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Canadian Agency for Drugs and Technologies in Health

**Triptans for Acute Migraine: Comparative Clinical
Effectiveness and Cost-effectiveness**

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Canadian Agency for
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HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Health technology assessment (HTA) agencies face the challenge of providing quality assessments of medical technologies in a timely manner to support decision making. Ideally, all important deliberations would be supported by comprehensive health technology assessment reports, but the urgency of some decisions often requires a more immediate response.

The Health Technology Inquiry Service (HTIS) provides Canadian health care decision makers with health technology assessment information, based on the best available evidence, in a quick and efficient manner. Inquiries related to the assessment of health care technologies (drugs, devices, and procedures) are accepted by the service. Information provided by the HTIS is tailored to meet the needs of decision makers, taking into account the urgency, importance, and potential impact of the request.

Consultations with the requestor of this HTIS assessment indicated that a systematic review would be required to meet their needs.

Systematic review of evidence

Systematic reviews are conducted by a minimum of two HTIS reviewers in consultation with two clinical experts. Research questions and selection criteria were developed jointly by the two HTIS reviewers and the clinical experts. The literature search was carried out by an information specialist using a defined search strategy.

Each HTIS reviewer independently selected studies for inclusion according to the predetermined selection criteria. All articles considered potentially relevant by at least one reviewer were acquired from library sources. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

The draft was written by the research team with input from external clinical experts. The draft was also externally peer reviewed. The draft was finalized based on the input received.

Reviewers

CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not the reviewers.

CADTH thanks the external reviewers who kindly provided comments on an earlier draft of this report. Reviewers who agreed to be acknowledged include:

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Conflicts of Interest

Marek Gawel has served on advisory boards and has received compensation from several pharmaceutical manufacturers.

Rose Giammarco has received reimbursement for clinical trials and speaker fees, and has held advisory board positions for pharmaceutical manufacturers.

Werner J. Becker serves on medical advisory boards or has done so in the past for GlaxoSmithKline, AstraZeneca, Pfizer, Merck, and Janssen-Ortho.

R. Allan Purdy has provided support for clinical research trials for GlaxoSmithKline Canada, Merck Frosst Canada, Endo Pharmaceuticals, Pfizer Canada, and AstraZeneca Canada.

Triptans for Acute Migraine: Comparative Clinical Effectiveness and Cost-Effectiveness

Technology and Condition

Serotonin receptor (5HT₁) agonists (triptans): almotriptan, eletriptan, naratriptan, sumatriptan succinate/hemisulfate, rizatriptan, and zolmitriptan for treatment of acute migraine in adults and adolescents

Issue

Acute migraine is associated with significant costs to public payers and society. The use of triptan therapy may lead to improved quality of life, and the cost of therapy may be offset by savings associated with reduction in need for healthcare services and increased productivity. Public funding policies across Canada are inconsistent.

Methods and Results

A systematic review was summarized and appraised to compare triptans in adults. A systematic review of the clinical literature was performed to compare triptans in adolescents. A systematic review of economic evaluations was conducted to identify the primary influential factors determining the cost-effectiveness of therapy, and identify compelling evidence of cost-effectiveness in a Canadian population.

Implications for Decision Making

- **Differences across all triptans have not been demonstrated in adults.** No trials were identified that directly compared all available triptans with each other. Instead, most of the evidence suggesting comparative differences in effectiveness are from trials comparing one triptan with sumatriptan. There was no evidence to suggest individuals could be identified who would benefit from a particular triptan versus any other. More comparisons among triptans are required to establish overall differences.
- **The generalizability of clinical evidence to current practice requires consideration.** None of the RCTs identified investigated the effect of triptan use for

early treatment or mild migraine, although this is commonly encouraged in current practice. This practice could change the magnitude of observed responses from that seen in clinical trials. Switching to a different triptan, rather than continuing with the same triptan, is encouraged in current practice and may result in different success measures than that observed in clinical trials.

- **Naratriptan may require special consideration in adults.** There is fair evidence to suggest that rizatriptan 10 mg is superior to naratriptan 2.5 mg in relieving headache pain, photophobia, and phonophobia at two hours, and providing sustained relief at 24 hours. Fair evidence suggests that sumatriptan 100 mg is superior to naratriptan 2.5 mg for relieving headache pain at four hours. Because these differences were demonstrated by one trial for each comparison, decisions regarding naratriptan should be reconsidered as new information becomes available.
- **Nasal sumatriptan requires consideration in adolescents.** The evidence of effectiveness in adolescents was derived from eight RCTS comparing five triptans to identical placebos. Only sumatriptan 20 mg nasal spray significantly increased the likelihood of a two-hour response, with the combined results of two trials suggesting a number needed-to-treat of 10 (95% CI: 6, 36). The combined response of sumatriptan recipients from both trials showed a 38% response rate for achieving freedom from pain at two hours, with a number needed-to-treat of 10 (95% CI: 6, 30].
- **No compelling economic evidence supporting one triptan over any other could be identified.** Only two of the 12 identified economic evaluations incorporated utility into their analyses. Neither study compared all available triptans or used credible estimates of effectiveness. Most cost-effectiveness evaluations harboured flaws, such as failure to identify major costs and benefits or resource use. Given their limitations, the applicability of these studies to Canadian decision makers remains questionable.

This summary is based on a rapid review assessment available from CADTH's web site (www.cadth.ca): Membe S, McGahan L, Cimon K, Gawel M, Giammarco R, Mierzwinski-Urban M. *Triptans for acute migraine: comparative clinical effectiveness and cost-effectiveness.*

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EXECUTIVE SUMMARY

Title: Triptans for Acute Migraine: Comparative Clinical Effectiveness and Cost-Effectiveness

Date: October 30, 2006

Context and Policy Issues

Migraine is a common disorder characterized by episodic intense throbbing headaches that are often accompanied by nausea; vomiting; and sensitivity to light, sound, or movement. It is estimated that among the more than three million Canadians who experience migraine, more than two million are women. The condition is costly to individuals and society in terms of consumption of health care resources, lost productivity, and impact on quality of life.

In Canada, the available treatments for acute migraine include analgesics such as acetaminophen; non-prescription combinations of aspirin or acetaminophen with caffeine; acetylsalicylic acid and ibuprofen, which are non-steroidal anti-inflammatory drugs; ergot derivatives such as dihydroergotamine mesylate and ergotamine; and a class of selective 5-hydroxytryptamine serotonin receptor agonists called triptans.

Triptans have become the preferred drug treatment for moderate to severe migraine attacks. The triptans that are available in Canada include almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. There is no consistent policy regarding their listing status in publicly funded drug plans across Canada. An evidence-based assessment of the comparative clinical effectiveness and cost-effectiveness of triptans is needed to support the development of a consistent public policy.

This review analyzes the clinical and economic evidence, with a focus on two research questions.

Research Questions

1. What is the evidence of comparative clinical effectiveness of available serotonin (5-HT₁) receptor agonists (triptans) (i.e., almotriptan, eletriptan, naratriptan, sumatriptan succinate/hemisulfate, rizatriptan, and zolmitriptan) in patients with acute migraine?
 - a) What is the comparative effectiveness in adult patients?
 - b) What is the comparative effectiveness in adolescent patients?
 - c) What is the evidence of the clinical advantage of sumatriptan succinate over placebo in adult and adolescent patients?
2. What is the evidence of comparative cost-effectiveness of the available triptans (i.e., almotriptan, eletriptan, naratriptan, sumatriptan succinate/hemisulfate, rizatriptan, and zolmitriptan) in adult and adolescent patients with acute migraine?

Methods

For question 1a, a recent systematic review was selected based on the consensus of the project team in discussion with the originator of the request for study. For questions 1b and 2, an original systematic review was undertaken. Question 1c was addressed by examining a subset of admissible evidence identified for questions 1a and 1b. Published literature was obtained by cross-searching BIOSIS Previews[®], EMBASE[®], and MEDLINE[®] databases on the OVID[®] search system. Regular alerts were established on BIOSIS, EMBASE, and MEDLINE. Information retrieved through alerts is current to October 3, 2006. Parallel searches were performed on PubMed and the Cochrane Library (Issue 3, 2006) databases. Supplementary searches were conducted on the incidence and prevalence of migraine with the focus on Canada. Language and publication date limits were not applied. Filters were applied to limit the retrieval to systematic reviews, clinical studies, economic studies, and clinical practice guidelines. The retrieval of systematic reviews and clinical studies was further limited by focusing on the adolescent population only. The manufacturers of all commercially available triptans were asked to provide relevant information.

The web sites of regulatory agencies, and health technology assessment and related agencies were searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. The Google[™] Internet search engine was used to search for information on the Internet. These searches were supplemented by hand searches of the bibliographies of selected papers.

Summary of Findings

Adults

A review, with minor flaws, by the Oregon Evidence-based Practice Center's Drug Effectiveness Review Project (DERP) suggests that, while several head-to-head trials of triptans have been conducted in adults, few good quality studies that examine 24-hour sustained relief or long-term consistency have been published in peer-reviewed journals. There is insufficient evidence to judge the balance of advantages and disadvantages of rizatriptan versus sumatriptan.

All studies included in the DERP report were assessed for quality and assigned a rating of good, fair, or poor by DERP reviewers.

Evidence from studies judged to be of good quality

- Thirteen head-to-head trials suggest that there are no differences in chest pain or tightness, or central nervous system effects with eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan.

Evidence from studies judged to be of fair quality

- Rizatriptan 10 mg is superior to sumatriptan 100 mg in relieving headache pain and nausea, and for resuming normal function at two hours (one trial).
- Rizatriptan 10 mg is superior to naratriptan 2.5 mg in relieving headache pain, relieving photophobia and phonophobia at two hours, and providing sustained relief at 24 hours (one trial).
- Sumatriptan 100 mg is superior to naratriptan 2.5 mg for relieving headache pain at four hours (one trial).
- Subcutaneous sumatriptan 6 mg is associated with more chest pain than oral eletriptan 80 mg (20 trials).

Evidence from studies judged to be of poor quality

- There is no evidence that any ethnic or racial group has a higher risk of adverse events from using triptans, or that one triptan has an advantage compared with the others.

Adolescents

It was not possible to determine the comparative clinical effectiveness of triptans in adolescents, because no head-to-head comparison trials were

identified. Eight randomized controlled trials (RCTs), all comparing triptans with placebo, were identified. The quality of the studies ranged from one to five on the Jadad scale, with a mean score of two. Three of eight trials were reported in abstract or poster format. No statistically significant differences in efficacy measures were found when comparing naratriptan, zolmitriptan, rizatriptan, oral sumatriptan, or eletriptan to placebo. Statistically significant differences were demonstrated in favour of nasal sumatriptan. Nasal sumatriptan recipients were 18% more likely than placebo recipients to achieve headache relief [NNT=10 (95% CI: 6, 36)] and 38% more likely to achieve freedom from pain [NNT=10 (95% CI: 6, 30)] two hours after dosing, compared to placebo recipients. Nasal sumatriptan recipients were three times more likely to experience mild adverse events involving nausea, vomiting, and taste disturbance, than placebo recipients [NNH=5 (95% CI: 3, 13)]. Several trials excluded patients who did not experience a migraine during the study period from the intention-to-treat population. This could lead to selection bias because patients with milder or fewer migraines may not have been represented, possibly underestimating triptan efficacy. The large placebo effect in these studies may have been influenced by the shorter duration of migraine in adolescents and the need for adult consent in obtaining study medication.

Sumatriptan versus Placebo

When sumatriptan is compared with placebo, evidence suggests that adult sumatriptan 50 mg and 100 mg recipients consistently experienced headache relief rates of 49% to 67% at two hours across nine attacks in two placebo-controlled trials. Adolescent sumatriptan nasal spray 20 mg recipients were 18% more likely than patients receiving identical placebos to achieve headache relief and 38% more likely to experience freedom from pain at two hours.

Cost-effectiveness

Economic studies show that eletriptan, rizatriptan, and almotriptan are the most cost-effective triptans, based on different methods, clinical data, and assumptions. No high-quality studies were found to support the use of these triptans compared to others. We found that most studies include only drug cost in their analyses, hence making their results inapplicable for public health care decision makers taking a societal perspective.

Our interpretation of the results of economic studies is limited by the diverse characteristics of the studies. First, available economic studies used different methods to evaluate outcomes. Second, most economic studies compare only a few triptans. Third, most economic studies only consider drug costs in their models, neglecting other parameters such as resource utilization, productivity loss, and cost of managing adverse events. Moreover, we were unable to identify any cost-effectiveness studies of triptans in adolescent populations.

Conclusions and Implications

In adults, several head-to-head trials have been conducted. There is evidence of differences in benefit between some triptans from unreplicated randomized controlled trials judged to be of fair quality. Good quality evidence suggests that there are no demonstrated differences in the harmful effects associated with oral triptans. It was not possible to draw reliable conclusions about the comparative effectiveness of triptans in adolescents, because no head-to-head trials were found. After evaluating the evidence, we found that there is a need for head-to-head comparison

trials, and measures should be taken to reduce selection bias and placebo effects in future studies.

In adults, evidence from several long-term placebo-controlled trials suggest that oral sumatriptan recipients consistently experience more headache relief. In adolescents, only nasal sumatriptan has been shown to improve pain relief while also demonstrating side effects, most commonly, taste disturbance.

Most of the literature evaluating the cost-effectiveness of triptans is of a limited utility to health care decision makers because of poor quality. Most economic studies do not compare all available triptans. The few studies that compare all triptans provide insufficient comparative information because they focus on drug cost only. Most economic studies use effectiveness data obtained from a meta-analysis of questionable methods and applicability, hence raising concerns about the validity of their results.

More comparisons among triptans other than sumatriptan are needed, and better evidence regarding the effectiveness of triptans for early and mild migraines should be considered.

ABBREVIATIONS

AE	adverse event
CEA	cost-effectiveness analysis
CI	confidence interval
CUA	cost-utility analysis
DERP	Drug Effectiveness Review Project (Oregon Evidence-based Practice Center)
DNT	doses needed to treat
ICER	incremental cost-effectiveness ratio
ITT	intention to treat
NNH	number needed to harm
NNT	number needed to treat
NR	not reported
PF	pain free
QALY	quality-adjusted life year
RCT	randomized controlled trial
RR	relative risk
SNAE	sustained pain-free patients who experience no adverse events
SPF	sustained pain free

GLOSSARY

Adverse events: unwanted effect detected in participants in a trial; term is used regardless of whether effect can be attributed to intervention under evaluation; adverse events believed to be attributable to triptans are also called adverse effects or side effects; they include chest pain or tightness, central nervous system effects (dizziness, paresthesia, somnolence, fatigue, and asthenia), and other effects (nausea, vomiting, dry mouth, and nasal symptoms); serious adverse events are any adverse event that is fatal, life-threatening, or permanently disabling, or that results in new or prolonged hospitalization.

Functional status: ability to perform all, some, or none of one's usual work, play, or academic activities.

Headache response: reduction of headache pain from "severe or moderate" to "mild or none" with neither a headache recurrence nor the need for rescue medication until 24 hours after dosing.

Pain free: absence of headache pain without headache recurrence or need for rescue medication.

Pain relief: reduction of headache pain from "severe or moderate" to "mild or none" without headache recurrence or need for rescue medication.

Preference: patient's preference for one study drug versus another.

Rescue medication: use of additional (triptan or non-triptan) medication, indicating inadequate or unsustained pain relief from test triptan or placebo.

Reliability or consistency of response: ability of triptan to consistently relieve pain or symptoms during series of headaches.

Response to treatment: relief of nausea, vomiting, sensitivity to light (photophobia), sensitivity to sound (phonophobia), and other symptoms associated with migraine, after treatment.

Satisfaction: patient's acceptance of or satisfaction with treatment.

Short-term consistency of response: consistency of response across two or more migraine attacks.

Speed of response: time from administration of drug to headache relief.

Sustained headache response: sustained headache relief or pain free for 24 hours.

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1 INTRODUCTION

1.1 Definition of Migraine

Migraine is a recurrent neurological disorder. It is characterized by episodic, intense throbbing headaches that are often accompanied by nausea, vomiting, and sensitivity to light, sound, or movement.¹ Migraine attacks last from four to 72 hours and are preceded or accompanied by transient focal neurological symptoms known as aura in 10% to 20% of patients.^{1,2} The estimated average frequency of migraine attacks is 1.5 per month,³ but in many cases, migraineurs (people who experience migraines) have >2 attacks per week.⁴

The International Headache Society has set criteria to define different types of headache. The criteria for migraines with or without aura and for cluster headaches are available.⁵

1.2 Prevalence and Incidence

Migraine affects more than three million Canadians, with most migraineurs at their most productive ages (between 25 and 55 years).³ A 1994 migraine prevalence survey showed that more than two million Canadian women (approximately 22% of women) and about one million Canadian men (approximately 7% of men) experience migraine.⁶ In the US, migraineurs form 17.2% of the female population and 6% of the male population.⁷ Migraine affects adolescents, predominately girls after the age of 13 years, and has a prevalence of 3% to 19% in studies where International Headache Society criteria for diagnosis have been used.^{8,9}

The rates for migraine are probably underestimates of the true prevalence. Not all people who experience migraines consult a physician, and those who do may be misdiagnosed. Some people can obtain relief by using over-the-counter medication and do not seek further treatment.

About half of female migraineurs who responded to the Canadian Women and Migraine Survey of 2005 had never consulted a physician regarding migraines.¹⁰ A telephone survey conducted in the US in 1998 found that about 31% of the migraineurs identified had never consulted a doctor concerning migraines in their lifetime.⁷

1.3 Socioeconomic Burden

Migraine is costly to individuals and society in terms of consumption of resources, lost productivity, and impact on quality of life. It is the most common pain-related condition that patients present to physicians.¹¹ A self-administered questionnaire about the impact of migraine symptoms on health care use and work loss in Canada³ showed that in 2000, 89% of migraine patients visited clinics, 23% visited emergency rooms, and 5% were hospitalized. Respondents also reported missing an average of 6½ days of work and attending work while experiencing migraine for an average of 44 days per year.

Health care resource utilization and lost productivity due to migraine cost the Canadian health care system an estimated \$3.2 billion annually.³ Health care resource utilization is estimated to cost \$427 million. Of this, an estimated \$193 million is due to hospitalizations, \$182 million to clinic visits, and \$52 million to emergency room visits.³ The estimated annual productivity loss due to migraine is \$2,761 billion. This amount is an underestimate, because it excludes the cost of drugs. In the US, annual direct and indirect costs due to migraine amount to \$1 billion and \$13 billion respectively.¹²

Migraine affects productivity by reducing the number of days worked and affecting the quality of work produced. In a prospective diary study based on a sample of 122 migraineurs during a three-month period, Lipton *et al.*⁴ found that the mean number of work days lost was 4.4 per year.

In a study by Lipton *et al.*, based on a self-administered questionnaire mailed to a sample of 20,000 households in the US, 53% of migraineur respondents reported that severe headaches had caused substantial impairments in their activities or required bed rest, 31% had missed at least one day of work or school in the previous three months, and 51% reported that their work or school productivity was reduced by at least 50%.¹³ When compared with an identical study from 1989, this 1999 study found that the number of migraineurs had increased from 23.6 million to 27.9 million. The psychological and social impacts of migraines extend to patients' partners, family members, and colleagues.¹⁴ Migraineurs will avoid planning for events, fearing that a migraine might necessitate a

cancellation of plans and lead to disappointment for family members, partners, and colleagues. The anticipation of an attack can be as disabling as the attack, and there is misunderstanding about the condition. In the workplace, migraineurs will often work despite their pain to avoid the stigma. Migraineurs cope not only with the attack, but also with the impact that it may have on those around them. It is difficult to measure this.

In the adolescent population, migraine is insidious. In addition to causing pain, it adversely affects a range of abilities. Studies show that cognitive function declines before, during, and for several days after an attack.¹⁵ Migraine affects adolescents in terms of concentration during classes, school attendance, and their ability to undertake extracurricular activities. The more days that are lost to illness, the more difficult it is for adolescents to return to school because of the pressure of keeping up with academic work and isolation from peer groups. Migraine during adolescence may affect interpersonal development by restricting participation in sports, work, recreation, and family activities.¹⁶

1.4 Valuation of Socioeconomic Burden

The indirect costs associated with productivity loss and impact on migraineurs' quality of life are difficult to quantify.^{17,18} Two approaches to estimating productivity loss due to illness are the human capital approach (HCA) and the friction-cost approach (FCA).

The HCA has been used in most cost-effectiveness publications. In this approach, lost productivity is equated to expected or potential earnings lost because of illness. This approach captures absenteeism, but excludes costs associated with any decreased productivity in individuals with migraine who report to work.¹⁹ Michel found that there were higher absentee rates for migraineurs than for members of a comparison group, but noted that these were due to other health problems, not migraines.²⁰ His explanation was that migraineurs avoided taking sick leave during the days with headache.

The FCA estimates productivity loss by incorporating the cost associated with the hiring, replacing, and training of new employees, initial low levels of productivity from new employees,

and productivity output loss before a replacement is hired.²¹ This approach may be inapplicable for migraineurs because migraine is a short-term condition. The FCA does not account for the reduced productivity of a person with migraine symptoms who reports to work.

Measuring reduced productivity at work is one of the more difficult aspects of assessing the costs that are associated with migraine. Reduced productivity is measured using four methods:

- patients' estimates of the number of workdays during which migraine symptoms were present in the previous month multiplied by the self-assessed level of performance affected by migraine²²
- patients' estimates of the number of hours worked while experiencing migraine symptoms each time a migraine attack occurred multiplied by the number of attacks per month and by the self-assessed level of performance affected by migraine²²
- patients' estimates of additional hours that they should have worked in the past two weeks to make up productivity losses on days when they attended work despite experiencing migraine¹⁴
- patients' estimates of the portion of the day worked (either a full or half day) multiplied by the self-assessed percentage of reduced effectiveness (the method used in a prospective design).²³

Lofland *et al.*²¹ estimated the productivity loss related to migraine treatment with sumatriptan, using HCA and FCA. The authors concluded that, depending on the approach and method of valuing productivity loss, the results may vary.

1.5 Acute Migraine Therapies

Acute migraine is treated using analgesics (acetaminophen), non-steroidal anti-inflammatory agents (acetylsalicylic acid, ibuprofen), ergot derivatives (dihydroergotamine mesylate, ergotamine), and triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, frovatriptan). The choice of which drug to use depends on the severity of the attack, the drug's potential effectiveness, and the patient's tolerance. Over-the-counter analgesics and non-steroidal anti-inflammatory agents are usually the mainstay treatment for mild to moderate migraine headache.²⁴

Ergotamine derivatives, the only specific therapy for acute migraine for almost a century,²⁵ are of limited use because of associated adverse events (AEs). Triptans are the first-line therapy for acute migraine.

Triptans are a class of selective 5-hydroxytryptamine serotonin receptor agonists (5-HT_{1B/1D}). Migraine causes a disturbance of 5-hydroxytryptamine systems, and triptans act on 5-HT_{1B/1D} receptors to relieve migraine by constricting dilated cranial blood vessels and selectively inhibiting neurogenic inflammation.²⁶ Clinical studies that were conducted in the past decade indicate that triptans are efficacious and well tolerated in the treatment of acute migraine.²⁷

The number of triptan products available in Canada continues to grow. As of April 2006, six triptans (i.e., almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) were being funded or evaluated for funding by Canadian provincial drug plans. A generic version of sumatriptan was recently commercialized. The current listing status of these pharmaceuticals in Canadian publicly funded drug plans varies. An evidence-based assessment of the comparative clinical effectiveness and cost-effectiveness of triptans can inform consistent listing policies across medical jurisdictions.

This review analyzes existing clinical studies and economic evaluations, with a focus on two research questions. The clinical review consists of two parts. The first part evaluates triptan use in adults by summarizing and assessing the Drug Effectiveness Review Project (DERP) report published by the Oregon Evidence-based Practice Center. The second part provides a systematic review of clinical trials on migraine treatment using triptans in an adolescent population.

2 RESEARCH QUESTIONS

1. What is the evidence of comparative clinical effectiveness of available serotonin (5-HT₁) receptor agonists (triptans) (i.e., almotriptan, eletriptan, naratriptan, sumatriptan succinate/hemisulfate, rizatriptan, and zolmitriptan) in patients with acute migraine?

- a) What is the comparative effectiveness in adult patients?
- b) What is the comparative effectiveness in adolescent patients?
- c) What is the evidence of the clinical advantage of sumatriptan succinate over placebo in adult and adolescent patients?

Sumatriptan succinate has a less costly generic form, thus question 1c is of importance regarding policy.

2. What is the evidence of comparative cost-effectiveness of the available triptans in adult and adolescent patients with acute migraine?

3 METHOD

3.1 Clinical Review of Triptans in Adult Population

3.1.1 Assessment of DERP report

A systematic review report by the Oregon Evidence-based Practice Center was chosen for evaluation of the comparative clinical effectiveness of available triptans in adult patients with acute migraine. The DERP systematic review was selected based on consensus from the project team in discussion with the originator of the request for study. LM and KC extracted efficacy and safety data from the DERP systematic review using a data extraction and quality assessment form created a priori (Appendix 1). The methodological quality of the DERP report was assessed based on the Oxman-Guyatt assessment tool for systematic reviews, after its use was piloted on three reviews chosen by an independent source. The findings and limitations of the report were synthesized qualitatively.

3.2 Clinical Review of Triptans in Adolescent Population

3.2.1 Literature search

Published literature was obtained by cross-searching BIOSIS Previews[®], EMBASE[®], and MEDLINE[®] databases on the OVID[®] search system. Regular alerts were established on BIOSIS, EMBASE, and MEDLINE, and information retrieved through alerts is current to October 3, 2006. Parallel searches were performed

on PubMed and the Cochrane Library (Issue 3, 2006) databases. Language and publication date limits were not applied. Filters were applied to limit the retrieval to systematic reviews, clinical studies, and clinical practice guidelines. The retrieval of systematic reviews and clinical studies was limited to those focusing on the adolescent population only.

The web sites of regulatory agencies, and health technology assessment and related agencies were searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. The Google™ search engine was used to search for Internet information. These searches were supplemented by hand searches of the bibliographies of selected papers. A description of the literature search appears in Appendix 5.

3.2.2 Selection criteria and methods

KC and SM independently reviewed the citations retrieved from the literature search and applied the eligibility criteria established a priori (Appendix 6). The decision to order an article was based on the title and abstract, when available. In cases of insufficient information to make an informed decision on inclusion, the article was ordered. A study was included for review according to the following criteria:

Population

adolescents (13 to 18 years old) with acute migraine (with or without aura) or cluster headache

Intervention

- almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, or zolmitriptan versus each other or placebo
- sumatriptan versus placebo

Study Design

- randomized controlled trials (RCTs) (efficacy and AEs)
- observational studies (AEs)

Outcome Measures (any of)

- short term (reduction or resolution of symptoms such as pain, nausea, vomiting, photophobia, phonophobia; duration of improvement, proportion of headaches successfully treated per patient; functional outcome; quality of life)

- long term (consistency, patient satisfaction, academic or workplace productivity)
- AEs

3.2.3 Data extraction and quality assessment

LM and KC independently reviewed the full text of articles retrieved from the literature search and applied the eligibility criteria for the inclusion of relevant articles. Discrepancies were resolved by consensus. They extracted clinical efficacy and safety data from the clinical trials using data extraction and quality assessment forms created a priori (Appendix 7). The quality of clinical trials was based on randomization, concealment of randomization, degree of blinding, use of intention-to-treat analysis, description of dropouts and withdrawals, and allocation concealment. The validated Jadad instrument that assesses randomization, blinding, withdrawals, and dropouts was used to score the study quality from low (0 to 2) to high (3 to 5) (Appendix 7).

3.2.4 Data analysis and synthesis

The characteristics and quality of clinical trials, patient characteristics, measures of efficacy, and AEs were synthesized qualitatively. Data extracted from RCTs were pooled for meta-analyses when there was >1 trial and it was appropriate to pool data, otherwise, results were tabulated. Cochrane Review Manager 4.2 software was used to compute statistics and generate forest plots comparing outcomes between triptan versus placebo recipients. Dichotomous data were reported as relative risk (RR) and risk difference (RD). The I^2 statistic was used to measure heterogeneity (25% low, 50% moderate, 75% high). A random effects model was used to pool studies to calculate an estimate of effect. The number needed to treat (NNT), the number needed to harm (NNH), and 95% confidence intervals (CIs) were calculated using the Visual Rx 2.0 NNT Calculator at <http://www.nntonline.net>.

3.3 Economic Review

3.3.1 Literature search

Published literature was obtained by cross-searching BIOSIS Previews®, EMBASE®, and MEDLINE® databases on the OVID search system. Regular alerts were established on BIOSIS,

EMBASE, and MEDLINE. Information retrieved via alerts is current to October 3, 2006. Parallel searches were performed on PubMed and the Cochrane Library (Issue 3, 2006) databases. Supplementary searches were conducted on the incidence and prevalence of migraine with the focus on Canada. Language and publication date limits were not applied. Filters were applied to limit the retrieval to economic studies.

The web sites of regulatory agencies, and health technology assessment and related agencies were searched, as were specialized databases such as those of the University of York Centre for Reviews and Dissemination. The Google™ Internet search engine was used to search for information. These searches were supplemented by hand searches of the bibliographies of selected papers.

3.3.2 Selection criteria

Two reviewers (SM and KG) independently reviewed the citations and abstracts, and applied the selection criteria (Appendix 13). If the citation title or abstract met all criteria, or if there was uncertainty or disagreement, the article was obtained in full text. SM and KG independently applied selection criteria to the articles obtained in full text, to make the final selection of the relevant articles to be included in the review. Disagreements were resolved through consensus and a third party.

Population

- adults and adolescents with acute migraine (with or without aura) or cluster headache.

Intervention

- triptans (almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, or zolmitriptan) versus each other.

Study Design

- full economic evaluation such as cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-minimization analysis, or cost-consequence analysis.

Outcome

- cost per quality-adjusted life years and costs associated with intermediate health outcomes such as reduction or resolution of symptoms from severe or moderate to mild or none; pain free (PF) status; health care resources use; duration of improvement; functional

outcomes; patient satisfaction; productivity loss; AEs; or rescue medication.

3.3.3 Quality assessment

The quality and perspective of each cost-effectiveness study were critically examined to determine the studies that used appropriate methods and produced valid results that apply to Canadian settings.

4 CLINICAL REVIEW OF TRIPTANS IN ADULT POPULATION

4.1 Research Question

What is the evidence of comparative clinical effectiveness of available triptans in adult patients with acute migraine?

4.2 Findings

The Oregon Evidence-based Practice Center conducted a systematic drug class review to study the comparative effectiveness of oral almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan for the treatment of acute migraine in adults.²⁸ To address research question 1a, the DERP systematic review was selected for evaluation and synthesis based on consensus by the project team in discussion with the originator of the request for study. CADTH assessed the quality of this report to identify its strengths and weaknesses.

4.2.1 DERP objectives

The following objectives guided the DERP review:

- What are the comparative effectiveness and duration of response of different oral triptans in reducing the severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?
- What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely affect compliance) of different triptans in adult patients being treated for migraine?
- Are there subgroups of patients based on demographics, other medications, or

comorbidities for which one medication or preparation is more effective or associated with fewer AEs?

A synopsis of the methods used by DERP to fulfil these objectives can be found in Appendix 3.

4.2.2 Summary of DERP results

Results from the DERP report are summarized in Tables 1 and 2, and detailed in Appendix 4.

a) Cluster Headache

DERP also reviewed the evidence on the efficacy of triptans for cluster headaches. Randomized trials evaluated sumatriptan (subcutaneous, oral, and nasal spray) and zolmitriptan tablets in the treatment of cluster headaches. Two double-blind crossover trials found that sumatriptan (subcutaneous) reduced the duration of cluster headaches. Between 50% to 75% of sumatriptan recipients experienced relief within 15 minutes of dosing, versus 26% to 35% of placebo recipients. Nasal sumatriptan 20 mg reduced time to relief in a placebo-controlled, double-blind, two-attack study (12.4 minutes versus 17.6 minutes, $p=0.01$). Evidence from two uncontrolled studies of subcutaneous sumatriptan 6 mg showed that patients continued to obtain relief from cluster headaches with repeated use over two years. According to one double-blind, randomized, crossover study, zolmitriptan 10 mg or 5 mg provided greater pain relief than placebo.²⁸

b) Active-controlled trials

Three trials with similar patient populations, comparator drugs, and outcomes reported were used to conduct indirect comparisons of triptans. Across the trials, eletriptan 40 mg (54% versus 33%, $p<0.01$); rizatriptan 10 mg (75.9% versus 47.3%, $p<0.001$); and sumatriptan 100 mg (66% versus 48%, $p<0.001$) were all superior to ergotamine 2 mg with caffeine 200 mg in rates of patients who experienced pain relief after two hours.²⁸

c) Function, Work, Productivity, and Quality of Life

Eighteen fair quality, placebo-controlled studies of subcutaneous sumatriptan reported functional capacity, work, productivity, and quality of life outcomes. Subcutaneous sumatriptan consistently reduced time to return to work, clinical disability, and time to emergency room discharge; and improved quality of life. Eletriptan (40 mg) also reduced total time loss (four hours versus nine hours, p not reported) and work time loss (2.5 hours versus four hours, $p=0.013$) in one placebo-controlled trial. In a placebo-controlled trial, rizatriptan (10 mg) improved quality of life as measured by the validated 24-hour Migraine Quality of Life Questionnaire. A four-attack, placebo-controlled, double-blind RCT demonstrated reductions in self-reported work and productivity loss among oral rizatriptan recipients.²⁸

Table 1: DERP Comparison of Triptan Efficacy

Drug and Dose	Number of Studies: 2-hour Pain Relief	Overall % of Patients with 2-hour Pain Relief (95% CI)	Number of Studies: 2-hour Freedom from Pain	Overall % of Patients Pain Free at 2 Hours (95% CI)
sumatriptan 50 mg	7	60.1 (54.7, 65.3)	6	27.5 (22.4, 33.4)
sumatriptan 100 mg	17	58.9 (56.5, 61.2)	9	28.7 (24.4, 33.3)
almotriptan 12.5 mg	4	60.4 (55.4, 65.3)	4	29.7 (19.5, 42.3)
rizatriptan 10 mg	8	66.2 (60.0, 71.8)	8	39.8 (36.2, 43.4)
naratriptan 2.5 mg	4	47.6 (43.4, 51.8)	2	19.3 (15.8, 23.4)
zolmitriptan 2.5 mg	5	63.5 (60.7, 66.3)	4	29.2 (24.2, 34.9)
eletriptan 40 mg	8	62.1 (60.0, 65.2)	8	31.8 (29.4, 34.3)
eletriptan 80 mg	6	68.0 (62.8, 72.8)	6	40.6 (31.4, 50.7)

Table 2: DERP Findings

Drug, Dosage, and Form	Level of Evidence According to DERP report*	DERP Conclusion
Question 1: What are comparative effectiveness and duration of response of oral triptans in reducing severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?		
RIZ 10 mg versus SUM 100 mg oral	fair (1 trial)	RIZ 10 mg superior to SUM 100 mg in: 1-h pain relief (NNT=12); 1-h normal function (NNT=21); 2-h PF (NNT=15); 2-h normal function (NNT=12); 2-h nausea free (NNT=13); return to normal function 42% RIZ versus 33% SUM, p=0.015; evidence insufficient to judge overall balance of advantages and disadvantages of RIZ versus SUM
RIZ 10 mg versus NAR 2.5 mg oral	fair (1 trial)	RIZ 10 mg superior to NAR 2.5 mg in: 1-h pain relief (NNT=10); 1-h PF (NNT=17); 2-h pain relief (NNT=6); 2-h PF (NNT=5); 2-h photophobia-free (NNT=9); 2-h phonophobia-free (NNT=9); 24-h sustained relief (NNT=9); mean satisfaction score 3.55 RIZ versus 4.2 NAR, p<0.001 (using 7-point scale, where 1=completely satisfied and 7=completely dissatisfied); return to normal function 39.3% RIZ versus 22.6% NAR, p<0.001
ZOL 5 mg versus SUM 100 mg oral	fair (3 trials)	fair quality evidence of no differences in efficacy
NAR 2.5 mg versus SUM 100 mg oral	fair (1 trial)	NAR 2.5 mg and SUM 100 mg provide similar 1-h, 2-h, and 24-h sustained pain relief; SUM 100 mg superior to NAR 2.5 mg (NNT=7) for 4-h pain relief; no difference in patient satisfaction
ELE versus other triptans oral	fair (5 trials)	evidence from 5 head-to-head trials insufficient to make conclusion about comparative efficacy of ELE and encapsulated SUM, NAR, and ZOL because of effects associated with unilateral encapsulation
rapid release SUM oral	poor (2 trials)	indirect comparisons of placebo-controlled trials suggest reformulated SUM equivalent in efficacy to conventional SUM 100 mg and other triptans
ALM Oral	fair (2 trials)	2 head-to-head trials had poor internal validity, not analyzed in DERP review
Question 2: What are comparative incidence and nature of complications (serious or life-threatening, or those that may adversely affect compliance) of triptans in adult patients being treated for migraine?		
ELE, NAR, RIZ, SUM and ZOL oral	good (13 trials)	good evidence from 13 head-to-head trials suggests no difference in chest pain or tightness, and central nervous system effects for these triptans
ALM oral	poor (2 trials)	2 head-to-head trials with poor internal validity not analyzed in DERP review
SUM subcutaneous and disintegrating tablet	fair, subcutaneous (20 trials); poor, tablet (2 trials)	subcutaneous SUM 6 mg associated with more chest pain than oral ELE 80 mg
Question 3: Are there subgroups of patients based on demographics, other medications, or comorbidities for which one medication or preparation is more effective or associated with fewer AEs?		
all triptans	poor	no evidence any ethnic or racial group has higher risk of AEs from triptans or 1 triptan has advantage over others

h=hour; NNT=number needed to treat; RIZ=rizatriptan; NAR=naratriptan; SUM=sumatriptan; ELE=eletriptan; ZOL=zolmitriptan; ALM=almotriptan; AEs=adverse events; *All studies or systematic reviews included for assessment in DERP report assessed for quality and assigned rating of "good," "fair," or "poor." Studies having fatal flaw in ≥1 criteria rated poor quality; studies that met all criteria rated good quality; remainder rated fair quality based on criteria in Appendix B of DERP report.²⁸

4.3 Assessment of DERP Review

After applying the Oxman-Guyatt tool, two CADTH reviewers scored the DERP review as having minor flaws, a score of five (on a scale of one to seven; one=extensive flaws to seven=minimal flaws). Inclusion criteria were well defined, and the criteria for assessing internal validity were applied to all included studies. The methods used to combine findings were reported, and the reviewers' conclusions were supported by the data. Other aspects of quality were partially fulfilled, and the possibility of selection bias is prevalent (Appendix 2).

It is unclear if clinicians were involved in designing the literature search to ensure that all relevant materials were retrieved. Searching of the electronic databases seemed to be comprehensive. It is unclear if EMBASE, an electronic database that captures a wide scope of international journals, was searched. Searching MEDLINE but not EMBASE risks the introduction of bias by finding studies that show larger estimates of effect.²⁹ The literature search and retrieval conducted for the DERP systematic review lacked a comprehensive search of the grey literature and was limited to studies published in the English language, both of which can lead to an overestimation of the intervention's effectiveness.

Attempts should be made to identify all grey and published literature. Many studies published in technical reports may be indexed on databases such as the System for Information on Grey Literature, the National Technical Information Service, and the British National Bibliography for Report Literature. Dissertations and theses can be found in databases such as Dissertation Abstracts and CINAHL (Cumulative Index to Nursing and Allied Health Literature). Conference proceedings may be found through the Index of Scientific and Technical Proceedings and the Conference Papers Index.

There is potential for bias in the selection of studies for inclusion in the review. While selection criteria and exclusion criteria were stated, it is unclear whether these criteria were established a priori. There is no indication regarding the number of reviewers involved in applying the selection criteria or the degree of agreement between reviewers. There are discrepancies in the number

and type of included publications in the text versus the flowchart of included studies in the appendix.

The DERP report used strict inclusion criteria for migraine based on the International Headache Society's criteria. Only triptan-naïve patients without comorbid disease, run-in pre-randomization periods, drug switching, or early drug treatment, were studied. These restrictions do not mirror clinical practice, where there is drug switching, and early treatment is encouraged.

There is a potential for bias in the abstraction of data from eligible studies. While one reviewer abstracted data from included head-to-head trials, and a second reviewer verified the data in the tables, data from active-control trials were abstracted by one reviewer only. The potential for error is theoretically greater with single data extraction than

double data extraction. The lack of data extraction forms and varied terminology used to describe outcomes made this review difficult to replicate.

There were discrepancies in the reporting of the number of systematic reviews identified and whether they contained a meta-analysis. While the DERP evaluation reported the limitations of the two reviews that pooled the results of studies comparing triptan with placebo, rather than direct comparison studies, the DERP review did not discuss the results of another publication that summarized 24-hour response rates in text.

There were discrepancies in the reporting of the number of randomized and observational studies in the text compared with the flowchart of studies. Two placebo-controlled trials suggested that patients taking fast-disintegrating, rapid-release formulations of sumatriptan experienced faster pain relief than those taking placebo. The DERP report concluded that reformulated sumatriptan is likely to be at least equivalent to conventional sumatriptan and other triptans. This could only be determined in head-to-head trials.

4.4 Summary of DERP Review

The DERP review, with minor flaws, suggests that while several head-to-head trials of triptans have been conducted in adults, few have been published in peer-reviewed journals. Few of the head-to-head

trials are of fair or better quality, and few examine 24-hour sustained relief or long-term consistency.

The DERP review suggests:

- Evidence is insufficient to judge the overall balance of advantages and disadvantages of rizatriptan versus sumatriptan, because head-to-head trials do not examine outcomes such as 24-hour sustained relief and long-term consistency. Fair evidence from one trial suggests that rizatriptan 10 mg is superior to sumatriptan 100 mg in relieving headache pain, nausea, and resuming normal function at two hours.
- Rizatriptan 10 mg is superior to naratriptan 2.5 mg in relieving headache pain, photophobia, and phonophobia at two hours; and providing sustained 24-hour relief.
- Sumatriptan 100 mg is superior to naratriptan 2.5 mg in relieving headache pain at four hours.
- Subcutaneous sumatriptan 6 mg reduces the duration of cluster headaches with continued relief after two years of use.

No differences were found in chest pain or tightness, or central nervous system effects among eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan.

5 CLINICAL REVIEW OF TRIPTANS IN ADOLESCENT POPULATION

5.1 Research Question

What is the evidence of comparative clinical effectiveness of available serotonin (5-HT₁) receptor agonists (triptans) in adolescent patients with acute migraine?

5.2 Findings

To answer research question 1b, CADTH conducted a systematic review and meta-analysis.

No head-to-head trials were identified. Eight RCTs were identified, all comparing a triptan with an identical placebo.^{9,16,30-35}

5.2.1 Quantity of evidence

The electronic literature search yielded 430 citations; 422 were excluded based on inappropriate study design, population, intervention, or outcome measure. Eight clinical trials were chosen for study (Figure 1).

5.2.2 Trial characteristics

Eight industry-sponsored RCTs were reported as five peer-reviewed publications,^{9,16,30-32} two abstracts,^{33,34} and a poster,³⁵ all comparing a triptan with an identical placebo. No head-to-head trials were identified. Of the eight trials, placebo was compared with oral naratriptan (one trial),³³ oral zolmitriptan (one trial),³⁰ oral rizatriptan (two trials),^{9,31} sumatriptan nasal spray (two trials),^{16,32} oral sumatriptan (one trial),³⁴ and oral eletriptan (one trial).³⁵ All the RCTs were multicentre (ranging from 20 to 65) studies conducted in outpatient settings in the US to treat one migraine attack. Except in one study where conflict of interest was not reported,³⁰ study investigators were funded by the manufacturer.

A description of trials is shown in Table 3. Overall quality scores ranged from one to five (mean=2.4) using the Jadad quality scale for RCTs. Withdrawals and dropouts were described in one trial,¹⁶ partially described in another,³² and not reported or not described in the remaining six studies.^{9,30,31,33-35} No trials reported how many patients were eligible for study. While all trials reported eligibility criteria for study, none reported how patients were selected. Randomization was stratified by age in two studies,^{9,31} computer generated by the sponsoring company in two studies,^{30,32} computer generated block randomized in another study,¹⁶ and not reported in the remaining three trials. Trials did not report how patients were sampled, or their method of sampling was unclear. While all trials were reported as being double-blinded, two used appropriate methods of blinding, and none reported encapsulation.^{16,32}

5.2.3 Data Analysis and Synthesis

A description of patient characteristics is presented in Appendix 8. Between 350 and 850 adolescent migraineurs were randomized to receive a triptan or placebo for the treatment of a moderate to severe migraine attack, with as many as two to four recurrences. Participants were diagnosed with

migraine based on the International Headache Society's criteria for migraine (with or without aura). Patients treated their attack at home and recorded responses in terms of headache relief, freedom from pain, need for rescue medication, and functional abilities. Patients were predominantly Caucasian females (50% to 60%) with a mean age of 14 years. Previous triptan use was reported in three of eight trials.^{16,32,35}

a) **Clinical Outcomes**

Clinical efficacy measures and AEs for each study appear in Appendix 9. Meta-analysis was only possible for rizatriptan versus placebo and sumatriptan versus placebo.

The efficacy outcomes from two trials of rizatriptan versus placebo, reporting two-hour pain relief and freedom from pain at two hours, were pooled and reported as relative risk of response with 95% CI (Figures 2 and 3). While there are limitations to pooling these two low quality studies, no statistically significant difference between groups was noted for either outcome.

The efficacy outcomes from two trials of sumatriptan nasal spray versus placebo, reporting two-hour pain relief and freedom from pain at two hours, were pooled and reported as relative risk of response with 95% CI (Figures 4 and 5). A significant difference, favouring sumatriptan, was noted for both outcomes. The relative and absolute risks of achieving headache relief at two hours were 1.18 (95% CI: 1.05, 1.33) and 0.10 (95% CI: 0.03, 0.17) respectively (Table 4). The relative and absolute risks of achieving freedom from pain at two hours were 1.38 (95% CI: 1.12, 1.70) and 0.11 (95% CI: 0.04, 0.18) respectively. For two-hour relief, sumatriptan recipients were 18% more likely to achieve headache relief with a NNT of 10 (95% CI: 6, 36). Sumatriptan recipients were 38% more likely to achieve freedom from pain at two hours, with a NNT of 10 (95% CI: 6, 30). It was impossible to calculate NNT in studies where there were insufficient data or no significant difference between groups. While the studies pooled were of moderate quality, there are limitations to pooling so few studies.

b) **AEs**

AEs are listed in Appendix 11. The most common AEs across all groups were nausea and vomiting.

Other events frequently reported included dizziness, somnolence, and asthenia. Chest tightness was reported by 6.7% of zolmitriptan recipients. Sumatriptan nasal spray resulted in taste disturbances.

Pooling of AE data showed that while sumatriptan recipients showed significant improvement in headache pain, they were three times more likely to experience nausea, vomiting, and taste disturbances than placebo recipients. Relative and absolute risks of experiencing an adverse event were 3.02 (95% CI: 1.70, 5.39) and 0.24 (0.19, 0.30) respectively (Figure 6, Table 4).

The I^2 value of 70.5% indicates considerable heterogeneity, possibly due to combining three diverse events, as I^2 values for efficacy measures were both 0%. The results were significant in favour of placebo. Overall, 36% of sumatriptan recipients and 11% of placebo recipients experienced a mild AE. The results suggest that under similar conditions, for every five patients treated, an additional patient will experience nausea, vomiting, or taste disturbance [NNH 5, (95% CI: 3, 13)].

5.3 Summary

- No head-to-head trials evaluating the use of triptans in adolescent migraineurs or cluster headache sufferers were identified. Eight RCTs were identified, all comparing a triptan with an identical placebo in adolescent migraineurs. It was not possible to determine the comparative effectiveness of triptans in adolescents, because no head-to-head comparison trials were found.
- While there are limitations to pooling two studies of moderate quality, adolescent sumatriptan nasal spray 20 mg recipients were 18% more likely to achieve headache relief and 38% more likely to experience freedom from pain two hours after dosing than those receiving an identical placebo. Migraineurs receiving sumatriptan nasal spray were three times more likely to experience nausea, vomiting, or taste disturbance than placebo recipients.

The results of the clinical trials comparing triptans versus placebo in the adolescent population appear in Table 5.

Figure 1: Selected studies for clinical review

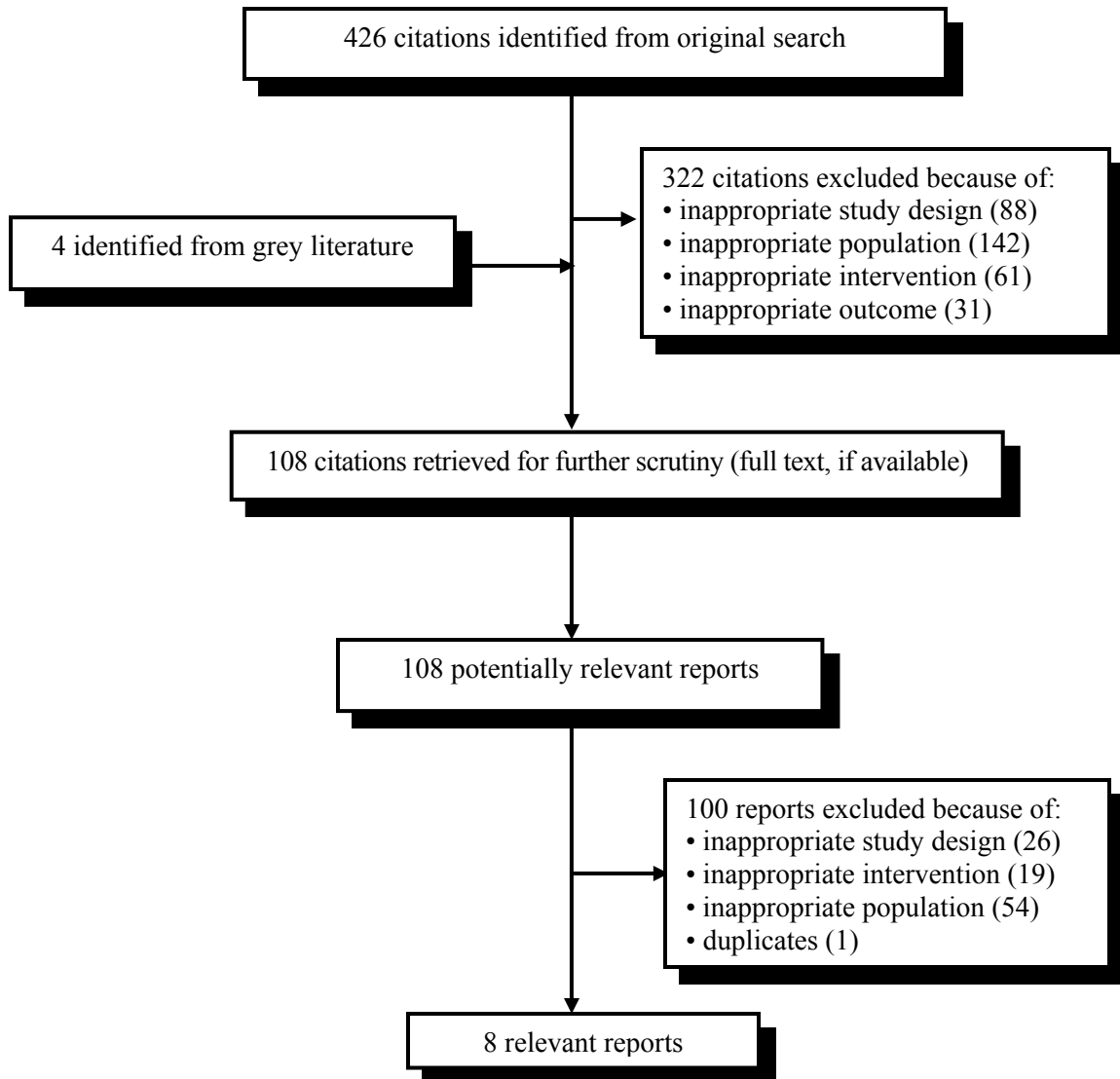


Table 3: Description of Clinical Trials

Author	Format	Triptan	Dosage	Form	Comparator	Jadad Score
Rothner ³³	A	naratriptan	0.25 mg, 1.0 mg, 2.5 mg	oral	placebo	2
Rothner ³⁰	F	zolmitriptan	2.5 mg, 5 mg, 10 mg	oral	placebo	2
Visser ³¹	F	rizatriptan	5 mg	oral	placebo	2
Winner ⁹	F	rizatriptan	5 mg	oral	placebo	2
Winner ¹⁶	F	sumatriptan	5 mg, 10 mg, 20 mg	nasal spray	identical placebo	5
Winner ³²	F	sumatriptan	5 mg, 20 mg	nasal spray	identical placebo	3
Winner ³⁴	A	sumatriptan	25 mg, 50 mg, 100 mg	oral	placebo	2
Winner ³⁵	P	eletriptan	40 mg	oral	placebo	1

A=conference abstract; F=full-length publication; P=poster presentation.

Table 4: Clinical Relevance of Sumatriptan Nasal Spray 20 mg versus placebo in adolescent population

Outcome	Rate in Placebo Group	Rate in Sumatriptan Group	Relative Risk (95% CI)	Risk Difference (95% CI)
2-hour relief	209 of 374 (56%)	234 of 354 (66%)	1.18 (1.05, 1.33)	0.10 (0.03, 0.17)
2-hour PF	106 of 374 (28%)	139 of 354 (39%)	1.38 (1.12, 1.70)	0.11 (0.04, 0.18)
Adverse events	126/354 (36%)	43/374 (11%)	3.02 (1.70, 5.39)	0.24 (0.19, 0.30)

Table 5: Quality Assessment and Clinical Trial Results

Triptan Dosage, and Form versus Placebo	Jadad Score, (number of trials, publication type)	Conclusion
naratriptan 0.25 mg, 1.0 mg, 2.5 mg, oral	score=2 (1 trial, abstract)	no statistically significant differences in efficacy outcomes between naratriptan and placebo recipients; percentages of patients reporting ≥ 1 AEs higher in naratriptan recipients compared with placebo ³³
zolmitriptan 2.5 mg, 5 mg, 10 mg, oral	score=2 (1 trial, full publication)	no statistically significant differences in efficacy outcomes between zolmitriptan and placebo ³⁰
rizatriptan 5 mg, oral	mean score=2 (2 trials, 2 full publications)	no statistically significant difference noted between groups when measures of efficacy pooled ^{9,31}
sumatriptan 5 mg, 10 mg, 20 mg, nasal spray	mean score=4 (2 trials, 2 full publications)	statistically significant differences noted in favour of sumatriptan; for 2-hour relief, sumatriptan recipients 18% more likely to achieve headache relief; sumatriptan recipients 38% more likely to achieve freedom from pain at 2 hours; ^{16,32} sumatriptan recipients 3 times more likely to experience nausea, vomiting, and taste disturbance than placebo recipients
sumatriptan 25 mg, 50 mg, 100 mg, oral	score=2 (1 trial, abstract)	sumatriptan tablets 25 mg, 50 mg, and 100 mg similarly effective in acute treatment of migraine in adolescent patients; no clinically meaningful benefit to increasing dose in this population ³⁴
eletriptan 40 mg, oral	score=1 (1 trial, poster)	high placebo response observed; high response seen for eletriptan; eletriptan 40 mg showed significant advantage compared with placebo in reducing headache recurrence and rescue medication use; in post-hoc analysis, eletriptan 40 mg significantly improved sustained headache response and sustained pain-free (SPF) response rates ³⁵

Figure 2: Rizatriptan versus placebo – two-hour headache relief

Review: Triptans for Acute Migraine in Adolescents
 Comparison: 01 Rizatriptan versus Placebo
 Outcome: 01 Rizatriptan (5 mg) versus Placebo-2 hour relief

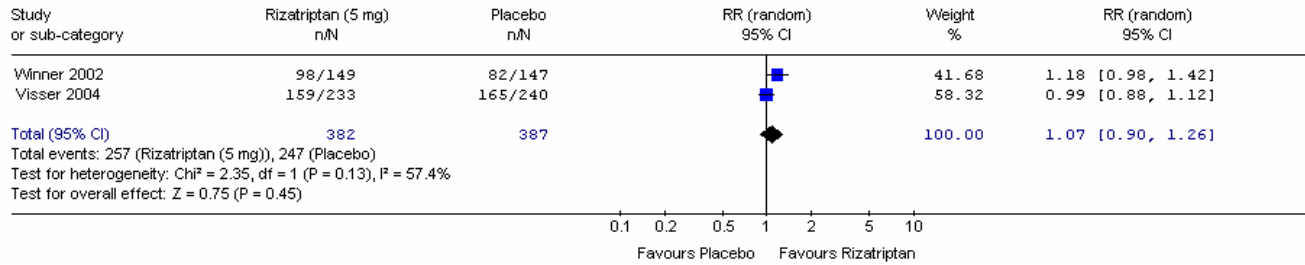


Figure 3: Rizatriptan versus placebo – freedom from pain at two hours

Review: Triptans for Acute Migraine in Adolescents
 Comparison: 01 Rizatriptan versus Placebo
 Outcome: 02 Rizatriptan (5 mg) versus Placebo-2 hour pain-free

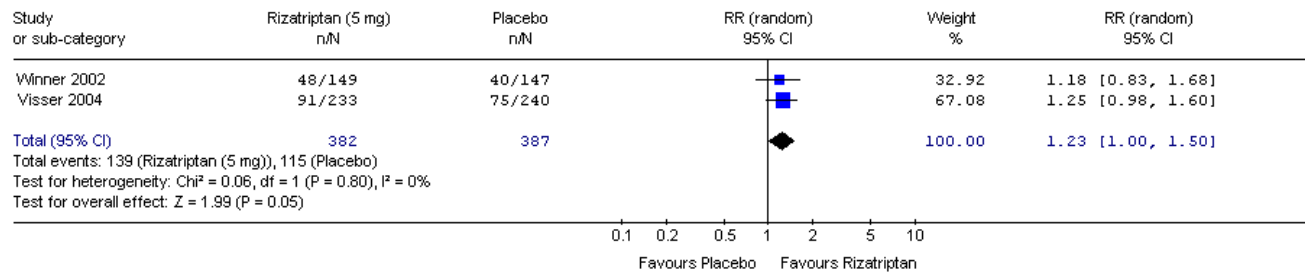


Figure 4: Sumatriptan (nasal spray) versus placebo – two-hour pain relief

Review: Triptans for Acute Migraine in Adolescents
 Comparison: 03 Sumatriptan (20mg nasal) versus Placebo
 Outcome: 01 Sumatriptan (20 mg nasal) versus Placebo-2 hour Relief

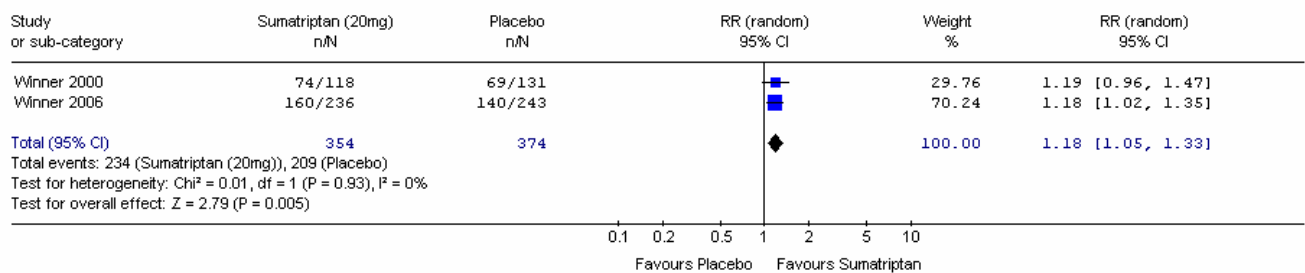


Figure 5: Sumatriptan (nasal spray) versus placebo – freedom from pain at two hours

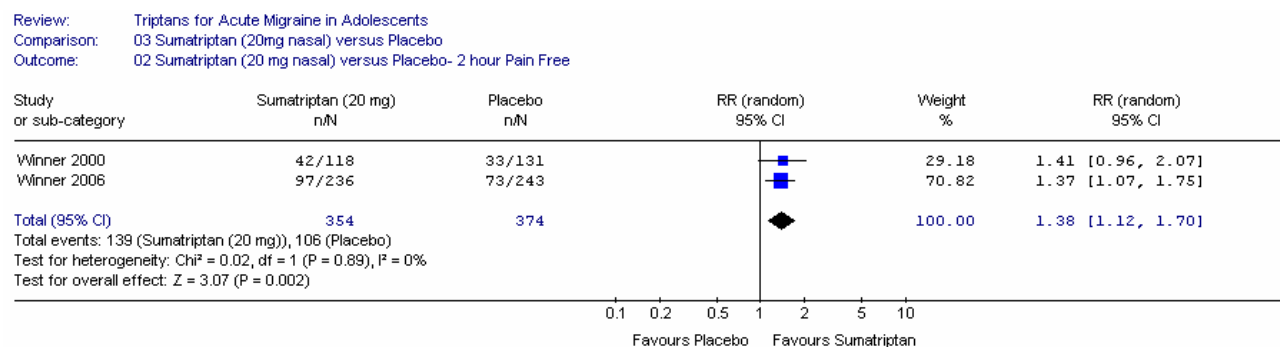
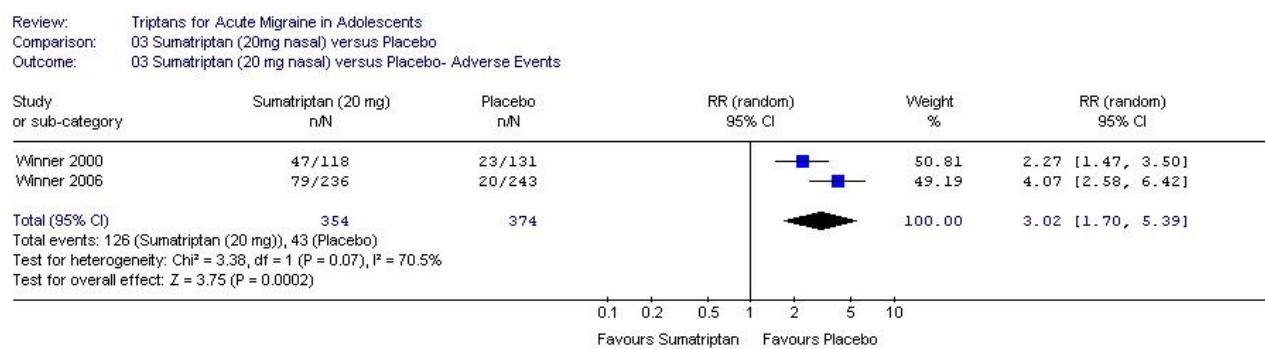


Figure 6: Sumatriptan (nasal spray) versus placebo – adverse events



6 CLINICAL REVIEW OF SUMATRIPTAN VERSUS PLACEBO IN ADULTS AND ADOLESCENTS

6.1 Research Question

What is the evidence of the clinical advantage of sumatriptan compared with placebo in adult and adolescent patients?

6.2 Findings

No head-to-head trials were identified comparing sumatriptan with its generic form in adult or adolescent migraineurs.

In the DERP report, which reviewed an adult population, two-hour pain relief was a reliable measure of consistency across six attacks in one of two head-to-head trials of zolmitriptan and

sumatriptan. Two-hour pain relief rates (49% to 67%) were consistent across nine attacks in placebo-controlled trials of sumatriptan 50 mg and 100 mg.²⁸

We performed a meta-analysis on two trials that evaluated the efficacy of sumatriptan nasal spray 5 mg, 10 mg, and 20 mg compared with identical placebo for the treatment of acute migraine in adolescents.^{16,32} The efficacy outcomes at two hours were pooled for headache relief and freedom from pain, and were reported as relative risk and absolute risk of response with 95% CIs. While there are limitations to pooling two studies of moderate and high quality, a significant difference favouring sumatriptan was noted for both measures of efficacy. The relative and absolute risks of achieving headache relief at two hours were 1.18 (95% CI: 1.05, 1.33) and 0.10 (95% CI: 0.03, 0.17) respectively. The relative and absolute risks of achieving freedom from pain at two hours were 1.38 (95% CI: 1.12, 1.70) and 0.11 (95% CI: 0.04, 0.18) respectively. For two-hour relief, sumatriptan recipients were 18% more likely to achieve

headache relief with a NNT of 10 (95% CI: 6, 36). Sumatriptan recipients were 38% more likely to achieve freedom from pain at two hours, with a NNT of 10 (95% CI: 6, 30). While sumatriptan recipients showed significant improvement in headache pain, they were three times more likely to experience nausea, vomiting, and taste disturbances than placebo recipients. Relative and absolute risks of experiencing an adverse event were 3.02 (95% CI: 1.70, 5.39) and 0.24 (0.19, 0.30) respectively. One of every five sumatriptan recipients may experience nausea, vomiting, or taste disturbance [NNH 5, (95% CI: 3, 13)].

The efficacy of oral sumatriptan 25 mg, 50 mg, and 100 mg versus placebo was evaluated in one trial involving adolescent migraineurs.³⁴ There were no statistically significant differences between groups at two hours. Significantly more sumatriptan 25 mg, 50 mg, and 100 mg recipients experienced headache relief at three hours and four hours ($p < 0.05$).³⁴ Across attacks, sumatriptan 25 mg, 50 mg, and 100 mg showed similarly significant differences from placebo in pain-free (PF) rates, clinical disability, phonophobia, photophobia, and the use of rescue medication.

6.3 Summary

- No head-to-head trials were identified comparing sumatriptan with its generic form in adult or adolescent migraineurs or cluster headache sufferers.
- Sumatriptan 50 mg and 100 mg recipients consistently experienced headache relief rates of 49% to 67% at two hours across nine attacks in placebo-controlled trials.
- Adolescent sumatriptan nasal spray 20 mg recipients were 18% more likely to achieve headache relief and 38% more likely to experience freedom from pain at two hours than patients receiving identical placebos. Adolescent sumatriptan nasal spray recipients were three times more likely to experience nausea, vomiting, and taste disturbance than placebo recipients.
- Significantly more adolescents receiving oral sumatriptan 25 mg, 50 mg, and 100 mg experienced headache relief at three hours and four hours after dosing. Similar differences were noted in clinical disability, photophobia, phonophobia, and rescue medication use.

7 ECONOMIC REVIEW

7.1 Research Question

What is the evidence of comparative cost-effectiveness of the available triptans (i.e., almotriptan, eletriptan, naratriptan, sumatriptan succinate/hemisulfate, rizatriptan, and zolmitriptan) in patients with acute migraine?

7.2 Findings

7.2.1 Quantity of research available

The electronic literature search yielded 696 citations; six additional studies were identified through grey literature and other sources; 690 were excluded because of inappropriate study design, population, intervention, or outcome measure. There are 12 economic studies relevant to this study. One was conducted in Canada,³⁶ eight were conducted in the US,³⁷⁻⁴⁴ one in the UK,⁴⁵ and two in Spain.^{46,47} We did not identify any economic study on the cost-effectiveness of triptans in the adolescent population. Also, none of the 12 economic evaluations included generic sumatriptan in the analysis (Figure 6).

7.2.2 Review of Economic Studies

Because the included studies vary in terms of effectiveness measure, methods, and cost-outcome measure, no effort was made to pool the results quantitatively. The characteristics and results of each study appear in Tables 6 and 7. The cost parameters of each economic model are examined to determine the extent to which the results can be applied in Canadian settings.

Thompson *et al.*³⁶ conducted a CEA of rizatriptan 10 mg compared with usual care or other triptans (naratriptan, sumatriptan, and zolmitriptan) from a public payer perspective [the Ontario Ministry of Health and Long-term Care (MOH<C)] and the broader societal perspective. Using clinical data from a meta-analysis performed by Ferrari *et al.*,²⁵ the authors constructed a decision analysis model to estimate the costs of treating migraine with triptans during a 24-hour period. Efficacy outcome measures consisted of PF response at two hours after therapy initiation and SPF for two to 24 hours. The loss of productivity for paid and unpaid work was calculated by multiplying the estimated

number of paid hours lost because of migraine by the national average wage and adjusting for age-specific employment rates. Productive work time lost because of migraine was assumed to be 38.6 minutes or 77.2 minutes when migraine was resolved within two or four hours, or eight hours when migraine was not resolved within four hours.

From the perspective of the Ontario MOH<C, rizatriptan 10 mg was associated with the lowest total cost per migraine attack aborted (PF at two hours) of all triptans (\$24.78 in 2002 Canadian dollars). The total costs for naratriptan, zolmitriptan, and sumatriptan were \$25.13, \$25.69, and 27.75 respectively. When compared with usual care, rizatriptan produced a cost per quality-adjusted life year (QALY) of \$31,845. From a societal perspective, which included paid and unpaid work, rizatriptan dominated other triptans with the total cost per migraine attack aborted of \$89.86. Naratriptan, zolmitriptan, and sumatriptan had total costs per migraine attack aborted of \$97.04, \$100.98, and \$106.69 respectively.

Thompson *et al.* assumed that AEs were mild and short-lived, and hence not cost generating. While the exclusion of AEs is negligible from the Ontario MOH<C's perspective, it may underestimate the overall cost of treatment from a societal perspective. Also, because eletriptan and almotriptan were excluded from the analysis, the study lacks sufficient comparative evidence across the triptans.

The cost-effectiveness of rizatriptan is also supported in a study by Zhang and Hay. The study examined the cost-effectiveness of rizatriptan 10 mg in comparison with sumatriptan 50 mg from a societal perspective for the US migraine patient cohort.⁴⁰ The authors used clinical effectiveness data (measured as two-hours PF, sustained within 24 hours) from published literature^{25,48} to develop a decision model. The cost-effectiveness ratio was expressed as incremental cost per QALY gained. Rizatriptan 10 mg was reported to produce annual net savings of US\$433.45 (in 2003 values) per patient, with an incremental QALY of 0.0001. The results of the Thompson *et al.* and Zhang and Hay studies support the findings by Adelman and Belsey,³⁷ who performed a meta-analysis and calculated NNT for each triptan except eletriptan, which was not approved by the US Food and Drug Administration when the study was conducted.

The results were presented as cost to attain PF status within two hours of initial treatment, calculated by applying per-dose costs to each NNT. Rizatriptan 10 mg and almotriptan 12.5 mg were reported to have the lowest cost-effectiveness ratios: \$48.34 and \$48.57 respectively.

Naratriptan 2.5 mg and frovatriptan 2.5 mg were associated with the highest cost-effectiveness ratios (\$141.43 and \$162.49).

Williams and Reeder compared the cost-effectiveness of almotriptan 12.5 mg and sumatriptan 50 mg and 100 mg from the health care payer's perspective.⁴² Using data from the Ferrari *et al.* meta-analysis,²⁵ and the published total direct cost of treating one migraine attack, the authors calculated the average cost-effectiveness ratios per SPF patient who experiences no adverse events (SNAE). Almotriptan 12.5 mg had the lowest average cost-effectiveness ratio (US\$82). Average cost-effectiveness ratios for sumatriptan 50 mg and 100 mg were US\$133 and US\$138 respectively. When compared with sumatriptan 50 mg, almotriptan produced an incremental cost-effectiveness ratio (ICER) of US\$12 per SNAE and US\$16 per SNAE when compared with sumatriptan 100 mg.

In another study, Williams and Reeder used a similar composite endpoint (SNAE) to compare almotriptan 12.5 mg and rizatriptan 10 mg.⁴¹ Almotriptan had a lower average cost-effectiveness ratio (US\$91.12) than rizatriptan (US\$131.26). Incremental analysis showed that almotriptan had an incremental cost of US\$6.94 per SNAE.

The cost advantage of almotriptan from the health care payer's perspective has been demonstrated by Kelman and von Seggern.⁴⁴ The authors used data from the Ferrari *et al.* meta-analysis²⁵ and the average wholesale drug prices of 2004 to compute total drug costs to attain 100 SPF patients and 100 SNAE. SPF status was defined as PF at two hours post-dosing with no recurrence of headache and no rescue medication use for two to 24 hours. Almotriptan 12.5 mg and rizatriptan 10 mg were reported to have the lowest total cost to attain 100 SPF: \$7,120 and \$7,427 respectively. Eletriptan 20 mg and naratriptan 2.5 mg were associated with the highest total cost per 100 SPF: \$16,104 and \$13,736 respectively. Almotriptan

12.5 mg was reported to have the lowest total cost per 100 SNAE (\$8,298) followed by rizatriptan 10 mg (\$12,545). Eletriptan 20 mg and 80 mg were associated with the highest total cost per 100 SNAE: \$25,521 and \$26,614 respectively.

Reeder *et al.*³⁸ compared relative cost-effectiveness among triptans by integrating the results from the meta-analysis performed by Ferrari *et al.*²⁵ with the standardized drug cost. Cost-effectiveness measures consisted of the cost to attain 100 SPF patients and the cost to attain 100 SNAEs. Almotriptan was reported to have the lowest cost-effectiveness ratios for both measures (US\$4,000 for each measure), followed by rizatriptan (US\$6,000 for SPF patients and US\$7,000 for SNAE). Naratriptan was associated with the highest cost-effectiveness ratios (US\$12,000 for each measure).

Gracia-Naya⁴⁷ used effectiveness data obtained from their meta-analysis and per unit drug prices to calculate the cost to attain a two-hour pain response, two-hour PF status, and 24-hour sustained pain-free status (SPF). Zolmitriptan 2.5 mg and sumatriptan 50 mg were associated with the lowest cost per two-hour pain response: €20.16 and €19.38 respectively. Almotriptan 12.5 mg and naratriptan 2.5 mg were reported to have the highest cost per two-hour PR: €26.58 and €27.78 respectively. Rizatriptan 10 mg had the lowest cost per two-hour PF (€23.79) followed by sumatriptan 50 mg (€30.24). Zolmitriptan 2.5 mg and naratriptan 2.5 were associated with the highest cost per two-hour PF: €34.75 and €38.20 respectively. Rizatriptan 10 mg and sumatriptan 50 mg were reported to have the lowest cost per 24-hour SPF: €33.00 and €33.60 respectively. Almotriptan 12.5 mg had the highest cost per 24-hour SPF (€54.93).

Gracia-Naya *et al.*⁴⁶ used data from their meta-analysis to perform a CEA comparing almotriptan 12.5 mg, naratriptan 2.5 mg, rizatriptan 10 mg, eletriptan 40 mg, sumatriptan 50 mg, sumatriptan 100 mg, zolmitriptan 5 mg, and zolmitriptan 2.5 mg. The study was conducted from the perspective of Spain's national health care system.

Treatment success consisted of a two-hour anti-migraine response, two-hour PF status, and 24-hour SPF. Eletriptan 40 mg was associated with the lowest cost per two-hour anti-migraine response and

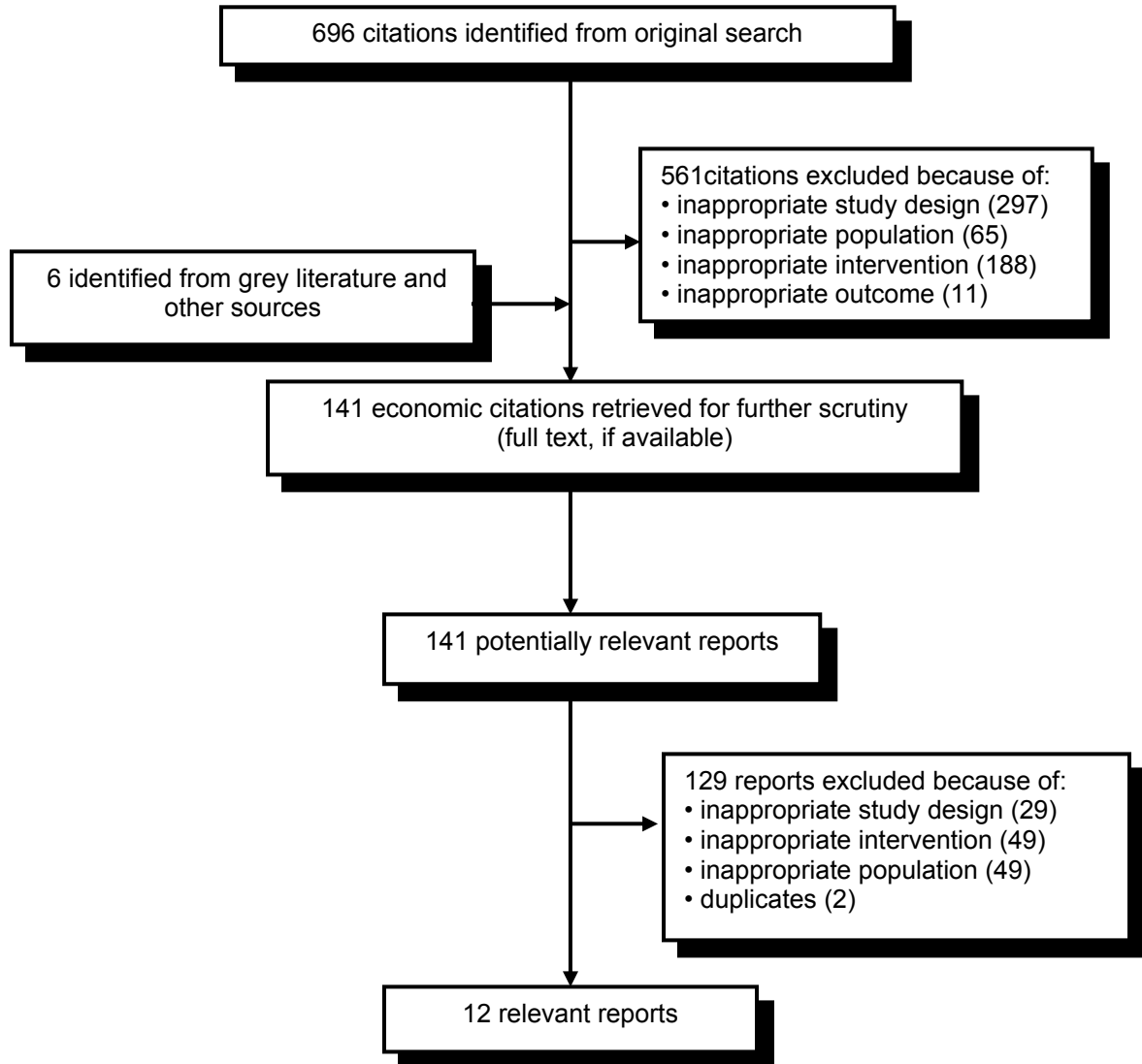
the lowest 24-hour SPF (€16,50 and €31,47 respectively), followed by sumatriptan 50 mg with a cost per two-hour anti-migraine response of €17,44 and cost per 24 hours SPF of €33,61 (in 2003 values). The lowest cost per two-hour PF status was observed for rizatriptan 10 mg (€21.36) and eletriptan 40 mg (€22.99). Sumatriptan 100 mg and zolmitriptan 5 mg were reported to have the highest cost per two-hour anti-migraine response (€37.18 and €44.40 respectively), cost per two-hour PF (€53.38 and €56.37 respectively), and cost per 24-hour SPF (€80.14 and €81.83 respectively).

Perfetto *et al.*³⁹ used clinical data from the Ferrari *et al.* meta-analysis²⁵ to compare total triptan cost to treat 100 migraine attacks and cost per successfully treated patient.³⁹ Authors defined treatment success as pain response within two hours of one dose of triptan and no headache recurrence within a 24-hour period after the initial pain response. Followed by zolmitriptan and sumatriptan, eletriptan was found to have the lowest total cost to treat 100 patients and the lowest cost to successfully treat a patient: US\$1,560 and US\$56.36 respectively. Naratriptan was reported to have the highest total cost to treat 100 patients (US\$1,945) and the highest cost to successfully treat a patient (US\$111.44).

The cost advantage of eletriptan has been demonstrated by Mullins *et al.*⁴³ The authors used a published meta-analysis²⁵ to calculate the numbers needed to successfully treat, doses needed to successfully treat, and corresponding costs for each triptan. Successful treatment was defined as two-hour pain response, sustained through a 24-hour post-dose period. Eletriptan was associated with the lowest number of doses (388) and the lowest total triptan cost (US\$5,630) to successfully treat 100 patients. Zolmitriptan and sumatriptan were associated with the second and third lowest total triptan costs respectively. Naratriptan was reported to have the highest total cost to successfully treat 100 patients (US\$11,136).

Wells *et al.* conducted a CEA comparing sumatriptan 50 mg and 100 mg with eletriptan 40 mg and 80 mg from the UK health care system's perspective.⁴⁵ The study used data from a randomized, double-blind, placebo-controlled clinical trial of oral eletriptan and oral sumatriptan.⁴⁹ Clinical outcomes consisted of two

Figure 7: Selected studies for economic review



composite measures. The first was the attainment of PF status at two hours with no recurrence within four hours of the initial dose and no rescue medication needed (PSTA I). The second was the improvement of headache in one hour, followed by achievement of pain-free status by two hours, sustained at four hours, and no recurrence in a 24-hour post-dose period (PSTA II).

Results were presented as cost-effective ratios per successfully treated attack for each outcome measure. For the first outcome measure (PSTA I), the costs in the eletriptan 40 mg and 80 mg groups were £17.55 and £31.37 respectively. For the sumatriptan 50 mg and 100 mg groups, the costs were £63.98 and £80.50 respectively. For the second outcome measure (PSTA II), the eletriptan 40 mg and 80 mg groups had costs per PSTA of £29.61 and £48.13 respectively, while the sumatriptan 50 mg and 100 mg groups had costs per PSTA of £95.63 and £124.28 respectively. Only drug costs were included in the study, and the authors did not account for resource utilization and indirect costs (productivity loss and time loss).

7.3 Interpretation of Results

The studies reviewed show that eletriptan, rizatriptan, and almotriptan are the most cost-effective triptans. These results are similar to those of other reviews of the cost-effectiveness of triptans by Lofland and Nash,¹⁸ McCormack and Foster,⁵⁰ and Perfetto *et al.*⁵¹ Lofland and Nash found that rizatriptan and almotriptan are the most cost-effective triptans, based on meta-analyses in which eletriptan data were unavailable. McCormack and Foster selectively reviewed economic evaluations that compared rizatriptan with other triptans. They found that rizatriptan is the more cost-effective triptan when compared to sumatriptan, zolmitriptan, and naratriptan. The review by Perfetto *et al.* demonstrated that rizatriptan, almotriptan, and eletriptan are the most dominant cost-effective triptans across studies that use data from meta-analyses.

The studies reviewed are based on studies using different sets of assumptions, methods, clinical-effectiveness measures, and cost-outcome measures. Therefore, a cross-study comparison of cost-effectiveness among triptans cannot be projected numerically. Instead, the results of each

study are interpreted in light of study quality and study perspective.

7.3.1 Interpretation of Study Quality

We assessed the quality of economic studies by critically appraising each study with regards to inclusion of all triptans; inclusion of major costs (direct and indirect) and benefits in the model; inclusion of resource use in the model; and use of a credible source of effectiveness data (Table 8).

In the study by Thompson *et al.*,³⁶ rizatriptan was associated with the lowest cost to treat a migraine attack. The study had insufficient comparative evidence across the triptans because almotriptan and eletriptan were excluded from the analysis. Because rizatriptan, eletriptan, and almotriptan are the most cost-effective triptans based on available studies, their inclusion in economic analyses is important in demonstrating the superiority of one over the rest.

The authors identified the costs and effects of triptans. The cost associated with side effects was not considered in the analysis. The authors assumed that AEs were mild and short-lived, and hence, not cost-generating. While the exclusion of AEs is negligible from the health care payer's perspective, it may underestimate the overall cost of treatment from a societal perspective.

The study provided a description (and valuation) of resource utilization, and measured cost and effects in physical units such as numbers of hospitalizations and doctor visits, hours lost, and lost productivity. The study adapted effectiveness data of questionable credibility. Data from the Ferrari *et al.* meta-analysis²⁵ used in the analysis have limitations. First, the meta-analysis included clinical trials that initiated treatment within eight hours of the migraine attack. Such inclusion overestimates the efficacy data because of the self-resolve tendency of migraine headaches,⁵² more so if patients took triptans at different times during the trials.

Second, the conclusion of the meta-analysis is questionable because included clinical trials differed in terms of design, size, scope, and sampling of patients. Some included studies had small placebo groups, and some had multiple doses, while other studies had patients who were on non-triptan medications before the study.⁵³

Such disparities in study characteristics may invalidate the results of the meta-analysis, and hence, the results of the cost-effectiveness study. Third, the results of the Ferrari *et al.* meta-analysis differ from those of individual trials. A review of two head-to-head trials by the US Food and Drug Administration (FDA) found that rizatriptan was as effective as sumatriptan in terms of percentage of pain-free patients at two hours.⁵⁴ The result is contrary to the findings of the Ferrari *et al.* meta-analysis in which rizatriptan outperformed sumatriptan. Because of such questionable methods in the Ferrari *et al.* meta-analysis, the FDA requires most triptan labels to include a statement stating that “comparison of drug performance based on results obtained in different clinical trials are never reliable.”⁵³

The study by Zhang and Hay⁴⁰ found that rizatriptan was more cost-effective than sumatriptan. While the study examined the costs associated with resource use and measured them in their appropriate units, two of six triptans were examined. Unlike other cost-effectiveness studies, this study expressed the clinical outcome in QALYs instead of outcomes related to migraine relief such as pain response. The study used clinical data of questionable credibility from the Ferrari *et al.* meta-analysis.

The study by Adelman and Belsey³⁷ found that rizatriptan and almotriptan were the most cost-effective. The study included all triptans but eletriptan. The authors discussed the costs associated with migraine treatment but did not consider all the effects of therapy. They considered PF status within the two hours post-dose period. Because the authors did not account for a 24-hour sustainability of PF status, they might have underestimated the cost of treating a migraine. Patients with migraine recurrence are likely to repeat medication, thus increasing the overall cost of treatment.

The authors excluded resource utilization (physician visits, emergency room visits, and hospitalizations) in their analysis. They did not take into account the cost of managing AEs and migraine recurrence rates in their calculations. The authors used data from their meta-analysis to minimize the likelihood of inheriting limitations from published meta-analyses. They failed to report recurrence rates in their meta-analysis, hence reducing the credibility of their findings.

The findings would be more appropriate, for example, if recurrence rates for rizatriptan (which in some studies range between 35% to 47%)^{25,55,56} and associated costs were considered.

The cost-effectiveness study by Reeder *et al.*³⁸ reported that almotriptan had the lowest cost per 100 SPF patients and per 100 SNAEs. The study compared all triptans but eletriptan. The authors did not identify other costs besides drug cost. The costs associated with physician visits, emergency room visits, and hospitalizations were not valued in the study. Furthermore, the study used questionable data from the Ferrari *et al.* meta-analysis.

Perfetto *et al.*³⁹ and Mullins *et al.*⁴³ used similar methods and effectiveness measures to demonstrate the cost-effectiveness of eletriptan. In both studies, eletriptan was associated with the lowest total cost to successfully treat 100 patients and the lowest cost to successfully treat a migraine attack. The costs associated with hospitalization, doctor visits, and emergency room visits were excluded. Moreover, neither study included the cost of rescue medication that might be used by patients who failed to respond to the triptan or who had recurrence after an initial two-hour response. Both studies used clinical data of questionable credibility from the Ferrari *et al.* meta-analysis.

In the cost-effectiveness study by Kelman and von Seggern,⁴⁴ almotriptan was associated with the lowest cost per 100 sustained PF patients and the lowest cost per 100 SNAEs. The authors included all triptans in the study but failed to include non-drug costs (health care resource use and productivity loss), which account for the largest portion of the total cost to treat migraine (>70%).^{3,36} The study used questionable effectiveness data from the Ferrari *et al.* meta-analysis.

Wells *et al.*⁴⁵ demonstrated the superiority of eletriptan over sumatriptan in terms of cost per PF patient at two hours with no recurrence and rescue medication within 24 hours. Two of six triptans were examined. The authors considered drug cost only; costs due to resource utilization and management of AEs were excluded in the model. To minimize the likelihood of inheriting limitations from published meta-analyses, the authors used data from a randomized, double-blind, placebo-controlled clinical trial of oral eletriptan and oral sumatriptan.⁴⁹

The results of the study by Gracia-Naya⁴⁷ showed that zolmitriptan 2.5 mg had the lowest cost per two-hour pain response, while rizatriptan 10 mg was associated with the lowest cost per two-hour PF status and the lowest cost per 24-hour SPF status. All triptans but eletriptan were included in the study, and drug cost was the only parameter in the model. The author excluded other costs such as resource utilization (physician visits, emergency room visits, and hospitalizations) in the analysis. In this study, the author used effectiveness data from his meta-analysis.

In the cost-effectiveness study by Gracia-Naya *et al.*⁴⁶ eletriptan was associated with the lowest cost per two-hour anti-migraine response and per sustained 24-hour PF status, followed by sumatriptan and rizatriptan. Rizatriptan had the lowest cost per two-hour PF status, followed by eletriptan and sumatriptan. While all triptans were included in the study, drug cost was the only parameter in the cost equation of the model. Costs due to health care resource utilization and management of AEs were excluded. The authors provided few details about their meta-analysis.

Williams and Reeder performed two cost-effective analyses.^{41,42} The 2003 study compared rizatriptan with almotriptan, and the 2004 study compared almotriptan with sumatriptan. In both studies, almotriptan was associated with a lower average cost-effectiveness ratio. Both studies considered drug cost and costs associated with health care resource utilization. The clinical data used in both studies were obtained from the Ferrari *et al.* meta-analysis, which is of questionable credibility.

Overall, the quality of the economic studies reviewed is poor. Eight studies^{36,38-44} (66%) did not use a credible source of clinical data and failed to include all the triptans in the analyses. Eight studies^{37-39,43-47} (66%) included only drug costs in their analyses. The poor quality of the reviewed studies restricts their usefulness to health care decision makers seeking information on the comparative cost-effectiveness of triptans.

Given the poor quality of the studies, the applicability of the studies to Canadian jurisdictions is questionable. Nonetheless, it is important to examine the perspectives of studies and their applicability in different settings. Cost-effectiveness studies can be performed from health

care payer, societal, and third-party payer perspectives.

7.3.2 Interpretation based on Study Perspective

Our focus is on health care payer and societal perspectives, because the reviewed economic studies were performed from either perspective. The difference between the two is the inclusion of indirect costs (productivity loss for paid and unpaid work) in the model parameters used for the societal perspective. There are functional differences in health care systems. Some health care payers only pay for the drug, not for health care resource utilization such as physician and emergency room visits. The cost-effectiveness model that applies to them will only include the drug cost.

Indirect costs (productivity loss) due to migraine account for >70% of the total cost to treat a migraine attack, while triptan costs make up about 22%.^{3,36} Accordingly, cost-effectiveness studies that consider direct cost only (resource utilization and drug cost) neglect the largest portion of costs associated with a migraine. Of 12 economic studies reviewed, eight^{37-39,43-47} were performed from the health care payer's perspective and considered drug cost only. The results of these studies are inapplicable for decision makers taking a societal perspective. Also, the results are less applicable for the health care payer who pays for doctor visits and emergency room visits.

Of the four remaining studies, two that were conducted from the health care payer's perspective (Williams and Reeder)^{41,42} included all direct costs (drug cost and resource utilization costs). While the results of these studies are less useful for decision makers from a societal perspective, they could be applicable for the public health care payer who pays for doctor visits and emergency room visits, if the studies compared all triptans and used a credible source of effectiveness data.

The remaining two studies, Thompson *et al.*³⁶ and Zhang and Hay⁴⁰ (performed from a societal perspective) included direct and indirect costs. The results of these studies could be applicable for decision makers from the societal perspective if both studies compared all triptans and used credible clinical data.

Table 6: Characteristics of Reviewed Pharmacoeconomic Studies on Triptans

Author	Triptans Compared	Study Perspective	Study Design	Endpoint(s)	Source of Clinical Data
Thompson <i>et al.</i> ³⁶	SUM, RIZ, ZOL, NAR	societal, health care payer (Canada)	CUA, CEA	cost per QALY, cost per 24-h-SPF patient	Ferrari <i>et al.</i> ²⁵
Adelman and Belsey ³⁷	ALM, RIZ, NAR, SUM, ZOL, FRO	health care payer (US)	CEA	cost per 2-h-PF	authors' meta-analysis
Reeder <i>et al.</i> ³⁸	RIZ, NAR, ZOL, SUM, ALM	health care payer (US)	CEA	cost per 100 SPFP, cost per 100 SNAE	Ferrari <i>et al.</i> ²⁵
Perfetto <i>et al.</i> ³⁹	ELE, ZOL, SUM, ALM, NAR, RIZ	health care payer (US)	CEA	cost per 2-h-PFR, cost per 24-h-SPF	Ferrari <i>et al.</i> ²⁵
Zhang and Hay ⁴⁰	RIZ, SUM	societal (US)	CUA, CEA	cost per QALY	Ferrari <i>et al.</i> ²⁵
Williams and Reeder ⁴¹	ALM, RIZ	health care payer (US)	CEA	cost per 24-h-SNAE	Ferrari <i>et al.</i> ²⁵
Williams and Reeder ⁴²	ALM, SUM	health care payer (US)	CEA	cost per 24-h-SNAE	Ferrari <i>et al.</i> ²⁵
Mullins <i>et al.</i> ⁴³	ELE, ZOL, SUM, ALM, NAR, RIZ	health care payer (US)	CEA	cost per 2-h-PFR, cost per 24-h-SPF	Ferrari <i>et al.</i> ²⁵
Wells <i>et al.</i> ⁴⁵	ELE, SUM	health care payer (UK)	CEA	cost per 2-h-PFP-4-h; cost per 1-h-PR-2-h-PFP-24-h	randomized clinical trial ⁴⁹
Kelman and von Seggern ⁴⁴	ELE, ZOL, SUM, ALM, NAR, RIZ	health care payer (US)	CEA	cost per 100 SNAE, cost per 100 SPF	Ferrari <i>et al.</i> ²⁵
Gracia-Naya ⁴⁷	ZOL, SUM, ALM, NAR, RIZ	health care payer (Spain)	CEA	cost per 2-h-PR, cost per 2-h-PF, cost per 24-h-SPF	authors' meta-analysis
Gracia-Naya <i>et al.</i> ⁴⁶	ELE, ZOL, SUM, ALM, NAR, RIZ	health care payer (Spain)	CEA	cost per 2-h-PR, cost per 2-h-PF, cost per 24-h-SPF	authors' meta-analysis

SUM=sumatriptan; ALM=almotriptan; RIZ=rizatriptan; NAR=naratriptan; ELE=eletriptan; ZOL=zolmitriptan; FRO=frovatriptan; CEA=cost-effectiveness analysis; ICER=incremental cost-effective ratio; CER=cost-effective ratio; CUA=cost-utility analysis; 2-h-PFR=2-hour pain-free response; 2-h-PF=2-hour pain-free status; 24-h-SPF=24-hour sustained pain-free status; 24-h-SPF-100=100 24-hour SPF patients; SPFP=sustained pain-free patient; 100 SPFP=100 sustained pain-free patients; SNAE=24-hour sustained pain-free patients who experience no adverse events; 2-h-PFP-4-h=2-hour pain-free patients, sustained within 4 hours; 1-h-PR-2h-PF-24-h=1-hour pain response leading to pain-free status within 2 hours that is sustained within 24 hours.

Table 7: Results of Reviewed Pharmacoeconomic Studies

Author (funding source)	Costs Considered	Study Endpoint(s)	Study Results
Thompson <i>et al.</i> ³⁶ (Merck Frosst, Montréal Canada)	drug cost, resource use, productivity loss	cost per migraine attack treated (cost per 24-h-SPF) (values in 2002 C\$)	societal perspective: RIZ \$89.86, NAR \$97.04, ZOL \$100.00, SUM \$106.69; third-party payer's perspective (MOH&LTC): RIZ \$24.78, NAR \$25.13, ZOL \$25.69, SUM \$27.75, cost per QALY=\$31,845 RIZ versus usual care
Adelman and Belsey ³⁷ (Merck & Co. Inc., US)	drug cost	cost per 2-h-PF (values in 2002 US\$)	RIZ 10 mg \$48.34, ALM 12.5 mg \$48.57, ZOL 5 mg \$65.18, SUM 100 mg \$70.83, SUM 50 mg \$75.67, ZOL 2.5 mg \$78.74, NAR 2.5 mg \$141.43, FRO 2.5 mg \$162.49
Reeder <i>et al.</i> ³⁸ (not reported)	drug cost	cost per 24-h-SPF-100; cost per SNAE-100 (values in 2001 US\$)	24-h-SPF-100: ALM 12.5 mg \$4,000, RIZ 10 mg \$6,000, SUM 100 mg \$8,000, ZOL 5 mg \$8,000, NAR 2.5 mg \$12,000; SNAE: ALM 12.5 mg \$4000, RIZ 10 mg \$7,000, SUM 100 mg \$9000, ZOL 5 mg \$10,000, NAR 2.5 mg \$12,000
Perfetto <i>et al.</i> ³⁹ (Pfizer)	drug cost	cost per 24-h-SPF; cost per 24-h-SPF-100	24-h-SPF: ELE 40 mg \$56.36, ZOL 2.5 mg \$75.62, SUM 50 mg \$77.59, RIZ 10 mg \$82.53, ALM 12.5 mg

Pharmaceuticals)		(values in 2004 US\$)	\$90.52, NAR 2.5 mg \$111.44; cost 24-h-SPF-100 : ELE 40 mg \$1,560, ZOL 2.5 mg \$1,629, ALM 2.5 mg \$1,670, SUM 50 mg \$1,731, RIZ 10 mg \$1,802, NAR 2.5 mg \$1,945
Zhang and Hay ⁴⁰ (Merck & Co. Inc., California)	drug cost, resource use, productivity loss	cost per QALY (values in 2003 US\$)	RIZ 10 mg versus SUM 50 mg=\$433.45 net annual savings per patient for RIZ 10 mg
Williams and Reeder ⁴¹ (Pharmacia Corporation, Peapack, New Jersey)	drug cost, resource use	CER per SNAE; ICER (values in 2003 US\$)	ALM 12.5 mg \$91.12, RIZ 10 mg \$131.26; ICER for ALM \$6.94 per SNAE
Williams and Reeder ⁴² (Pharmacia Corporation, Peapack, New Jersey)	drug cost, resource use	CER per SNAE; ICER (values in 2003 US\$)	ALM 12.5 mg \$82, SUM 50 mg \$133, SUM 100 mg \$138; ICER for ALM compared with SUM 50 mg and 100 mg \$12 and \$16 respectively per SNAE
Mullins <i>et al.</i> ⁴³ (Pfizer Inc.)	drug cost	cost per 24-h-SPF-100 (values in 2004 US\$)	ELE 40 mg \$5,630, ZOL 2.5 mg \$7,549, SUM 50 mg \$7,779, RIZ 10 mg \$8,246, ZOL 5 mg \$8,499, SUM 100 mg \$8,549; ALM 12.5 mg \$9,073, RIZ 5 mg \$10,579, NAR 2.5 mg \$11,136
Wells <i>et al.</i> ⁴⁵ (Pfizer Global Research and Development)	drug cost	cost per 2-h- PFP-4-h; cost per 1-h- PR-2-h- PF-24-h-SPF (values in 2000 UK£)	2-h-PFP-4-h : ELE 40 mg £17.55, ELE 80 mg £31.76, SUM 50 mg £63.98, SUM 100 mg £80.50; 1-h-PR-2-h-PFP-24-h : ELE 40 mg £29.61, ELE 80 mg £48.13, SUM 50 mg £95.63, SUM 100 mg £124.28
Kelman and von Seggern ⁴⁴ (Pfizer, Merck Inc., and Ortho-McNeil Pharmaceuticals)	drug cost	cost per 100 SPFP; cost per 100 SNAE (values in 2004 US\$)	100 SPFP : ALM 12.5 mg \$7,120, RIZ 10 mg \$7,427, ELE 40 mg \$8,167, ZOL 5 mg \$9,096, ZOL 2.5 mg \$9,221, SUM 100 mg \$9,415, SUM 50 mg \$9,470, RIZ 5 mg \$9,942, SUM 25 mg \$12,623, ELE 80 mg \$13,652, NAR 2.5 mg \$13,736, ELE 20 mg \$16,104; 100 SNAE : ALM 12.5 mg \$8,298, RIZ 10 mg \$12,545, SUM 50 mg \$13,189, ELE 40 mg \$14,155, SUM 100 mg \$14,179, ZOL 2.5 mg \$15,166, RIZ 5 mg \$15,342, SUM 25 mg \$16,786, ZOL 5 mg \$17,425, NAR 2.5 mg \$20,023, ELE 20 mg \$25,521, ELE 80 mg \$29,614
Gracia-Naya ⁴⁷ (funding source not reported)	drug cost	cost per 2-h-PR (euros); cost per 2h-PF (euros); cost per 24-h-SPF (values in 2000 euros)	2h-PR : SUM 50 mg €20.16, ZOL 2.5 mg €19.38, ALM 12.5 mg €26.58, RIZ 10 mg €21.49, NAR 2.5 mg €27.78; 2h-PF : SUM 50 mg €30.24, ZOL 2.5 mg €34.75, ALM 12.5 mg €32.78, RIZ 10 mg €23.79, NAR 2.5 mg €38.20; 24-h-SPF : SUM 50 mg €33.60, ZOL 2.5 mg €36.76, ALM 12.5 mg €54.93, RIZ 10 mg €33.00, NAR 2.5 mg €52.09
Gracia-Naya <i>et al.</i> ⁴⁶ (funding source not reported)	drug cost	cost per 2-h-PR; cost per 2-h-PF; cost per 24-h-SPF (values in 2003 euros)	2-h-PR : ELE 40 mg €16,50, SUM 50 mg €17,44, RIZ 10 mg €18,45, NAR 2.5 mg €20,78, ZOL 2.5 mg €22,07, ALM 12.5 mg €28,79, SUM 100 mg €38,17, ZOL 5.0 mg €44,40; 2-h PF : RIZ 10 mg €21,36, ELE 40 mg €22,99, SUM 50 mg €23,89, NAR 2.5 mg €27,70, ALM 12.5 mg €32,72, ZOL 2.5 mg €34,78, SUM 100 mg €53,38, ZOL 5.0 mg €56,37; 24-h SPF : ELE 40 mg €31,47, SUM 50 mg €33,61, RIZ 10 mg €33,94, NAR 2.5 mg €35,22, ALM 12.5 mg €46,08, ZOL 2.5 mg €56,27, ZOL 5.0 mg €80,14, SUM 100 mg €81,83

SUM=sumatriptan; ALM=almotriptan; RIZ=rizatriptan; NAR=naratriptan; ELE=eletriptan; ZOL=zolmitriptan; FRO=frovatriptan; ICER=incremental cost-effective ratio; CER=cost-effective ratio; MOH=Ministry of Health; LTC=long-term care; 2-h-PF=2-hour pain free; 2-h-PFR=2-hour pain-free response; 2-h-PF=2-hour pain-free status; 24-h-SPF=24-hour sustained pain free; 24-h-SPF-100=100, 24-hour sustained pain-free patients; SPFP=sustained pain-free patient; 100 SPFP=100 sustained pain-free patients; SNAE=24-hour sustained pain-free patients who experience no adverse events; 2-h-PFP-4-h=2-hour pain-free patients, sustained within 4 hours; 1-h-PR-2h PF-24-hS=1-hour pain response leading to pain-free status within 2 hours that is sustained within 24 hours.

Table 8: Quality Assessment of Economic Studies – Critical Appraisal

Study	Inclusion of All Triptans	Inclusion of Major Costs and Benefits	Inclusion of Resource Use	Use of Credible Clinical Data Source
<i>Cost-utility Studies</i>				
Zhang and Hay ⁴⁰	not fulfilled	fulfilled	fulfilled	not fulfilled
Thompson <i>et al.</i> ³⁶	not fulfilled	fulfilled	fulfilled	not fulfilled
<i>Cost-effectiveness Studies</i>				
Adelman and Belsey ³⁷	not fulfilled	not fulfilled	not fulfilled	fulfilled
Reeder <i>et al.</i> ³⁸	not fulfilled	not fulfilled	not fulfilled	not fulfilled
Perfetto <i>et al.</i> ³⁹	fulfilled	not fulfilled	not fulfilled	not fulfilled
Williams and Reeder ⁴¹	not fulfilled	fulfilled	fulfilled	not fulfilled
Williams and Reeder ⁴²	not fulfilled	fulfilled	fulfilled	not fulfilled
Mullins <i>et al.</i> ⁴³	fulfilled	not fulfilled	not fulfilled	not fulfilled
Kelman and von Seggern ⁴⁴	fulfilled	not fulfilled	not fulfilled	not fulfilled
Gracia-Naya ⁴⁷	not fulfilled	not fulfilled	not fulfilled	fulfilled
Wells <i>et al.</i> ⁴⁵	not fulfilled	not fulfilled	not fulfilled	fulfilled
Gracia-Naya <i>et al.</i> ⁴⁶	fulfilled	not fulfilled	not fulfilled	fulfilled

7.4 Summary

We identified 12 economic evaluations that concluded eletriptan, rizatriptan, and almotriptan were the most cost-effective triptans. We found that the evidence from these studies supporting eletriptan, almotriptan, and rizatriptan is of poor quality. Most studies (66%) did not compare all triptans and did not use a credible source of clinical data. When societal and health care payer costs are considered, we found that most studies include only drug costs in their analysis, hence making their results inapplicable for a health care decision maker taking the societal perspective.

8 DISCUSSION

A review of the evidence on the comparative clinical effectiveness and cost-effectiveness of triptans is complex because of the variety of outcome measures and the insufficient number of studies comparing all triptans. The primary outcome measures in most studies are PF response at two hours after therapy initiation and SPF response for two to 24 hours. The DERP report concludes that “the evidence is insufficient to judge overall balance of advantages and disadvantages of rizatriptan vs. sumatriptan.” Fair evidence from the quality assessment of the DERP report suggests that rizatriptan 10 mg is superior to naratriptan 2.5 mg in relieving headache pain, photophobia, and phonophobia at two hours and providing sustained relief at 24

hours. Fair evidence suggests that sumatriptan 100 mg is superior to naratriptan 2.5 mg for relieving headache pain at four hours.

Good evidence from 13 head-to-head trials suggests that there are no differences in chest pain and tightness or central nervous system effects among eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Fair evidence suggests that subcutaneous sumatriptan 6 mg was associated with more chest pain than oral eletriptan 80 mg.

This review found that adolescent migraineurs who received naratriptan, zolmitriptan, rizatriptan, oral sumatriptan, or eletriptan showed no statistically significant differences in measures of efficacy compared to placebo recipients. Migraineurs who received 20 mg sumatriptan nasal spray were 18% more likely to achieve headache relief [NNT=10 (95% CI: 6, 36)] and 38% more likely to achieve freedom from pain [NNT=10 (95% CI: 6, 30)] two hours after dosing. They were three times more likely to experience nausea, vomiting, and taste disturbance than placebo recipients [NNH 5 (95% CI: 3, 13)].

The available clinical effectiveness and cost-effectiveness evidence on triptans is of questionable credibility and hence, of questionable usefulness to decision makers. The DERP report excluded EMBASE and grey literature in the literature search, and its search was limited to studies published in English only. There is a

potential for bias in the abstraction of data from eligible studies in the DERP report. While one reviewer abstracted data from included head-to-head trials, and a second reviewer verified the data in the tables, data from active-control trials were abstracted by one reviewer only. The lack of data extraction forms and varied terminology used to describe outcomes made this review difficult to replicate.

There were discrepancies in the reporting of the number of systematic reviews identified and whether they contained a meta-analysis. While the DERP evaluation reported the limitations of the two reviews that pooled results of studies comparing triptans with placebo, rather than direct comparison studies, DERP did not discuss the results in the text of another publication that summarized 24-hour response rates.

For the adolescent population, three of the eight trials assessed were published in abstract or poster form, and there can be discrepancies in data when abstracts are compared to full publications. Several trials excluded patients who did not experience a migraine during the study period as part of the intention-to-treat population. This could lead to selection bias, because patients with milder or less incidence of migraine may not be represented, possibly underestimating triptan efficacy. The large placebo effect noted in these studies may be influenced by the shorter duration of migraine noted in adolescents and the need for an adult's consent to obtain their study medication.

In adolescents, significant differences in favour of sumatriptan were noted for measures of efficacy. Of every 100 migraineurs treated with sumatriptan, 66 experience headache relief, and 39 are pain-free two hours after dosing. Relative-risk values indicate that sumatriptan recipients are 18% more likely to achieve headache relief and 38% more likely to be pain-free, but they are three times more likely to experience nausea, vomiting, and taste disturbance than placebo recipients. Ten migraineurs need to be treated with sumatriptan for one to achieve headache relief or freedom from pain; an additional sumatriptan recipient experienced nausea, vomiting, or taste disturbance for every five treated.

Most of the literature evaluating the cost-effectiveness of triptans is of a limited utility to

health care decision makers. First, few studies compare all triptans available in Canada. We identified one Canadian economic study³⁶ comparing cost-effectiveness among four of six triptans. Other Canadian economic studies that were identified compared one triptan with a usual non-triptan therapy.^{11,57-59} There are a few non-Canadian economic studies that make a cost-effectiveness comparison among the six triptans. Three^{39,43,46} examine the cost-effectiveness of all triptans. The remaining seven compare two triptans with one another^{40-42,45} or a few triptans among each other.³⁶⁻³⁸

Second, most of the economic studies reviewed consider drug cost only.^{37-39,43,45} Two of 12 economic studies considered direct and indirect costs. The costs associated with managing AEs, rescue medications, and migraine recurrence were not captured in most studies.^{36-39,43} The neglect of other cost parameters in economic models restricts the usefulness of these studies for some health care decision makers.

Third, disparities between the methods used to evaluate cost outcomes make it difficult to interpret the results of the existing economic evaluations. CADTH guidelines for economic evaluation suggest that “emphasis should be placed on using the relevant and valid outcomes of the highest importance for the health of patients” and “in determining effectiveness, the evidence on final outcomes is preferred to that of validated surrogate outcomes.”⁶⁰ The reviewed economic studies use different clinical outcomes and methods. Some studies^{37-39,43} express the denominators of the cost-effectiveness ratio in traditional clinical outcomes related to migraine PF status, whereas others^{36,40} use QALYs. Reeder *et al.*³⁸ estimated the cost per 100 SPF patients (two-hour PF, sustained within a 24-hour period), whereas Adelman and Belsey³⁷ calculated the cost to attain PF status within the two hours of the post-dose period. Thompson *et al.*³⁶ excluded the costs associated with managing AEs from their analysis, whereas Zhang and Hay⁴⁰ included them. Such disparities restrict the comparability of results across studies and hence their utility for decision makers.

Fourth, reliance on one source of clinical data brings into question the quality of most cost-effectiveness studies. Eight of 12 economic studies relied on clinical data from the meta-analysis

conducted by Ferrari *et al.*²⁵ While the Ferrari *et al.* meta-analysis serves a role in understanding the effectiveness of each triptan in the absence of clinical data comparing multiple triptans across composite measures of efficacy, the validity of the results is dismissible based on the findings of the DERP and the FDA reviews. Given concerns about the validity of the results of the Ferrari *et al.* meta-analysis,²⁵ a cost-effectiveness study that is useful to health care decision makers would demonstrate the sensitivity of cost-effectiveness results to different sources of clinical data.

An investigation to determine the most cost-effective triptan should also consider generic sumatriptan, which is available in Canada at half the average cost of other triptans.^{61,62} Because triptans are associated with increases in direct health care costs due to high drug costs,¹⁸ half-priced generic sumatriptan could be the most cost-effective triptan from the health care payer's perspective. While the cost-effectiveness potential of generic sumatriptan has not been studied, in the absence of a credible comparative clinical effectiveness profile of all triptans, generic sumatriptan may appear economically attractive to health care payers.

9 CONCLUSION

In the adult population, the results of a systematic review, with minor flaws, suggest that there is insufficient evidence to judge the balance of advantages and disadvantages of rizatriptan versus sumatriptan because head-to-head trials do not examine outcomes such as 24-hour sustained relief and long-term consistency. Fair evidence from one trial suggests that rizatriptan 10 mg is superior to sumatriptan 100 mg in relieving headache pain, nausea, and for resuming normal function at two hours. There is fair evidence that rizatriptan is superior to naratriptan in relieving headache pain, photophobia, and phonophobia, with sustained response at 24 hours. Fair evidence suggests that sumatriptan is superior to naratriptan in relieving headache pain at four hours, and good evidence suggests that there are no differences in chest pain or tightness, or central nervous system effects among eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. More comparisons among triptans, other than sumatriptan, are needed.

In the adolescent population, six low quality trials suggest migraineurs who receive naratriptan, zolmitriptan, rizatriptan, oral sumatriptan, or eletriptan show no significant differences in measures of efficacy compared to placebo recipients. When efficacy measures were pooled from two trials of moderate and high quality, the relative-risk values indicate that migraineurs who received 20 mg sumatriptan nasal spray were 18% more likely to achieve headache relief and 38% more likely to be free from pain two hours after dosing than placebo recipients. They were three times more likely to experience nausea, vomiting, and taste disturbance than placebo recipients. After evaluating the evidence, we found that there is a need for head-to-head comparison trials, and measures should be taken to reduce selection bias and placebo effects in future studies.

Evidence on the clinical advantage of sumatriptan succinate compared with placebo suggests that adult sumatriptan 50 mg and 100 mg recipients consistently experienced headache relief rates of 49% to 67% at two hours across nine attacks in two placebo-controlled trials. Adolescent sumatriptan nasal spray 20 mg recipients were 18% more likely to achieve headache relief and 38% more likely to experience freedom from pain at two hours than patients receiving identical placebos. Sumatriptan nasal spray recipients were three times more likely to experience nausea, vomiting, and taste disturbance than placebo recipients.

Economic studies show that eletriptan, rizatriptan, and almotriptan are the most cost-effective triptans based on different sets of methods, clinical data, and assumptions. We found no high-quality studies supporting these triptans; and we found that most studies include only drug costs in their analyses, hence making their results inapplicable to health care decision makers who wish to examine the societal perspective.

Our interpretation of the results of economic studies is limited by several characteristics of the studies. First, available economic studies differ in the methods used to evaluate outcomes. Second, most economic studies compare a few triptans. Third, most economic studies only consider drug costs in their models, neglecting other cost parameters such as resource utilization, productivity loss, and cost of managing AEs.

This review of comparative clinical effectiveness does not address some issues that are accepted by clinicians, including the fact that the response of individuals to any given triptan is unpredictable, and that early treatment while migraine pain is mild is encouraged. While response rates from patient groups are a valuable guide, there are individual differences in patients' preferences, responses, and side effects. One patient may find a particular triptan more effective and side-effect-free than another triptan, but another patient may experience the opposite. Several poor quality studies have investigated how well poor responders to one triptan do when switched. Studies of early treatment suggest that PF rates at two hours post-treatment are higher if treatment is started when migraine is mild. In practice, drug switching between triptans is common, earlier

treatment is encouraged, and there may be differences in the pharmacokinetics of these drugs.

While the quality assessment and synthesis of the DERP report provided an opportunity to use research that CADTH funded to minimize duplication of research and to meet timelines, it also posed limitations. To overcome the fact that the adolescent population was not assessed in the DERP report, an additional systematic review was conducted. The evidence presented for the adult population is current up to May 2005 because the literature search was not updated for this review. Relevant evidence that may have been published since then has not been included in our review of the effectiveness of triptans in adults, and there may be trials in the clinical trials registry that could assist in future policy making.

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APPENDICES

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