ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

Comprehensive Research Plan: Triptans for treatment of acute migraine in adults

Instructions:
The ODPRN is conducting a review of triptans in the treatment of migraine in adult patients. We want to make sure that the final report reflects the needs of the public and are therefore asking for feedback on our Comprehensive Research Plan.

- You may send us your comments via the online submission form, by emailing us your comments to info@odprn.ca or mailing them to ODPRN, Applied Health Research Centre, St. Michael's Hospital, 30 Bond Street, M5B 1W8 c/o Sandra Knowles
- Please provide your name and contact information in your correspondence. As well, complete the "Declaration of Competing Interests" (see below).
- Comments can be submitted until September 26th, 2013, 11:59pm EST.
- The information you submit on this form will be used and retained by ODPRN for the purposes of developing the report. Your personal information will not be disclosed to third parties.

Points to consider in the review:
- Are there any relevant issues (for example, how well the drug works, safety, cost, accessibility, quality of life issues) that have not been addressed?
- Are there certain settings or populations which should be included?
- Are the questions clear?

Declaration of Competing Interests
You must declare any potential areas of competing interest (often referred to as conflict of interest) that may influence or have the appearance of influencing the objectivity of your comments. Examples may include, but are not limited to, financial support from the pharmaceutical industry (such as educational/research grants, honoraria, gifts and salary), as well as affiliations or personal/commercial relationships with the drug manufacturers or other interest groups.

Do you have any Competing Interest(s) to declare?
If yes, describe any Competing Interest(s).

A. Introduction

Triptans are effective medications used for the management of moderate to severe migraine attacks. In Canada there are seven triptans available: almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan. These products are available in different dosage forms including oral tablet, oral disintegrating tablets (wafers), nasal spray and injection. In Ontario, select triptans are currently available under the Exceptional Access Program (EAP).

The objective of the triptan drug class review is to provide evidence-informed recommendations for the use of triptans through the publicly funded drug program in Ontario. This comprehensive review will include:

- systematic review of the literature,
- reimbursement-based economic analyses and drug utilization and studies using administrative claims data from Ontario and across Canada,
- environmental scans of national and international drug policies,
- contextualization of the available evidence and experience from other regions, with consideration given to health equity,
- qualitative analyses of perspectives of patients, pharmacists and prescribers
- identification of barriers to, and enablers of, successful policy implementation,
- recommendations of potential drug reimbursement models.

B. Research questions

Proposal	Research question(s)
Patient and Healthcare Professional Perspectives	• What are the key issues patients face when dealing with migraine headaches (i.e. what's important to the patient)? What would be an ideal therapy for the patient? • What are patients', prescribers' and pharmacists' experiences with triptan use for acute migraines, including the accessibility of these drugs under Ontario Drug Benefit?
Systematic Reviews and Network Meta-Analyses	• 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, acetaminophen, antiemetics, acetylsalicylic acid (ASA), opioids or ergots?
Costs and Utilization Trends	• How are triptans currently being used in Ontario and across Canada? • What is the impact of historical changes to provincial formulary listings on triptan use and costs? • What are the characteristics of patients using triptans in Ontario?
Local and Historical Context	• What is the impact of different drug reimbursement schemes for triptans (e.g. quantity limits, restricted access) on patient access, patient satisfaction, quality of life and/or utilization and costs?
Environmental Scan and Barriers to Implementation	• How are triptans currently being used in publicly funded programs across Canada as well as internationally? What mechanisms are in place to maximize access while minimizing costs? How successful are these mechanisms in achieving a cost-access balance?
Health Equity	• Does sex, gender or socioeconomic status play an important role in any of the analyses described?

Proposal	Research question(s)
Stakeholder input / acceptability	• What is the stakeholder feedback on the proposed research questions, study plans to address research questions, findings and proposed policy options?
Reimbursement-based Economics	• What is the current evidence for the *cost-effectiveness* of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetics, acetylsalicylic acid (ASA), opioids and ergots? • What is the economic impact of alternative changes to the funding status of triptans (e.g. restricted vs. more open access)?

C. PICO (population, intervention, comparator, outcomes) criteria

Patient population and inclusion criteria

- Adult patients with acute migraine headache
- Inclusion Criteria:
  - Adult patient (18 years and older)
  - Diagnosis of migraine
- Exclusion Criteria:
  - Patients with cluster, tension or other headaches

- Subgroups: Where possible, the review will consider age, gender and socioeconomic status. As well, other possible subgroups to consider include migraine type, migraine severity, frequency of migraine, placebo response rate and weight of patient.

Intervention

- Triptans for acute treatment of migraine:
  - almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
- Include:
  - All dosage forms (e.g., tablets, oral disintegrating tablets, injection, nasal spray, rectal suppositories, transdermal application)
  - All doses
  - Self-administered

Comparator

There will be 2 key comparisons of interest in this review:

- Comparative effectiveness of triptans: triptans vs. triptans
  - Note that studies of triptans vs. placebo will be considered to allow for network meta-analyses that would provide triptan vs. triptan comparisons.
- Comparative effectiveness of migraine treatment options: triptans vs other acute treatment (e.g., NSAIDs, ASA, acetaminophen, ergots, opioids, antiemetics)

Other considerations:

- Studies will consider triptans used in combination with other acute migraine therapies (e.g., triptan vs. triptan+ other drug)

- Only randomized controlled trials will be included in the systematic review of effectiveness, efficacy and safety; however other study designs may be included in the economic and drug policy reviews

Outcomes

Efficacy/Effectiveness Outcomes:

- All headache relief outcomes will be considered.
- Examples of outcome measures may 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 medications
  - Headache specific QOL
  - Functional health status and health related QOL

Safety Outcomes:

- All drug safety and adverse event outcomes as reported in the literature and through patient interviews will be considered
- Examples of outcome measures include (but are not limited to):
  - Participants with any adverse event during the 24 hours postdose
  - Participants with particular adverse events during the 24 hours postdose
  - Withdrawals due to adverse events

Drug Reimbursement Criteria and Policies:

- Quantity Limits
- Restricted Access vs. General Benefit
- Public vs. private drug coverage

Information obtained from the qualitative analysis of patient, prescriber and pharmacist perspectives and the quality of the evidence will be used to prioritize outcomes identified above.

C. Specific Proposals

The Drug Class Review is comprised of 5 different reviews, namely the Knowledge Translation unit, Systematic Review unit, Pharmacoepidemiology unit, Environmental scan/local and historical context and Pharmacoeconomics unit. Further information on each of the proposals is provided below.

Knowledge Translation Unit (see Appendix 1 for the complete proposal)

In the qualitative part of the overall study, we aim to gather opinions and experiences of stakeholders in two phases.

Phase one: our goal is to uncover factors related to the experience of migraines, and the prescription, dispensing and use of triptans and other drugs to treat migraines. We will hold one-on-one telephone interviews with primary care practitioners (PCPs), neurologists, pharmacists, and patients with migraines. We will ask interview participants about their experiences having or treating migraines, and about their thoughts on the effectiveness of triptans and access to necessary medications. All of the interviews will be digitally recorded and transcribed. The interview transcripts will be analyzed by two analysts using a method called the framework approach. This approach helps the analysts summarize information from the interviews that will answer important policy questions, while also considering any unexpected or emerging issues that are important to the interview participants.

Phase two: our goal is to determine the social acceptability and feasibility of the policy recommendations that will be generated at the end of the overall study. We will accomplish this by holding a meeting with members of the general public. These individuals will be recruited to discuss and prioritize the recommendations using a method called the RAND Appropriateness Method, which is a common and rigorous approach used to help groups come to consensus. We will also send the recommendations and an online survey to clinicians (PCPs and neurologists) and patients, interest/lobby groups and industry to collect feedback on the social acceptability of the recommendations.

Systematic Review Unit (see Appendix 2 for the complete proposal)

Objective: The goal is to compare the efficacy and safety of triptan pharmacologic agents, used alone or in combination with other agents, in the acute treatment of migraine headaches in adults compared to other triptan agents, nonsteroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), acetaminophen, ergots, opioids or antiemetics.

Method: The strategy for gathering and analyzing this evidence for triptans consists of three fundamental steps. First, a method, known as a systematic review, will be used to find and evaluate the available evidence from medical studies in the literature on triptan treatment for acute migraine headaches using a clear and transparent approach. Second, a statistical approach, known as meta-analysis, will be used to synthesize this evidence comparing any two specific treatments for migraine headaches by combining or pooling, if appropriate, the results from individual studies found in the systematic review comparing these two treatments. This method will produce a summary estimate of the direct evidence between these two alternatives treatments for migraine headaches. Finally, a network meta-analysis will be used to compare multiple treatments and their alternatives for migraine headaches simultaneously. This method involves combining direct and indirect evidence in a single analysis, resulting in summary estimates of efficacy or safety for treatments that may not have been compared head-to-head in a study. The systematic review and meta-analysis will be

conducted, following the established methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions. The methods and procedures for network meta-analysis will follow 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.

Pharmacoepidemiology Unit (see Appendix 3 for the complete proposal)

Analysis 1 – National and provincial trends in migraine therapy use

Study questions: How are triptans being used across Canada? How does use differ between different types of coverage?

Short description of analysis: We will examine trends in the use of triptans and other migraine therapies (for example, ergot alkaloids (such as migranal and cafergot) and butalbital-containing analgesics (such as fiorinal)) between 2008 and 2012. In particular, we will look at medication use by type of coverage (public or private) across all provinces and territories in Canada.

Analysis 2 – Cross-provincial changes in listing status of triptans

Study questions: How did changes in public drug formulary listing status (for example, change from restricted use to general benefit) affect the use of triptans across Canada?

Short description of analysis: We will examine and describe changes in use and costs of triptans among public drug plan beneficiaries in several provinces, between 2000 and 2012, and assess the impact of any formulary changes on these trends using interventional time series analyses.

Analysis 3 – Cross-provincial comparisons of triptan users

Study questions: What are the characteristics of people who use triptans today? How do triptan users differ between provinces?

Short description of analysis: We will look at descriptive characteristics, such as age, gender, socioeconomic status, triptan dose, and the quantity of triptan medication dispensed among triptan users in several provinces. In Ontario, where more data is available, several other factors will be included (e.g. residence in long-term care facility, public drug plan type, prevalence of potential contraindications).

Environmental scan/Local and historical context (see Appendix 4 for the complete proposal)

1. To summarize the pharmacy benefit programs for triptans and other migraine-specific treatments in Ontario, across Canada and in select international jurisdictions

Method: Summary of available information available through the Internet; interviews with individuals at the government agencies responsible for public drug plans

Intervention: Triptans and other specific treatments (e.g., ergots) for acute treatment of migraine

2. To determine the impact of different drug reimbursement schemes for triptans (e.g. quantity limits, restricted access) on patient access, patient satisfaction, quality of life and/or utilization and costs

Method: Literature review

Intervention: various drug reimbursement schemes, including general benefits, quantity limits, step therapy (including use of prophylactic treatment of migraines)

3. To summarize the guidelines for management of acute treatment of migraines

Method: Literature review

Intervention: Guidelines/recommendations for the management of adult patients with acute migraine headache

Pharmacoeconomics Unit (see Appendix 5 for the complete proposal)
Study Question 1: What is the current evidence for the cost-effectiveness of triptans?
Methods: Systematic Review of Published Economic Evaluations: We will conduct a review of the available literature on the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetics, acetylsalicylic acid (ASA) and ergots.

Study Question 2: What is the economic impact of alternatives policies for reimbursing triptans? *Methods:* Reimbursement Based Economic Assessment: We will develop a model which will identify the optimal policy relating to reimbursing triptans. Analysis will identify the change in the forecasted drug budget for the next three years associated with different reimbursement policies and will be discussed in conjunction with any impact on clinical effectiveness.

If there is any additional information you would like to add, please use the button below to add your comments.

Thank you for your input!

Appendix 1:

ODPRN Drug Class Review Proposal: Qualitative Study

Study Title: Triptans for the treatment of migraines in adults

Objectives:	To explore factors related to the experience of triptan prescription, dispending and use for acute migraines. To determine the social acceptability of resultant policy recommendations.
Study Questions:	What are patients', prescribers' and pharmacists' experiences with triptan use for acute migraines, including accessibility of these drugs under Ontario Drug Benefit? To what extent are the policy recommendations feasible and acceptable? *Note that the qualitative component will be conducted in two phases.*

Phase 1: Exploration of factors affecting the dispensing and utilization of drugs within the drug class of interest

Study Design:	This phase will utilize qualitative methods in a framework approach, which is an accepted practice in applied health studies.[2] The framework approach will guide the data collection and analysis processes. The primary source of data for this study will be one-on-one interviews. Field notes from interviews will also be made by the interviewer, and will be used a secondary source of data to incorporate into analysis.
Study Population:	Identified stakeholders for the triptans drug class review include primary care physicians (PCPs), neurologists, pharmacists, and patients. Inclusion criteria are: clinicians (PCPs, neurologists, pharmacists) who have prescribed or dispensed triptans; and patients with migraine who have current or prior experience using triptans.
Methods	A purposive sampling approach using a convenience sample will be used in order to elicit the specific perceptions and opinions of those who will be involved in or affected by drug policy decisions. Clinicians will be recruited through circles of contact, professional networks and snowball recruitment. Publicly available contact information will also be searched to develop contact lists. An ODPRN member or study coordinator will make contact with clinicians by phone, e-mail or fax. Patients will be recruited through circles of contact. A patient recruitment flyer will also be sent to participating clinicians who agree to distribute the flyer to patients using triptans. Patient networks will be used to send recruitment notices by e-mail. General calls for recruitment of all eligible groups will be placed in

	professional newsletters, e-blasts and social media (Twitter, Facebook). We will aim to recruit 6 to 8 participants from each identified stakeholder group and 20-25 patients, which may be sufficient to reach saturation amongst homogenous groups of participants. 1 Data Collection and Analysis Qualitative data will be collected through one-on-one, semi-structured telephone interviews. Interviews with PCPs, neurologists and patients will be 45 minutes in length. Interviews with pharmacists will be 30 minutes in length. All interviews will be guided by a semi-structured interview guide, and will be audio recorded and transcribed verbatim. Interview transcripts will comprise the primary source of data. A secondary source of data will be field notes, made by a note taker that will be present at each interview. Data will be analyzed using a framework approach. A framework for analysis will be developed after an initial review of the primary and secondary data sets. The framework will be applied to the data in subsequent sets to derive key policy-relevant concepts. Emerging codes will be incorporated to the framework to integrate unexpected results. A final framework will be developed and reported to the ODPRN after thorough analysis of all data.
Outcome(s) of Interest:	• Experiences of migraine and migraine therapy • Experiences accessing triptans through Ontario Drug Benefit • Experiences accessing triptans through other means • Experiences treating and dispensing medication to patients with triptans • Perceived safety and effectiveness of triptans • Perceived barriers to access and health equity issues

Phase 2: Assessment of the social acceptability of recommended policy actions related to the drug class of interest

Study Design:	RAND Appropriateness Method and Survey
Study Population:	Representatives of the general public, stakeholder groups (PCPs, neurologists, pharmacists, patients), patient advocacy groups, topic-specific interest groups, and industry
Methods	- To determine the social acceptability of each of the recommendations at the level of the general population, we will recruit a diverse set of individuals meant to represent the general population. Feedback from participants will be obtained in a half-day meeting using the RAND Appropriateness Method3. Participants will be invited to attend the meeting by an e-mail invitation sent by the study coordinator. At the workshop, we will present key issues, findings and clinical implications. Group members will then be asked to rate or prioritize a series of questions, discuss these questions, then re-rate and prioritize them. This approach allows each person to express their idea(s); each person's opinion is taken into account (compared to traditional voting where only the largest group is considered).

- To determine the social acceptability of each of the recommendations among stakeholders, we will develop and distribute an online survey measuring aspects of social acceptability including affordability, accessibility and appropriateness. The survey will be developed in FluidSurvey. The study coordinator will send the survey link and report through e-mail to participants who took part in the phase 1 interviews and agreed to be contacted for follow-up. The survey link will also be sent to patient advocacy groups, topic-specific interest groups, and industry by e-mail. Contact information for these groups will be obtained through ODPRN circles of contact or on organization websites. Survey analysis will include descriptive statistics (e.g., mean, standard deviation, median) and thematic content analysis for open-ended questions.

Outcome(s) of Interest: Feasibility and acceptability of draft recommendations.

Deliverables

We will provide a detailed written report of our methods and results. Additionally, we will develop a publication to be submitted to an academic journal when appropriate.

Timelines

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The proposed timeline for Phase 1 of the drug class review is in three parts:

- Part 1 begins approximately 2 weeks prior to official start of review. This part will include steps 1 – 3 and will involve general preparation, including developing the interview guide, recruitment pool, and protocol.
- Part 2 (4 weeks) includes steps 4 – 6 and will involve conducting activities that will form the key concepts and messages to develop project proposals. At the end of this phase, a brief report will be delivered to all teams within the FMU to inform these proposals.
- Part 3 (14 weeks) includes steps 7 – 10 and will involve a more in-depth, rigorous qualitative analysis. This phase will end with the delivery of a qualitative report to inform the draft policy recommendations.

At the end of the formulation of draft policy recommendations, the social acceptability phase will begin and will last 4 weeks.

References

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1. Kuzel, AJ. (1999). "Sampling in qualitative inquiry." In BF Crabtrree and WL Miller (Eds.) Doing Qualitative Research (second edition). Thousand Oaks, CA: Sage Publications (pp. 33-45).
2. Ritchie J, Spencer L. (1994). Qualitative data analysis for applied policy research. In Bryman A, Burgess R, eds. *Analysing Qualitative Data*. London: Routledge: 173-194.
3. Brook, R.H. (1994). The RAND/UCLA Appropriateness Method. In McCormick, K.A., Moore, S.A., & Siegal, R.A. (eds.) Clinical practice guideline development. Methodology perspectives. US Department of Health and Human Services, Rockville, Maryland, 59-70

Appendix 2:
ODPRN Drug Class Review Proposal: Systematic Review Unit

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].

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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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Appendix 3:

ODPRN Drug Class Review Proposal Pharmacoepidemiology Unit

Study Title: Epidemiologic analyses of triptan use in Canada

Objectives:

1. To examine national and provincial trends in use of triptans and other migraine therapies (e.g. ergot alkaloids) over the past 5 years
2. To examine the impact(s) of changes in provincial formulary listing status (if any) on triptan utilization and costs among public drug plan beneficiaries
3. To perform cross-provincial comparisons of the characteristics of triptan users among a population of public drug plan beneficiaries
4. To describe current patterns of triptan use in Ontario

Objective 1: National and provincial trends in triptan use

Study Design:

Design: Time series analysis with quarterly time intervals
Study period: January 2008 to December 2012
Population: All provinces and territories
Data Source: *IMS Compuscript:* aggregated data for all prescriptions dispensed at retail pharmacies across Canada

Study Population:

Inclusion Criteria:

- All privately and publically-funded triptan prescriptions dispensed in Canada
  - Almotriptan
  - Eletriptan
  - Frovatriptan
  - Naratriptan
  - Rizatriptan
  - Sumatriptan
  - Zolmitriptan
- All privately and publically-funded prescriptions for other migraine therapies (not including prophylaxis) dispensed in Canada.
  - Ergot alkaloids (e.g. migranal, ergodryl, cafergot)
  - Butalbital-containing analgesics (e.g. fiorinal)
  - Butorphanol (e.g. stadol)
- Adults aged 18+ at time of triptan dispensing

Outcome(s) of Interest:	Measured over entire study period (quarterly): • Number and rate of triptan prescriptions dispensed • Number and rate of triptan units dispensed • Total cost of triptan prescriptions Stratify all analyses by: • Province • Payer (public, private) • Drug (triptan, ergot alkaloid, butalbital-containing analgesic, butorphanol) • Age (<65 vs. 65+) *(pending data availability)*
Limitations:	• There is no patient-level data available through IMS Compuscript; information is only available at the prescription and unit level.

Objective 2: Cross-provincial changes in listing status of triptans

Study Design:	Design: Time series analysis with annual time intervals Study period: January 2000 to December 2012 Data Sources: • *National Prescription Drug Utilization Information System Database (NPDUIS)*: aggregated data for all publically funded prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI, and NIHB
Study Population:	• Inclusion Criteria: o All publically-funded triptan prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI, and NIHB o Almotriptan o Eletriptan o Frovatriptan o Naratriptan o Rizatriptan o Sumatriptan o Zolmitriptan o Adults aged 18+ at time of triptan dispensing

Outcome(s) of Interest:	Measured over entire study period (annually): • Number and rate of triptan users • Total costs • Average cost per user Stratify all analyses by: • Province • Triptan (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan) • Age (<65, 65+)
Limitations:	• Publically-funded, patient-level prescription data for PEI is only available as of 2004. We are therefore unable to determine triptan use prior to that date. • There is no patient-level data available for publically paid prescriptions in British Columbia, Quebec, Newfoundland & Labrador or the Territories. Therefore, we will be unable to make comparisons between Ontario rates and rates of use in these provinces.

Objective 3: Cross-provincial comparisons of triptan users

Study Design:	Design: Cross-sectional analysis Study period: January 2012 to December 2012 Data Sources: • *National Prescription Drug Utilization Information System Database (NPDUIS)*: aggregated data for all publically funded prescriptions dispensed in Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI, and NIHB • *Ontario Drug Benefit Database (ODB)*: individual level data for all publically funded prescriptions dispensed in Ontario. This dataset contains additional variables (long-term care residence, public drug plan coverage) that is not available through NPDUIS
Study Population:	• Inclusion Criteria: o All publically-funded beneficiaries of Alberta, Saskatchewan, Manitoba, Ontario, New Brunswick, Nova Scotia, PEI, and NIHB o Adults aged 18+ at time of triptan dispensing

Appendix 4:

ODPRN Drug Class Review Proposal: Environmental Scan

Study Title: Triptans for the treatment of migraines in adults

Objectives:

1. To summarize the pharmacy benefit programs for triptans in Ontario, across Canada and in select international jurisdictions
2. To determine the impact of different drug reimbursement schemes for triptans (e.g. quantity limits, restricted access) on patient access, patient satisfaction, quality of life and/or utilization and costs
3. To summarize the guidelines for management of acute treatment of migraines

Study Questions: In adult patients with migraine headaches:

1. How are triptans currently being used in publicly funded programs across Canada as well as internationally? What mechanisms are in place to maximize access while minimizing costs? How successful are these mechanisms in achieving a cost-access balance?
2. What is the impact of different drug reimbursement schemes for triptans (e.g. quantity limits, restricted access) on patient access, patient satisfaction, quality of life and/or utilization and costs? Is the clinical outcome altered in patients with more (or less) restrictive pharmacy benefit programs?
3. Does sex, gender or socioeconomic status play an important role in any of the analyses described?

Objective 1: Pharmacy Benefit Programs in Ontario, across Canada and internationally

Study Design:

Design: summary of available information available through the Internet; interviews with individuals at the government agencies responsible for the public drug plan
Data sources: Internet, direct contact with individuals

Study Population:

- Canada: provincial/territorial public plans
- England, Wales, Northern Ireland, Scotland: NICE (National Institute for Health and Care Excellence)
- Australia: Pharmaceutical Benefits Scheme
- United States: Medicare, Veterans Affairs
- New Zealand: PHARMAC (Pharmaceutical Management Agency)

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Intervention:	• Triptans for acute treatment of migraine:
	  o almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
	• Include:
	  o All dosage forms (e.g., tablets, oral disintegrating tablets, injection, nasal spray, rectal suppositories, transdermal application)
	  o All doses
	  o Self-administered
	• Other specific treatments used for acute treatment of migraines (e.g., ergotamine)

Outcome(s) of Interest:	Drug Reimbursement Criteria and Policies: • Quantity Limits • Restricted Access vs. General Benefit • Specific restriction criteria
Objective 2: Impact of different drug reimbursement schemes for triptans	
Study Design:	Design: Literature review Data sources: Medline, EMBASE, Cochrane Collection, Grey literature
Study Population:	Adult patients with acute migraine headache
Intervention:	Various drug reimbursement schemes, including general benefits, quantity limits, step therapy (including use of prophylactic treatment of migraines)
Outcome(s) of Interest:	Indirect/direct measurements of clinical outcomes, patient satisfaction, quality of life, utilization and/or costs
Objective 3: Guidelines for management of acute treatment of migraines	
Study Design:	Design: Literature review Data sources: Medline, EMBASE, Cochrane Collection, Grey literature
Study Population:	Adult patients with acute migraine headache
Intervention:	Guidelines/recommendations for the management of adult patients with acute migraine headache

Outcome(s) of Interest:	Published guidelines by various organizations including Canadian Headache Society, American Academy of Neurology, Institute for Clinical Systems Improvement

Appendix 5:
ODPRN Drug Class Review: Triptans for the treatment of migraines in adults

Research Questions

RQ1. What is the current evidence for the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetics, acetylsalicylic acid (ASA) and ergots?

RQ2. What is the economic impact of alternatives reimbursement statuses for triptans (e.g. restricted vs. more open access)?

Methods

Systematic Review of Published Economic Evaluations

To address RQ1 we will conduct a systematic review of the available literature on the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetics, acetylsalicylic acid (ASA) and ergots.

A search of the medical literature will be conducted 1948 to present in Medline (indexed, in-process and other non-indexed), Embase, Cochrane database, NHS EED and Tufts CEA registry will be conducted in order to capture all relevant literature based on the NHS EED recommended search strategy. Key economic search words will include, “economics”, “costs”, “cost”, “costly”, “price”, “pricing”, “pharmacoeconomics”, “expenditure”, “value”, “budget”. These will be linked to the clinical search terms adopted by the clinical review In addition, the reference lists of retrieved studies will be hand searched.

Two reviewers will first review the abstracts of studies identified by the initial literature search literature searches in order to identify potential articles for inclusion within the critical appraisal. Any disagreements will be resolved through consensus with erring on the side of caution through inclusion.

Extracted studies will then be further reviewed with studies excluded for lack of context or for not being full economic evaluations.

The critical review will identify common methodological issues within studies. Each study will be assessed through a three step process: initial assessment for validity, assessment of study quality, assessment of study’s pertinence to the decision question.

Focus will be on the strength and quality of evidence addressing the cost-effectiveness of triptans (alone or in combination with other drugs) for acute treatment of migraines compared to: other triptans, acetaminophen, antiemetics, acetylsalicylic acid (ASA) and ergots.

De novo Economic Evaluation

Given the nature of the decision question and the consistent cost of triptans, there is no requirement for a traditional economic evaluation to assess the value for money for each of the candidate treatments. Evidence on differential clinical effectiveness will be sufficient to consider selective reimbursement strategies within the reimbursement based economic assessment.

Reimbursement Based Economic Assessment

The focus for this component of the proposal is to develop an applied, policy-oriented economic model which will help facilitate the reimbursement decision. Focus will be on identifying the optimal reimbursement criteria through considering both budget impact and clinical effectiveness as criteria with a focus on reimbursement strategies not just interventions. Analysis will identify the budget impact of alternative approaches to the current reimbursement status of triptans. This will be achieved through a three stage process.

1. Forecasting of triptan expenditure for the next three years

   We will obtain data on current usage of triptans from OPDP to allow identification of the number of claims, number of claimants, total costs and drug unit costs in a given year (broken down monthly) as well as data on claims per claimant. We will first standardize drug costs to the current year drug costs.

   We will use time series analyses to forecast the drug costs for the next three years adopting three approaches: simple linear interpolation (naïve approach), linear regression and polynomial regression. For regression methods we will include the number of triptans available on the formulary as a potential independent variable to assess the impact of market expansion.

   Similar analyses will be conducted for alternative therapies such as ergots.

2. Identification of candidate reimbursement strategies

   The second stage will involve identifying alternative approaches to reimbursement of triptans. This will rely heavily on strategies identified during the scoping assessment along with further consultation with OPDP. Strategies could include more open access through general benefit and quantity caps. Strategies could be general – applied to all triptans (either currently covered only or all regardless of current coverage) – or specific – targeted at specific triptans.

3. Assessment of budget impact of candidate strategies

   Using the techniques adopted in step 1 we will forecast the budget expenditure on triptans and ergots for each alternative reimbursement strategy. Three data sources will assist in this process: findings from the qualitative review, EAP information relating to triptans and historical evidence of market growth associated with opening access to a drug class.

   The qualitative review will inform the likely market growth for triptans by focussing on qualitative evidence regarding access to triptans.

   Data on EAP requests for triptans can similarly inform potential market growth. This will include the number of EAP request by triptan, the proportion of requests that are successful, the proportion of requests that are unsuccessful and the use opf ergots by those who were unsuccessful in their request,

   Historical evidence of market growth associated with opening access to a drug class will allow evidence on the likely hemorrhaging of the market for other alternative therapies – i.e.ergots. This requires the willingness of OPDP to provide any data relating to similar

reimbursement scenarios. Such analyses will facilitate further analyses pertinent to other drug classes.

Results will be presented in terms of budget impact as well as incorporating a discussion on the impact on clinical effectiveness.

Deliverables

We will provide a written report detaining methods adopted, results, discussion and summary policy recommendations. The report will comprise a two page executive summary followed by a detailed technical report. In addition, we will provide a fully executable excel based reimbursement economic model.

Timelines

On acceptance of this proposal, work will commence. The review of economic evaluations will be completed within 6 weeks of the commencement. The forecasting of triptan expenditures will be completed within 12 weeks of commencement to coincide with the completion of the clinical review. The reimbursement based economic modelling will be completed between 12 and 16 weeks to allow delivery of an aligned final report at 16 weeks, once information on the relative clinical effectiveness of triptans are available. Any reanalyses and a revised final report will be available 4 weeks after receipt of stakeholder reviews.