**Appendix 1**

**Details on Search Strategy**

We applied a variation of the Cochrane Highly Sensitive Search Strategy, 2008 sensitivity- and precision-maximizing version, to filter for randomized controlled trials. Where possible, we removed animal-only records and opinion pieces, and limit results to the publication years 2008 to the present. The records were downloaded and deduplicated using EndNote Version 9.3.3. (Clarivate).

We looked for additional unpublished studies using two registries: http:// clinicaltrials.gov and the WHO International Clinical Trial Registry Platform, and through hand-searches of journals and of the American Headache Society (AHS) and International Headache Society (IHS) conference proceedings for the past 3 years (2020-2023). In addition, we performed a separate search in MEDLINE, Embase and the Cochrane Database of Systematic Reviews to identify additional RCTs from these reviews, as well as review reference lists of included studies and any other relevant systematic reviews.

Details on Data Synthesis:

Suitability of the evidence for pairwise meta-analysis was determined by initially assessing the clinical and methodologic homogeneity of the trials based upon patient enrollment criteria, patient demographics and details of study design. When studies were considered similar in these elements, the degree of statistical heterogeneity observed between studies was assessed based upon the Cochrane Q and I2 measures. We used the Cochrane Collaboration’s Review Manager 5.3 software(1) to perform pairwise meta‐analyses. Odds ratios - OR (and 95% confidence intervals) of response comparing treatment with placebo/other therapies are estimated for dichotomous outcomes, while pooled mean differences (or standardized mean differences where different measurement scales are used) are reported for continuous outcomes (and 95% confidence intervals/p values). In line with recent guidelines in the field(2), for dichotomous measures such as responder rate at 50%, we used ORs and a prespecified a minimal clinically important difference of 1.25 between treatment and placebo, and we set the threshold for an OR of 1.10 to be clinically unimportant and may lead to downgrade for imprecision. For continuous outcomes such as headache day counts, we looked at mean difference, with a pre-specified minimal clinically important difference of more than a day. Here a mean difference of 0.5 or less is considered clinically unimportant and may lead to downgrade for imprecision.

Assessment of the clinical and methodologic homogeneity of included studies by the team helped to inform the team it was inappropriate to perform network meta-analyses as there was a very large difference in placebo response rates between studies, and there are some publications that note there is very little information on treatment effect modifiers to be able to correct for these.(3)

**PRISMA Flow Diagram**

Studies from databases/registers **(n = 4446)**

Embase (n = 2579)

MEDLINE (n = 1231)

CENTRAL (n = 644)

References from other sources **(n = 6)**

Citation searching (n = 3 )

Grey literature (n = 3)

**Identification**

Included studies ongoing **(n = 0)**

Studies awaiting classification **(n = 0)**

Studies included in review **(n = 61)**

Studies excluded **(n = 3986)**

Studies not retrieved **(n = 0)**

Studies assessed for eligibility **(n = 442)**

Studies sought for retrieval **(n = 442)**

Studies screened **(n = 4428)**

Studies excluded **(n = 381)**

Irrelevant (n = 2)

Wrong dose (n = 7)

Review paper (n = 1)

Abstract only (n = 299)

Wrong outcomes (n = 6)

Reported elsewhere (n = 14)

Wrong intervention (n = 7)

Wrong study design (n = 10)

Paper not available (n = 1)

Unable to translate (n = 1)

Not available in Canada (n = 8)

Wrong patient population (n = 1)

included in previous guideline (n = 4)

To discuss with Steering Committee (n = 18)

Inadequate definition of study population (n = 2)

References removed **(n = 32)**

Duplicates identified manually (n = 0)

Duplicates identified by Covidence (n = 32)

Marked as ineligible by automation tools (n = 0)

Other reasons (n = 0 )

**Screening**

**Included**

**Bibliography**

1. Collaboration C. Review Manager (RevMan) 5.3 [program]. 5.3. 5 (Build Date: 30/10/14 11: 54) version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. 2014;

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3. Tepper SJ, Cirillo J, Kim E, L’Italien G, Tweedie JM, Lodaya K, et al. The temporal trend of placebo response in migraine prevention from 1990 to 2021: a systematic literature review and meta-analysis with regression. The Journal of Headache and Pain. 2023;24(1):54.