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The Ontario Drug Policy Research Network

Drug Class Review on Triptans for the Treatment of Migraines

Protocol: A systematic review and network meta-analysis of triptans for the treatment of acute migraines in adults

Systematic Review Unit

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Objective

To determine, among adults, the comparative clinical effectiveness, efficacy and safety of triptan pharmacologic agents in the acute treatment of migraine headaches through a systematic review and Bayesian network meta-analysis.

Study Question: What is the evidence for the efficacy, effectiveness and safety of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans agents, nonsteroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or antiemetics?

PICO Statement

The population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest, is as follows.

Study Population:
Adult patients with acute migraine headache, satisfying the following eligibility criteria.

Inclusion Criteria:
- Adult patient (18 years and older)
- Definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004, IHS ICDH-2) (Other definitions are considered if they conform in general to IHS diagnostic criteria)

Exclusion Criteria:
- Patients with cluster, tension or other headaches
- Patients with chronic or recurrent migraines who are not experiencing an acute episode

Intervention:
Triptans for acute treatment of migraine, namely: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan. Inclusions are as follows.

Include:
- Triptans can be alone or in combination with other drugs
- All routes of administration and dosage forms (tablets, oral disintegrating tablets, injection, nasal spray, rectal suppositories)
- All doses (any frequency or strength)
- Self-administered

Definition of Combinations:

- Part of a single fixed drug combination (FDC) that includes a triptan; or
- Triptans or other pharmacological treatments that are not part of a single formulation must be administered no more than 30 minutes apart

Comparator Groups:

Allowable comparisons include:

- Triptans vs. placebo
- Triptans vs. triptans (alone or in combination with other acute migraine therapies) (e.g., NSAIDs, ASA, acetaminophen, ergots, opioids, antiemetics)
- Triptans vs. other acute pharmacologic migraine treatment options (e.g., NSAIDs, ASA, acetaminophen, ergots, opioids, antiemetics)

Outcome(s) of Interest:

Efficacy outcomes:

All headache relief outcomes will be considered. Examples of outcome measures include (but are not limited to):

- Time to freedom from pain
- Headache relief within 2 hours
- Headache relief within 4 hours
- Freedom from pain within 2 hours
- Freedom from pain within 4 hours
- Sustained headache response at 24 hours
- Sustained freedom from pain at 24 hours
- Use of rescue medication
- Headache specific quality of life (QOL)
- Functional health status and health related QOL

Safety outcomes:

All drug safety and adverse event outcomes as reported in the literature will be considered.
Examples of outcome measures include (but are not limited to):

- Participants with any adverse event during the 24 hours post-dose
- Participants with particular adverse events during the 24 hours post-dose
- Withdrawals due to adverse events

Included study designs:

Randomized controlled trials (RCTs) will be included. No limits placed on sample size, study duration, patient follow-up

Methods

The strategy for building and analyzing the evidence base for triptans in the treatment of acute migraines in adults consists of two fundamental steps:

1. A broad **systematic review** of the available randomized evidence in the published and grey literature will be conducted, following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions.

2. A pair-wise meta-analysis and **Bayesian network meta-analysis** of randomized evidence will be conducted relating the triptans to other acute pharmacologic migraine treatments in a network, for each of the benefit and harm outcomes specified a priori. The methods and procedures to be followed are those developed by the Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (CCNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research.

This protocol was developed using guidance from the PRISMA Statement [1] and follows the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions [2]. It has been peer-reviewed by experts in pharmacology, statistics, and systematic review methodology.

Our protocol is registered in the PROSPERO database *<registration pending, waiting for proposal approval>* [3].

The specific steps for the systematic review are as follows.

Electronic Search Strategy:

The literature search will be conducted by a professional Information Scientist (MLIS). Literature search strategies will be developed using medical subject headings (MeSH) and text words related to triptans, migraines and the other acute pharmacological treatments available. Searches will employ validated filters for RCTs. All studies will be included regardless of publication status (i.e., unpublished studies), year, or language of dissemination.

Proposed electronic databases are listed below, and may be augmented based on feedback from experts and/or the Information Scientist.

- Cochrane CENTRAL
- Medline (via OVID)
- Embase (via OVID)
- Oxford Pain Relief Database

Grey literature will be identified by searching the websites of health technology assessment and related agencies, professional associations, and other specialized databases (CADTH Grey Matters: A practical search tool for evidence based medicine).

Additionally, search engines (e.g., Google) will be employed to search for additional Internet-based materials and information. We will also hand search the reference lists of key papers and abstracts of conference proceedings, and contact appropriate experts and agencies.

Eligibility and Study Selection:
Studies will be included if the population, intervention, comparator, and outcome (PICO) criteria and type of study are appropriate.

Selection eligibility criteria will be applied to each title and abstract identified in the literature search by two independent review authors in a standardized manner. Any uncertainties will be resolved by discussion and consensus with a third review author. All RCTs passing the selection criteria will be obtained in full-text format. The eligibility criteria will then be applied and a final decision made for inclusion. The reviewers will not remain blinded to study authors or centre of publication prior to study selection as this can complicate the review process and only weak evidence suggests this would improve results.

Data Extraction and Management:
All information will be extracted using a standardized data abstraction form, which will be developed, piloted and modified as necessary.

Abstraction will include:

1. Characteristics of trial participants;
2. Study characteristics;
3. Details on each study arm/pharmacological intervention, including but not limited to: dose, frequency, route of administration, duration and co-medication/prophylaxis; and,
4. Results of the clinical safety and efficacy/effectiveness outcomes forthe overall study population and the *a priori* subgroups identified.

All extracted data will be checked for accuracy by two independent review authors. The original, primary publication for each unique study included will be used for data extraction, except where multiple publications for a single RCT are found. Multiple publications for a unique RCT (e.g. supplemental online appendices, companion publications of specific outcomes or populations from the original study) will be handled by extracting the most recently adjudicated data for each outcome specified a priori.

Risk of Bias Assessment:
A quality assessment instrument and risk of bias tool will be considered: the Scottish Intercollegiate Guidelines network (SIGN50) for RCT [4] and the Cochrane Collaboration's tool for assessing risk of bias (ROB) [2].

Assessment of Heterogeneity:
Results will be assessed for both clinical and methodological diversity. Clinical diversity will be assessed by checking that the participants, interventions, and comparators are not too different from each other such that combining them is not appropriate. Methodological diversity will be assessed by checking that the studies are similar in terms of study design and risk of bias.

Once satisfied that the studies are minimally diverse and that it makes sense to pool them together in a meta-analysis, an assessment of the statistical heterogeneity will be undertaken by examining the forest plot and result of the I^2 statistic; the forest plots providing a visual sense of heterogeneity and the I^2 statistic indicating the presence of statistical heterogeneity. If the effects observed across trials are inconsistent, and vary to a large extent (say I^2>50%), the results will again be explored to assess whether the differences can be explained by some clinical or methodological feature.

Inconsistency that cannot be reduced by pre-specified subgroup or meta-regression analyses will lead to an overall estimate with less confidence when interpreting the inference from the meta-analysis. In this case, a more conservative random-effects model approach would be used so that the uncertainty of the single effect estimate is reflected in wider confidence intervals.

Assessment of Reporting Bias:
Reporting bias will be assessed by constructing funnel plots, as well as bias indicators (e.g. Egger, Harbold-Egger) for each outcome.

Data Synthesis:
Data will first be summarized descriptively. A meta-analysis will be undertaken using fixed or random-effects models when data are available, sufficiently similar and of sufficient quality. The effect sizes for the identified dichotomous outcomes will be expressed in terms of the risk ratio (RR) or odds ratio (OR). In cases when events are rare, the Peto odds ratio will be used. For continuous outcomes such as QOL, the effect size will be expressed in terms of the mean difference (MD). Pair wise meta-analyses will be conducted using RevMan or R. Absolute differences in the important benefits and harms, absolute mean difference and relative percent change from baseline will be included in a summary of findings table.

Subgroup Analysis:
Major outcomes will be assessed in identified subgroups in the specific populations of adults with acute migraine (see above section on Eligibility). Subgroups were selected to confirm clinically sound hypotheses and as few subgroups as possible were pre-specified and justified against the criteria

proposed by Sun et al.; wherein the greater the number of criteria that are satisfied for each subgroup and outcome, the more plausible is the hypothesized subgroup effect [5, 6].
Planned subgroups include:

- *Age*
- *Sex*
- *Migraine type (e.g., with aura, without aura, menstrual)*
- *Migraine severity (e.g., severe, moderate, mild)*
- *Frequency of migraine*
- *Placebo response rate*

Sensitivity Analysis:
Sensitivity analysis will be conducted based on aspects of the PICO statement and study methodology to examine the robustness of the results to the risk of bias and the influence of other variables. In particular, the results of the low-risk-of-bias-studies will be compared to studies with a higher-risk-of-bias and if they differ substantively, the conclusions of the review will be based on analyses of low risk studies only.

Grading of Evidence:
To help in the understanding of the strength of the evidence included in the review, grading of the evidence for each major outcome will be provided using The 'Grading of Recommendation Assessment Development and Evaluation' (GRADE) approach [7].

Bayesian Network Meta-Analysis Methods
Bayesian network meta-analyses will be conducted using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) [8]. The use of a Bayesian network meta-analysis offers several advantages, including:

1. Triptans used alone or in combination with other pharmacological treatments for acute migraine have not been compared directly with each other in a large number of trials, and Bayesian network meta-analysis permits combination of all active and placebo-controlled evidence; and

2. The number of individual pair-wise comparisons between triptans used alone or in combination with other pharmacological treatments for acute migraine is unwieldy given the large number of available treatment options.

As a result, summary effect estimates against a common comparator are likely to be of greater utility for clinical and policy decisions. Further, we will also construct graphical aids to assist in decision making.

We will conduct a Bayesian network meta-analysis using a model which accommodates complex interventions, such as triptans used alone or in combination with other pharmacological treatments

for acute migraine [9]. The advantage of using the approach by Welton et al. [9] is that the proposed models (e.g., additive) may allow us to estimate treatment effects for comparisons that may not have been compared directly.

The essential methods for conducting the Bayesian mixed treatment comparison are summarized in Box 1.

Box 1: Methods for the Bayesian mixed treatment comparison

- Bayesian NMAs will be conducted for outcomes pre-specified in the DSEN request, following careful assessment of heterogeneity across trials in terms of subject characteristics, trial methodologies, and treatment protocols.
- The effect estimate chosen (e.g., relative risk) will depend on the outcome of interest and availability of data.
- For reference case network meta-analyses, appropriate comparators will be considered and some comparators may be stratified by dose.
- Both fixed and random-effects models will be conducted; model selection will be based on the Deviance Information Criterion (DIC) and residual deviance.
- R (R Foundation for Statistical Computing, Vienna, Austria) and WinBUGS (MRC Biostatistics Unit, Cambridge, UK) will be used for Bayesian network meta-analyses according to the routine which accommodates evidence structures which may consist of multi-arm trials as developed at the Universities of Bristol and Leicester (www.bris.ac.uk/cobm/research/mpes/).
- Specific therapy(ies) will be identified as the reference group for all Bayesian network meta-analyses.
- Posterior densities for unknown parameters will be estimated using Markov Chain Monte Carlo (MCMC) methods.
- Basic parameters will be assigned non-informative or vague prior distributions; more informative priors will be considered after evaluation of the information base and clinical expert advice.
- Point estimates and 95% credible intervals will be used to summarize findings.
- The probability of a comparator being optimal will be estimated for each outcome based on the proportion of MCMC simulations in which its relative measure of effect was best.
- The mean rank for each comparator will also be calculated.
- Consistency between direct and indirect evidence will be formally assessed using back-calculation and node splitting techniques [14].
- Graphical methods and numerical summaries will be developed for presenting results from network meta-analysis [15].
- Model diagnostics will also include trace plots and the Brooks-Gelman-Rubin statistic (reference) to assess and ensure model convergence.
- Two chains will be fit in WinBUGS for each analysis, each usually employing ≥20,000 iterations, with a burn-in of ≥20,000 iterations.
- Provided sufficient data is available to inform the evidence network, meta-regression and/or sub-groups analyses will be conducted to adjust for key demographic, medical, and study design characteristics to test the robustness of reference case analyses.
- In other sensitivity analyses, studies will be removed from the network that are of poor methodological quality, study design, etc.
- Examine whether novel agent effects are present and estimate their magnitude of effect [16].

Both fixed and random-effects network meta-analyses will be conducted; model fit for Bayesian analyses will be based on the Deviance Information Criterion (DIC) and comparison of residual deviance to number of unconstrained data points [10-13] . Selection of model/measure will depend on the outcome of interest and availability of data. Heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols will be carefully assessed. To further investigate heterogeneity, subgroup analyses and meta-regressions [12, 13] will be conducted exploring the effect of various characteristics including but not limited to the variables considered for the subgroup and sensitivity analyses. We will also perform analyses including removal of studies from the network of therapies that were not scored as being of high quality. We will formally [12] and informally assess consistency between direct and indirect evidence by comparing direct estimates obtained from pair wise meta-analysis with estimates from the Bayesian network meta-analysis [14]. Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic will be assessed to ensure model convergence. At least two chains will be fit in WinBUGS for each analysis, each employing at least 40,000 iterations, with a burn-in of at least 20,000 iterations [8, 11].

Timeline

Work will commence on acceptance of this proposal. The systematic review and Bayesian network meta-analysis will be completed in approximately 12 weeks. The preliminary report with efficacy, effectiveness and safety results will also be delivered at 12 weeks. An additional 3 to 4 weeks will be required following stakeholder review to conduct any additional analyses and make revisions to the final report.

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