fall short of this standard in multiple respects.

The PICOS criteria reported in the PROSPERO registration associated with Zhao *et al.* appear to be misaligned with the NMA evidence base as described in the final publication. For example, with respect to the Population criterion, the registered PICOS indicated only adult patients (≥18 years of age) were considered, however an adolescent patient (12 to <18 years of age) clinical trial appears to have been included based on Table 1 in Zhao *et al.* [16]. In addition, for the Outcomes criterion, while the registered PICOS indicated a narrowly focused set of outcomes of interest (i.e., migraine days per month, remission rate and adverse events), the NMA assessed outcomes beyond this (e.g., change in migraine disability assessment score).

In Yang *et al.*, the review's PICOS criteria are not presented in a centralized table resulting in a lack of search strategy transparency. The manuscript states that "*[t]he inclusion criteria applied in the current NMA included published randomized clinical trials with either placebo-controlled or active-controlled designs, human study, investigated CGRP interventions applied in patients with CM and patients diagnosed with CM based on the ICHD*". It is also stated that "*[t]o provide additional clinical information, we also included trials investigating the efficacy of topiramate*

or [onabotA] in patients with CM to serve as active controls". Indeed, multiple placebo-controlled and head-to-head trials of onabotA and topiramate (without CGRP agent arms) are included in the NMA. Yet, the search strategy as outlined in the database search terms presented in eTable 9 explicitly includes *only* search terms for CGRP agents in CM. It is thus unclear how the onabotA and topiramate trials included in the NMA were identified.

Data errors & lack of data transparency

Minimization of errors in the trial selection and data extraction process is a crucial component of ensuring systematic reviews and evidence synthesis produce valid, unbiased results. However, notable instances of data errors and/or insufficient transparency in trial selection can be identified in Zhao *et al.* and Yang *et al.*

While Zhao *et al.* overall concludes that "*[onabotA] has the best efficacy and safety profile*", a notable exception is found in the efficacy outcome "*≥50% reduction in monthly migraine days*" (hereby referred to as migraine response). In this outcome, the NMA finds topiramate to be the most effective treatment in migraine response, with a risk ratio (RR) of 50.06 (95% CI: 3.18, 787.30) compared with placebo. Additionally, the NMA finds topiramate to be statistically significantly more efficacious relative to all other assessed treatments with similarly large RRs. Such inflated RRs with statistical significance across all comparisons in a competitive treatment landscape should immediately raise red flags for a keen reader.

This finding initially appears driven, at least in part, by the inclusion of Diener *et al.*, a relatively small study (N = 59) with corresponding greater uncertainty in effect estimates, as the sole source of topiramate data for the migraine response outcome in the NMA [17]. However, a closer review of Table 1 in Zhao *et al.* in comparison with the original Diener *et al.* publication suggests that the findings of the NMA may be driven not merely by small sample size but potentially by a more substantive issue. Table 1, row 21, column "≥ Migraine responders (%)" of Zhao *et al.* appears to indicate Diener *et al.* reports migraine response rates of 90.91% for topiramate and 3.57% for placebo. These rates are in stark contrast to the primary Diener *et al.* publication, in which Figure 4 presents the trial's findings for achieving migraine response at week 16 as 29% among patients receiving topiramate and 0% among patients receiving placebo.

This disconnect between the values reported in Zhao *et al.* and Diener *et al.* is a potential primary driver of the large RR for topiramate in the migraine response outcome produced in the NMA. While presenting the underlying values used in the NMA is indeed aligned with PRISMA NMA extension guidance and allows for transparent review of the synthesized evidence, it is not immediately clear how Zhao *et al.* came to utilize these disconnected values, though perhaps by interpreting Diener *et al.* Figure 4 as "n" rather than "percent" and applying a continuity correction to address the zero cell of the trial's placebo arm. However, Zhao *et al.* make no mention of applying a continuity correction. Thus, there is seemingly a disconnect between the systematic review's extracted data and identified sources. In other words, the values synthesized in Zhao *et al.* cannot be found in the cited clinical trial. Accordingly, findings reported in Zhao *et al.* for the migraine response outcome may not be reliable and therefore should be interpreted with substantial caution.

Besides the lack of transparency in handling Diener *et al.*, the selective use of only the nonaligned values for the migraine response outcome obfuscates interpretability of NMA results. Table 1 in Zhao *et al.* also suggests a discrepancy in study inclusion: although Rothrock *et al.*, the primary report of the FORWARD trial comparing onabotA with topiramate, was included for other outcomes, it was omitted from the migraine response analysis without a clear rationale [18].

The exclusion of Rothrock *et al.* in this outcome is thus a key omission, especially as the findings of the NMA in migraine response appear to contradict the head-to-head FORWARD clinical trial data. Besides Rothrock *et al.*, several key onabotA studies also appear to be omitted entirely from the NMA without clear rationale [19,20]. Furthermore, potential trial duplicates appear in Zhao *et al.* Table 1 of Zhao *et al.* is presented as the studies/trials contained in the NMA, yet both Silberstein *et al.* and Lipton *et al.* – publications of the same PROMISE-2 clinical trial – are contained in the table as separate rows. It is thus unclear if duplicate data may be included in the NMA [21,22].

Yang *et al.* entirely omit Rothrock *et al.* from the NMA. Notably, FORWARD does not appear as an excluded publication in eTable 3 of Yang *et al.*, suggesting that it may not have been identified at all based on the information provided in the manuscript. This omission may reflect the previously discussed disconnect between the PICOS criteria and search strategy. However, given that other onabotA and topiramate trials were identified, it is unclear how Rothrock *et al.* was missed. This omission is of particular concern because the NMA findings contradict those of the FORWARD trial.

In addition to the opaque handling of onabotA and topiramate trials as noted above, data handling in the NMA is further obfuscated by the lack of reporting of NMA inputs. This is a key requirement in robust and transparent evidence synthesis. For example, the prior-discussed disconnect between Diener *et al.* and Zhao *et al.* may not have been identified if the NMA inputs were not published. Indeed, there is no reporting within Yang *et al.* of what values were purported to be utilized from which of the cited trials in the NMA. While "direct evidence" relative efficacy values are reported in eTable 8 as part of the GRADE assessment presented in Yang *et al.*, there is no indication as to what values or trials underlie the reported direct evidence. Given the demonstrable lack of reported NMA inputs, there is no robust way to verify that the values synthesized in the Yang *et al.* NMA align with the trials identified in the associated literature review. This is particularly problematic as it contradicts the PRISMA NMA extension checklist ("*Results of individual studies: For all outcomes considered [benefits or harms], present, for each study: simple summary data for each intervention group and effect estimates and confidence intervals.*"). The tables which Yang *et al.* point to as fulfilling this requirement in the checklist do not contain the applicable data. This disconnect with the PRISMA NMA extension further obscures interpretation of the NMA and raises additional concerns about the overall validity of the analysis.

Violation of NMA assumptions

To ensure results produced by NMA are valid and unbiased, the trials included in the analysis must adhere to the foundational assumption of exchangeability. However, multiple instances of heterogeneity which potentially violate this exchangeability assumption are present across the trials synthesized in Zhao *et al.* and Yang *et al*. Although both Zhao *et al.* and Yang *et al.* identify several sources of heterogeneity among the included trials, they do not discuss the potential impact of these differences as recommended by the PRISMA NMA extension guidelines.

For example, Zhao *et al.* note the wide timespan of included trials and heterogeneity of outcome assessment timepoints. Indeed, the NMA synthesized clinical trials published between 2005 and 2022, with CGRP trials generally conducted more recently than onabotA and topiramate trials. These more recent trials were conducted in a different clinical environment than earlier trials with potential differences in, among other factors, patient expectations, site experience, recruitment patterns and injection devices. As placebo response in migraine prevention is substantial and can vary by route of administration (e.g., placebo response from a more invasive route of administration, such as subcutaneous injection, may be greater than from a less invasive route of administration, such as an orally administered pill), this inherently threatens the exchangeability of trials in relation to network connectivity and thus weakens indirect comparisons that rely on placebo as the common comparator (namely, comparisons between onabotA and CGRPs). Furthermore, more recently-conducted trials include patients with prior preventive treatment failures while older trials were conducted before more recent CGRP agents became available. These trials may thus represent differing populations with different anticipated responses to treatment, given prior treatment failure is often considered a treatment effect modifier in multiple disease areas (with patients failing prior treatment generally at greater risk of failing subsequent treatment).

Heterogeneity in assessment timepoints is also particularly problematic. In addition to the general limitations of timepoint heterogeneity (namely, that treatment effects may differ when outcomes are measured earlier vs later), timing is especially important in CM because treatment administration differs across interventions. OnabotA is administered cyclically, with repeated injections every 12 weeks and an assessment timepoint of 24 weeks [19,20,23]. By contrast, CGRP trials generally assessed outcomes at 1–12 weeks [24,25]. As a result, a single 12-week assessment of onabotA may not fully capture the cumulative benefit achieved after repeated treatment cycles, potentially biasing the NMA against onabotA. The study authors could have explored sensitivity analyses of differing timepoints (as available) in order to elucidate potential relationships between assessment timepoints and NMA findings.

Similarly, Yang *et al.* identify notable outcome definition differences across trials (e.g., mean monthly migraine days vs mean monthly headache days). Evidence synthesis that pools outcomes across definitions may obscure clinically important distinctions and compromise comparability. For example, onabotA trials general report headache-day outcomes, while CGRP trials generally report migraine-day outcomes. While these outcomes are related, they are inherently distinct as a migraine is a specifically defined form of headache. As such, change in headache days may not be reflective of change in migraine days. Such discrepancies can introduce bias and threaten the exchangeability of trials, undermining the assumption of homogeneity. The study authors could have explored sensitivity analyses here as well by considering separate evidence synthesis of headache-day and migraine-day outcomes as to mitigate outcome definition heterogeneity.

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Conclusion

While guidelines outlining best practices to ensure methodologically robust systematic review and evidence synthesis are available, these guidelines may not be followed by a published NMA. When best practices for systematic review and evidence synthesis are not followed, bias can be introduced into NMA, rendering NMA findings to be unreliable. This is illustrated in two published NMAs in the CM disease space. While the two NMAs reviewed here may not be representative of the wider NMA literature, readers of NMAs in both the CM and wider clinical literature are nevertheless encouraged to critically review the associated systematic reviews informing these NMAs as well as the methods of the NMAs themselves.

Executive summary

- Network meta-analysis (NMA) is a methodology capable of synthesizing direct and indirect evidence to produce comprehensive estimates of comparative efficacy and safety.
- NMA is particularly useful in disease areas where comprehensive head-to-head trials of clinically relevant therapies do not exist, such as in chronic migraine (CM).
- However, the quality of an NMA is subject to the quality of the systematic review and the associated synthesized data which support said NMA.
- While guidelines for robust and transparent systematic reviews exist, such as the Centre for Reviews and Dissemination's Guidance for Undertaking Review in HealthCare and the Cochrane Handbook for Systematic Reviews of Interventions, along with guidelines for robust reporting of evidence synthesis via NMA, such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses NMA extension checklist, manuscripts in the literature exist which do not adhere to these standards of robustness and transparency.
- Lack of adherence to such standards may result in synthesis of data that does not adhere to NMA methodological assumptions, resulting in bias or lack of validity of NMA results.
- Two NMA publications in the CM disease space are thus critically reviewed as a case study of issues that may arise when standards are not followed.
- Zhao *et al.* appears to synthesize values which are discrepant with cited sources and omit outcomes of a key head-to-head trial without justification; Yang *et al.* utilizes search criteria which are not aligned with the stated Population Intervention Comparator Outcome and Study design criteria, selects trials for synthesis in an opaque manner, and does not report the actual values synthesized. Both publications do not recognize the impact to results of potential NMA methodological assumption violations.
- End users of systematic reviews and NMAs are thus encouraged to ensure manuscripts align with best practices and to consider if biases may be introduced into NMA results if best practices are not followed.

Author contributions

J Ailani, CD Saffore, I Ubamadu and S Perni were responsible for review conception; E Chertavian, EB Collins and S-T Wang were responsible for acquisition and interpretation of data; E Chertavian, EB Collins and S-T Wang were responsible for drafting; J Ailani, CD Saffore, I Ubamadu and S Perni were responsible for review of intellectual content; J Ailani, CD Saffore, I Ubamadu, S Perni, E Chertavian, EB Collins and S-T Wang were responsible for final review and approval of the submitted work.

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