Drug Class Review

Triptans

Final Report
Update 4

June 2009

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The literature on this topic is scanned periodically.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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EVIDENCE TABLES are available as a separate document

The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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INTRODUCTION

Triptans, also called serotonin 5-hydroxytryptamine (5-HT) receptor agonists, are used to treat migraine and certain other headaches. The cause of migraine is not known. Scientists have several hypotheses to explain how triptans work.[1]

Triptans may be taken subcutaneously, orally as tablets, capsules, or quick-dissolving wafers, or intranasally as a spray. The first triptan, sumatriptan, was introduced in 1991. Currently, 7 triptans are available in the United States (Table 1). As of June 2003, the original oral tablet form of sumatriptan was replaced by a rapid release tablet (RT® Technology) that was designed to facilitate early absorption into the bloodstream. Reformulated sumatriptan was approved as bioequivalent to original sumatriptan based on entire area under the curve ($AUC_{0\text{-}infinity}$) and maximum concentration (C_{max}) and the patent life was not extended. However, in vitro dissolution testing using USP II apparatus in 0.01 M HCL (aq) at 30 rpm found that at 2 minutes, dispersion rates were nearly 100% for reformulated sumatriptan and less than 20% for original sumatriptan.[2] In early 2009, the first generic forms of sumatriptan became available on the market. However, it is not yet clear whether these generic sumatriptan oral tablet products are formulated using RT® Technology or not.

In some cases, patients may treat their migraines using a triptan in combination with other types of pain relievers, such as aspirin or a nonsteroidal anti-inflammatory drug. The first fixed-dose combination product containing a triptan was introduced in 2008. This product, called Treximet®, contains sumatriptan 85 mg plus naproxen sodium 500 mg in a single tablet form.

Table 1. Triptans and triptan fixed-dose combination products

Generic name	Brand name	Form and dose (mg)
Almotriptan	Axert®	Oral tablet (6.25 or 12.5)
Eletriptan	Relpax®	Oral tablet (20 or 40)
Frovatriptan	Frova®	Oral tablet (2.5)
Naratriptan	Amerge®	Oral tablet (1 or 2.5)
Rizatriptan	Maxalt®	Oral tablet (5 or 10)
	Maxalt-MLT®[a], Maxalt RPD®[b]	Orally disintegrating tablet (5 or 10)
Sumatriptan	Imitrex®[a], Imitrex DF™[b]	Oral tablet (25, 50, or 100)
	Imitrex® Nasal Spray	Nasal spray (5 or 20)
	Imitrex® Injection, Imitrex StatDose®	Subcutaneous injection (6 or 8)[a]
Sumatriptan/naproxen	Treximet®[a]	Oral tablet (85/500)
Zolmitriptan	Zomig®	Oral tablet (2.5 or 5)[a]
	Zomig Nasal Spray®	Nasal spray (2.5[b] or 5)
	Zomig-ZMT®[a], Zomig Rapimelt®[b]	Orally disintegrating tablet[a] (2.5 or 5)[a]

[a] Not available in Canada.
[b] Canadian product. Not available in the United States.

Drugs for migraine are often classified by whether they are used to prevent migraine attacks (prophylaxis) or to shorten (abort) an attack. All of the triptans available in the United States and Canada are approved for the acute treatment of migraines in adults. None are approved for prophylaxis of migraine or for hemiplegic, ophthalmoplegic, or basilar migraine. Sumatriptan is the only triptan approved in the United States for cluster headache; it is not approved for this indication in Canada.

The clinical efficacy and adverse effects of the different triptans are of considerable interest to researchers and patients, and several review articles[3-8] and meta-analyses[9-12] have compared them between triptans.

Comparing triptans is complex, however, because of the large variety of outcomes that can be measured in studies. Table 2 lists many of these outcome measures. In most studies, the primary outcome, severity of headache pain after 2 hours, is measured on a 4-point scale (severe, moderate, mild, none). Typically, patients must wait until they have a moderate to severe headache before taking the study medication. Two hours after taking the medication, the patient rates the severity of headache again. A "response" is defined as a reduction in headache from "moderate" or "severe" to "mild" or "none."

Overdependence on the 2-hour pain-relief measure has been criticized. The main criticism is that a 2-hour response may not be as important to patients as some other measures, such as pain-free response or time to response. Another criticism is that the change from moderate/severe pain to none/mild may not always be significant. This criticism is based on the premise that a reduction by only 1 point on the scale (for example, from "moderate" to "mild") may not be associated with important differences in quality of life or function and should not always be counted as a response.[13]

A patient choosing a triptan might consider many other aspects of effectiveness, such as the completeness, speed, and duration of a single response and the consistency of response from headache to headache.[14] Moreover, individual patients may differ in the value they place on each of these attributes of effectiveness and on how they weigh the benefits of treatment against the side effects. For example, suppose that one triptan is more likely to relieve migraine pain within 2 hours, while another is less likely to provide relief but, when it does, it works faster. Or suppose that one triptan is more likely to relieve pain within 2 hours, but more of the patients who experience relief suffer a recurrence of severe pain later in the day. Or suppose that one triptan is more likely to provide headache relief but is also more likely to cause side effects. In each of these situations, the answer to the question "which triptan is better?" may not have a simple answer, or it may have several different answers among patients who have different preferences. For this reason, some experts argue that satisfaction over time may be the best overall measure for comparing triptans.[15] Other experts argue that preference is the best measure: A patient should try several different triptans, eventually settling on the one that offers the best combination of pluses and minuses for that individual.[4]

Finally, if a patient responds consistently well to a triptan, without experiencing disabling side effects, the patient may prefer it to triptans that act faster or have better single episode efficacy. Therefore, an individual patient's preference among the triptans does not necessarily depend only on which triptan has the highest overall response rate or overall rate of adverse events.

Table 2. Outcome measures

Outcome	Commonly used measurement method
Short-term	
Headache response	Headache relief within 2 hours or another period
Freedom from pain	Pain-free within 2 hours or another period
Speed of headache response	Headache relief or pain-free within 1 hour, other measures of speed (for example, hazard rate, survival curves)
Sustained headache response	Recurrence of headache within 24 hours, sustained headache relief for 24 hours, pain-free for 24 hours
Response of other migraine symptoms	Relief of nausea, vomiting, photophobia, and other symptoms associated with migraine within 2 hours or another period
Functional status, disability, lost work time, or "meaningful migraine relief"	Measured using questions such as "after 2 hours, were you able to resume all/some/none of your normal work or activities?"
Satisfaction	Measured using questions such as "how satisfied were you with the treatment?"
Health-related quality of life	Short Form-36 health survey, Migraine-Specific Quality-of-Life Questionnaire, 24-Hour Migraine-Specific Quality-of-Life Questionnaire
Preference	In patients who have tried 2 or more different drugs, measured using the question "which drug did you prefer?"
Short-term consistency of response	Proportion of patients with 2-hour pain-free in at least 2 out of 3 attacks
Need for rescue medication	Use of nontriptan medications, which may indicate inadequate or unsustained relief from the triptan
Adverse	Patients' report of *any* side effect, *serious* side effect, or specific side effects.
Severity and duration of adverse effects	Patients' report of the severity and duration of various side effects
Long-term	
Reliability or consistency of response	Over several months, does the triptan *consistently* relieve pain or other symptoms?
Functional status/disability	Migraine Disability Assessment Scale and various others

Within the research literature, what kinds of studies provide the best evidence by which to compare different triptans? It is widely agreed that well-designed, double-blind, randomized controlled trials that directly compare 2 or more triptans provide the best evidence, *if* they compare several effectiveness measures as well as adverse events, enabling the reader to judge the trade-offs between the compared drugs.[16] This review emphasizes these head-to-head trials.

For some outcome measures and some combinations of triptans, head-to-head trials do not exist. In these cases, trials using active or placebo controls may be helpful. Although they do not directly address how triptans compare, randomized trials comparing a triptan with a

nontriptan or a placebo can provide information on which triptans improve certain outcomes and which do not.

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one

under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying

whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The purpose of this review is to compare the triptans for treatment of migraine in adults. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project after considering comments received from the public following posting of a draft version to the Drug Effectiveness Review Project website. The participating organizations of the Drug Effectiveness Review Project are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. How do effectiveness and efficacy outcomes (reduced severity and duration of symptoms, functional outcomes, quality of life, etc) differ for adult patients with migraine within the following treatment comparisons:
   1a. Monotherapy compared with monotherapy
   1b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
   1c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

2. How do the incidence and nature of adverse effects (serious or life-threatening or those that may adversely effect compliance) differ for adult patients with migraine within the following triptan treatment comparisons:
   2a. Monotherapy compared with monotherapy
   2b. Fixed-dose tablets containing a triptan compared with triptan monotherapy
   2c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

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 adverse effects?

Inclusion Criteria

Populations

Adult patients with any level of migraine (mild, moderate, severe), with or without aura. Definition of migraine must be explicit, to exclude other types of headache (for example, tension headache).

Interventions (oral, nasal, and injectable)

Almotriptan (Axert®)
Eletriptan (Relpax®)
Frovatriptan (Frova®)
Naratriptan (Amerge®)
Rizatriptan (Maxalt®)
Rizatriptan orally disintegrating tablet (Maxalt-MLT®[a], Maxalt RPD[b])
Sumatriptan oral tablet, nasal spray, subcutaneous injection (Imitrex®[a], Imitrex DF[b], Imitrex StatDose®, Imitrex PD[b])
Sumatriptan-naproxen sodium fixed-dose combination product (Treximet®)[a]
Zolmitriptan oral tablet, nasal spray (Zomig®, Zomig Nasal Spray[b])
Zolmitriptan orally disintegrating tablet (Zomig-ZMT®, Zomig Rapimelt[b])

[a] Not available in Canada.
[b] Canadian product. Not available in the United States.

Effectiveness/efficacy outcomes

- Reduction or resolution of symptoms (pain, nausea, vomiting, photophobia, phonophobia), reduction of duration of symptoms, duration of improvement, consistency of effectiveness (proportion of headaches successfully treated per patient), functional outcome (for example, change in days of work lost), quality of life, or adverse effect (including drug interactions).
- Measures: Response, time to response, pain-free, sustained response, sustained pain-free, rescue (use of rescue medications), recurrence (reappearance of any degree of symptoms within 24 or 48 hours) after response or becoming pain-free, time to relief, relief of associated symptoms, tablets per attack, and patient satisfaction.

Harms

- Overall withdrawals
- Withdrawals due to any adverse events
- Withdrawals due to specific adverse events (central nervous system effects, chest tightness)

Study designs

- For effectiveness/efficacy, study is a controlled clinical trial in an outpatient setting or a good-quality systematic review.
- For harms, the study is a controlled clinical trial or observational study.

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® (1996 to week 4 of January 2009), the Cochrane Database of Systematic Reviews® (2nd Quarter 2008), Database of Abstracts of Reviews of Effects (3rd Quarter 2008), and the Cochrane Central Register of Controlled Trials® (3rd Quarter 2008) using terms for included drugs, indications, and study designs (see Appendix B for complete search strategies). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration's Center for Drug Evaluation and Research website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® version X2).

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Titles and abstracts of citations identified through literature searches were assessed for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion. Results published *only* in abstract form were not included because inadequate details were available for quality assessment.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but loss to follow-up was very small, we considered these results to be intention-to-treat results. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. Data abstraction was performed by one reviewer and was independently checked by a second reviewer.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.[17, 18] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal

flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events.

Appendix C also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality (see Appendix C). We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

The overall strength of evidence for a body of evidence pertaining to a particular key question or outcome reflects the risk of bias of the studies (based on quality and study designs), consistency of results, directness of evidence, and precision of pooled estimates resulting from the set of studies relevant to the question. Strength of evidence is graded as insufficient, low, moderate, or high.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one triptan against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. Direct comparisons were preferred over indirect comparisons. Similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

In theory, trials that compare triptans with other drug classes or with placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and are used as the primary comparison where no direct comparisons exist. Indirect comparisons should be interpreted with caution.

Quantitative analyses were conducted using meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When necessary, indirect meta-analyses were done to compare interventions where there were no head-to-head comparisons and where there was a common intervention across studies. All pooled relative risks and 95% confidence intervals were

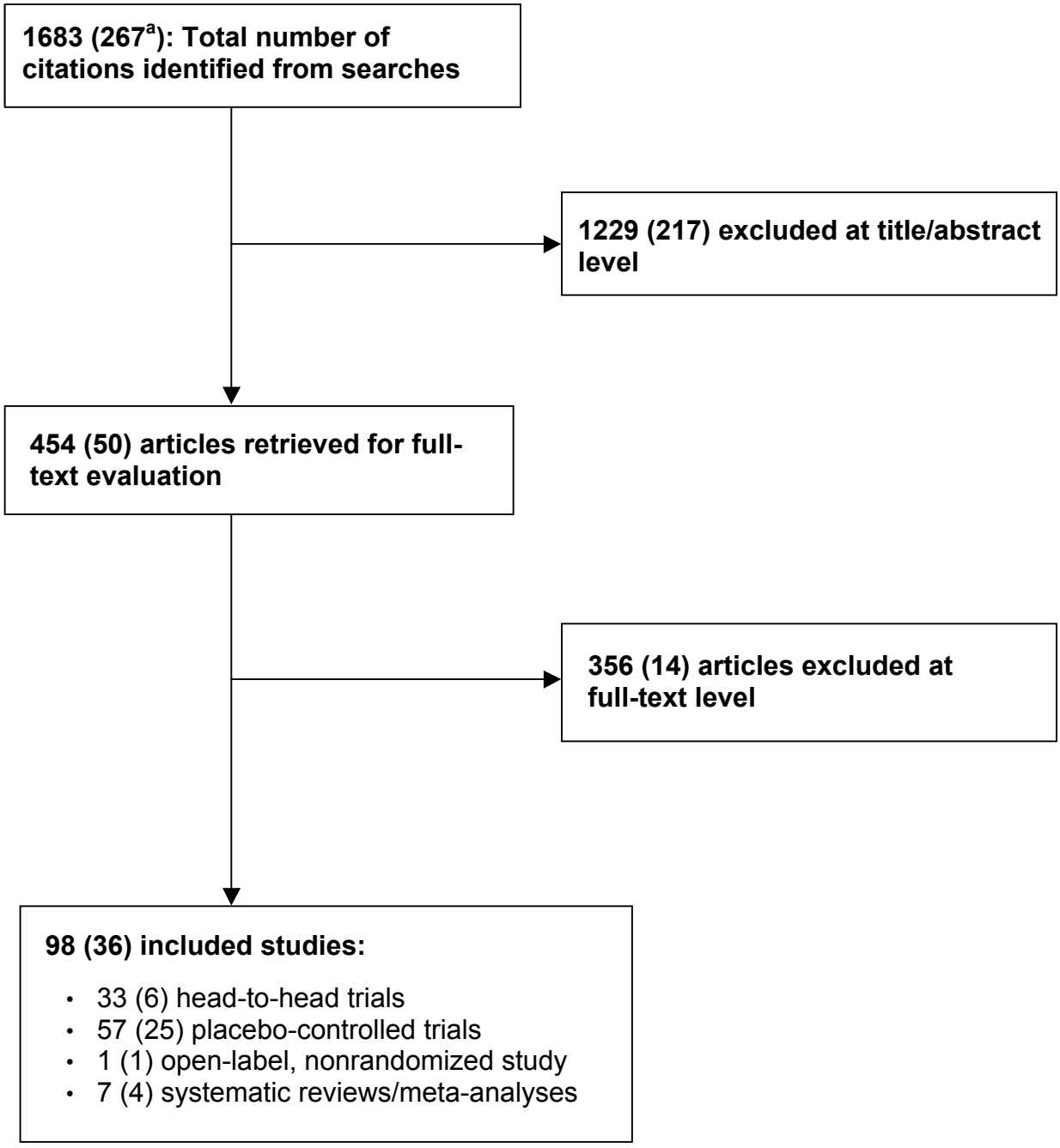
calculated based on random-effects models using StatsDirect statistical software package Version 2.7.0 (7/7/2008). The Q-statistic was calculated to assess heterogeneity in effects between studies. Otherwise, the data are summarized qualitatively.

RESULTS

Overview

Searches identified 1683 citations, with 267 new in Update 4. The results of study selection are outlined in Figure 1. Dossiers were received for Update 4 from the manufacturers of almotriptan, frovatriptan, rizatriptan, sumatriptan, and the fixed-dose combination product, Treximet® (sumatriptan/naproxen).

Figure 1. Study selection



[a] Parentheses show search results new to Update 4.

Summary of Findings

Efficacy/effectiveness

Eletriptan

- *Direct comparisons*
  - Evidence from 5 head-to-head trials was insufficient to make conclusions about comparative efficacy of eletriptan and encapsulated sumatriptan, naratriptan, and zolmitriptan due to the differential effects associated with use of unilateral encapsulation in these trials.
- *Placebo-controlled trials*
  - Early intervention (1 trial): Eletriptan 40 mg was superior to placebo in 2-hour pain-free (relative risk, 2.72; 95% CI, 1.92 to 3.84, number needed to treat, 2) and in 24-hour sustained pain-free (relative risk, 3.21; 95% CI, 2.09 to 4.94, number needed to treat, 3).
  - Work productivity (2 trials): Compared with placebo, eletriptan 40 mg reduced total hours lost, work hours lost, and improved scores on a work productivity questionnaire.
- *Gaps in controlled trial evidence:* Quality of life, consistency across multiple attacks

Rizatriptan

- *Direct comparisons*
  - Rizatriptan 10 mg compared with the conventional tablet form of oral sumatriptan 50 mg and 100 mg (4 trials)
    - Rate of 2-hour pain-free for rizatriptan 10 mg was significantly greater than for the conventional tablet form of sumatriptan 100 mg (pooled direct difference –7; 95% CI, –13 to –1) and similar to the conventional tablet form of sumatriptan 50 mg (pooled direct difference –3; 95% CI, –9 to +2).
    - Rate of 24-hour sustained pain-free was similar for rizatriptan 10 mg and the conventional tablet form of sumatriptan 100 mg (pooled direct difference, –4; 95% CI, –9 to +2) and the conventional tablet form of sumatriptan 50 mg (–2; 95% CI, –7 to +3) based on the meta-analysis by Ferrari and colleagues.
    - Based on unpublished data from the manufacturer, mean scores across the 5 domains of the Migraine-Specific Quality-of-Life Questionnaire were generally similar for rizatriptan 10 mg and the conventional tablet form of sumatriptan 50 mg and 100 mg.
  - Rizatriptan 10 mg compared with naratriptan 2.5 mg (1 trial): Rizatriptan was superior in time to pain relief, 2-hour pain-free, 2-hour normal functioning, and 2-hour overall satisfaction and similar in rate of recurrence and score on the Migraine-Specific Quality-of-Life Questionnaire.
  - Rizatriptan 10 mg compared with zolmitriptan 2.5 mg (1 trial): Rizatriptan was superior in rates of 2-hour pain-free and 2-hour normal functioning and similar in rate of recurrence and score on the Migraine-Specific Quality-of-Life Questionnaire.

- *Placebo-controlled trials*
    - Consistency (1 trial): Two-hour response rates were consistently greater for rizatriptan 10 mg than placebo across 4 headaches.
    - Early intervention (2 trials): Rizatriptan 10 mg was superior to placebo in 2-hour pain-free (pooled relative risk, 1.82; 95% CI, 1.57 to 2.21; number needed to treat, 3) and 24-hour sustained pain-free (relative risk, 3.52; 95% CI, 1.67 to 7.42; number needed to treat, 5)
- *Gaps in controlled trial evidence:* Work productivity

Rizatriptan orally disintegrating tablets

- *Direct comparisons*
    - Rizatriptan orally disintegrating tablet 10 mg compared with the conventional tablet form of sumatriptan 50 mg (2 open trials): Rizatriptan was superior on preference, rates of 2-hour pain-free, and 2-hour normal function and had comparable 24-hour recurrence rates. Rate of 24-hour sustained pain-free was reported in only 1 trial and was superior for rizatriptan.
    - Rizatriptan orally disintegrating tablet 10 mg compared with eletriptan 40 mg: Greater numbers of patients preferred rizatriptan to eletriptan. The 2 triptans were similar on satisfaction, pain-free, and functional disability outcomes, however.
- *Placebo-controlled trials*
    - Quality of life: Rizatriptan orally disintegrating tablet 10 mg was superior to placebo on all 5 domains of the Migraine-Specific Quality-of-Life Questionnaire.
- *Gaps in controlled trial evidence:* Early migraine, work productivity, consistency across multiple attacks

Zolmitriptan oral tablet, orally disintegrating tablet, nasal spray

- *Direct comparisons*
    - Zolmitriptan 5 mg compared with the conventional tablet form of sumatriptan 100 mg (1 trial): Similar rates of 2-hour pain-free, no activity impairment, 24-hour recurrence, 24-hour complete response, and 24-hour pain-free.
    - Zolmitriptan 5 mg compared with the conventional tablet form of sumatriptan 50 mg (2 trials): Similar 2-hour pain-free, sustained 24-hour pain-free outcomes, and consistency across 6 attacks.
    - Zolmitriptan 2.5 mg compared with naratriptan 2.5 mg (1 unpublished trial): Similar 2-hour pain relief rates after adjustment for higher rate of severe intensity pain at baseline in zolmitriptan group. Meaningful interpretation of other unadjusted outcomes is not possible.
    - Zolmitriptan 5 mg and 2.5 mg nasal spray compared with zolmitriptan oral tablet 2.5 mg (1 trial): Zolmitriptan 5 mg nasal spray demonstrated a significant advantage over zolmitriptan 2.5 oral tablet in rates of pain-free at the earliest timepoints, 30 minutes and 45 minutes, and in resumption of normal activities at all timepoints. Otherwise, the 5-mg nasal spray and 2.5-mg oral tablet were similar on other outcomes at 2 hours and 24 hours. Zolmitriptan 2.5 mg nasal spray had no advantage over zolmitriptan 2.5 mg oral tablet at the early timepoints and was inferior from 2 hours onward.

- *Placebo-controlled trials*
    - Early intervention (1 trial): Zolmitriptan oral tablet 2.5 mg was superior to placebo for rate of 2-hour pain-free (relative risk, 2.41; 95% CI, 1.81 to 2.30; number needed to treat, 4). Twenty-four-hour pain-free outcomes were not reported.
- *Gaps in controlled trial evidence:* We found no evidence on quality of life or work productivity outcomes for any form of zolmitriptan. For the orally disintegrating tablet and nasal spray forms, we also found no evidence on early treatment of mild migraine or in consistency of treatment across multiple attacks.

Almotriptan

- *Direct Comparisons*
    - Almotriptan 12.5 mg compared with the conventional tablet form of sumatriptan 50 mg (1 trial), the conventional tablet form of sumatriptan 100 mg (1 trial), and zolmitriptan 2.5 mg (1 trial): Almotriptan 12.5 mg was similar to the conventional tablet form of sumatriptan 50 mg and 100 mg and zolmitriptan 2.5 mg on rates of 2-hour pain-free, 24-hour recurrence, and 24-hour pain-free.
    - Almotriptan 12.5 mg compared with rizatriptan 10 mg (1 trial): Analysis of the intention-to-treat, 2-attacks population found patient preference was almost identical for both triptans, but 2-hour pain-free rates was superior for rizatriptan.
- *Placebo-controlled trials*
    - Consistency (1 trial): Almotriptan 12.5 mg was superior to placebo in rate of patients with 2-hour pain-free in 3 of 3 attacks.
    - Early intervention (2 trials): Almotriptan 12.5 mg was superior to placebo in rates of 2-hour pain-free (pooled relative risk, 1.71; 95% CI, 1.32 to 2.21; number needed to treat, 6) and 24-hour sustained pain-free (pooled relative risk, 2.08; 95% CI, 1.12 to 3.86; number needed to treat, 6). In 1 trial, almotriptan 12.5 mg was also superior to placebo in rate of 2-hour normal function and on mean quality-of-life score.
- *Gaps in controlled trial evidence:* Work productivity

Naratriptan

- *Direct comparisons*
    - Naratriptan 2.5 mg was similar to the conventional tablet form of sumatriptan 100 mg on rates of 2-hour pain relief, 4-hour pain relief, 2-hour mild to no disability, 24-hour recurrence, and 24-hour pain relief. Pain-free outcomes were not reported.
- *Placebo-controlled trials:* None were included.
- *Gaps in controlled trial evidence:* Quality of life, workplace productivity, consistency across multiple attacks, or early treatment of mild migraine

Reformulated oral sumatriptan

- *Direct comparisons:* No head-to-head trials were found.
- *Placebo-controlled trials*
    - Early intervention (1 trial): Reformulated oral sumatriptan 100 mg was superior to placebo for rates of 2-hour pain-free (relative risk, 3.38; 95% CI, 2.65 to 4.30;

number needed to treat, 2) and 24-hour sustained pain-free (relative risk, 4.09; 95% CI, 2.83 to 5.92; number needed to treat, 3). Rate of normal function was higher and number of hours in nonwork activities was lower for reformulated sumatriptan 100 mg as well.
    - Indirect comparison to the conventional tablet form of sumatriptan: Pooled relative risks and numbers needed to treat for rates of 2-hour pain-free compared with placebo were similar for reformulated sumatriptan (3.30; 95% CI, 2.51 to 4.34; number needed to treat, 4) and the conventional tablet form of sumatriptan (3.13; 95% CI, 2.09 to 4.68; number needed to treat, 3). Insufficient data were available for indirect comparison of rates of 24-hour sustained pain-free.
- *Gaps in controlled trial evidence:* Quality of life or consistency across multiple attacks

Sumatriptan injection and nasal spray

- *Direct comparisons*
    - Two trials comparing sumatriptan injection with the conventional oral tablet form of sumatriptan were rated poor quality. We found no head-to-head trials comparing sumatriptan nasal spray with another triptan.
- *Placebo-controlled trials*
    - Indirect comparisons with oral triptans: Pooled relative benefit for 1-hour pain-free compared with placebo was highest for sumatriptan injection 6 mg (3.2; 95% CI, 2.8 to 3.6) in a good-quality systematic review including it and oral triptans.
    - Functional capacity, work productivity, quality of life: Numerous placebo-controlled trials provided consistent evidence of the efficacy of subcutaneous injection of sumatriptan 6 mg in improving clinical disability, time to return to work, time to emergency room discharge, and quality of life.
- *Gaps in controlled trial evidence:* We found no head-to-head or placebo-controlled trials that examined the efficacy of sumatriptan injection in early treatment of mild migraine or in consistency of treatment across multiple attacks.

Frovatriptan

- *Direct comparisons:* None were included. One head-to-head trial that directly compared frovatriptan 2.5 mg with the conventional tablet form of sumatriptan 100 mg has been published only as an abstract, which did not provide adequate methodological detail for assessment of the quality of its internal validity.
- *Placebo-controlled trials*
    - Unadjusted indirect comparison to the conventional tablet form of sumatriptan 100 mg: A lower pooled risk difference for frovatriptan 2.5 mg (0.09; 95% CI, 0.07 to 0.10; number needed to treat, 12) than the conventional tablet form of sumatriptan 100 mg (0.20; 95% CI, 0.16 to 0.25; number needed to treat, 4) indicates that frovatriptan 2.5 mg probably has inferior efficacy.
    - *Early migraine:* Frovatriptan 2.5 mg was superior to placebo in rate of 2-hour pain-free (28% compared with 20%; P=0.04). 24-hour pain-free outcomes were not reported.
- *Gaps in controlled trial evidence:* Early treatment of migraine, quality of life, work productivity, consistency across multiple attacks

Fixed-dose combination tablet of reformulated sumatriptan 85 mg and naproxen 500 mg (Treximet®)

- *Direct comparisons*
  - Compared with monotherapy: We found no head-to-head trials comparing Treximet® with any triptan monotherapy at a dose that is commercially available in the United States or Canada. Treximet® was superior to monotherapy with reformulated sumatriptan 85 mg in 24-hour pain-free, return to normal function, overall productivity, and patient satisfaction in 2 trials conducted as part of its new drug application.
  - Compared with co-administration of its individual components: We found no head-to-head trials comparing Treximet® with co-administration of its components, sumatriptan 85 mg and naproxen 500 mg.
- *Placebo-controlled trials*
  - Early intervention (6 trials, 2 unpublished):
    - For 2-hour pain-free outcomes, Treximet® was superior to placebo in the 4 trials that enrolled patients regardless of their prior triptan treatment history (3.12; 95% CI, 2.64 to 3.69; number needed to treat, 3) and in the 2 trials which required prior poor response or intolerance to triptans (relative risk, 2.62; 95% CI, 1.92 to 3.58; number needed to treat, 3).
    - For 24-hour sustained pain-free outcomes, Treximet® was superior to placebo in the 4 trials of patients that enrolled patients regardless of their prior triptan history (relative risk 3.21; 95% CI, 2.63 to 3.91; number needed to treat, 4) and in the 2 trials of patients with a prior history of poor response or intolerance to triptans (relative risk, 3.77; 95% CI, 2.38 to 5.99; number needed to treat, 4).
    - Consistency: In protocols TRX103632 and TRX103635, the rate of patients who were pain-free at 2 hours postdose in at least 2 of the first 3 attacks treated with Treximet® was 52% to 55% across both trials. The rates of patients with a sustained pain-free response through 24 hours postdose in at least 2 of the first 3 attacks treated with Treximet® ranged from 14% to 15% across the 2 trials.
- *Gaps in controlled trial evidence:* Quality of life outcomes were lacking in controlled trials of Treximet®.

Harms

- *Monotherapy compared with monotherapy:* There were no consistent differences between triptan monotherapies in rates of overall adverse events or in rates of individual adverse events, including chest pain/tightness or central nervous system effects.
- *Fixed-dose combination therapy with reformulated sumatriptan 85 mg/naproxen 500 mg (Treximet®) compared with triptan monotherapy (2 trials):* There was no significant difference between Treximet® and monotherapy with reformulated sumatriptan 85 mg in rate of any adverse event, dizziness, paresthesia, or somnolence.

- *Fixed-dose combination therapy with reformulated sumatriptan 85 mg/naproxen 500 mg (Treximet®) compared with co-administration of individual components:* We found no head-to-head trials that reported harms outcomes.

Effectiveness/efficacy and harms in subgroups

- There is no consistent evidence that one triptan has any particular advantage or disadvantage over another in any subgroup based on age, race, gender, prophylactic treatment, or menstruation-associated migraine.

Detailed Assessment

Key Question 1. How do effectiveness and efficacy outcomes (reduced severity and duration of symptoms, functional outcomes, quality of life, etc) differ for adult patients with migraine?

Key Question 1a. Monotherapy compared with monotherapy

Overview

We included 32 head-to-head trials.[19-50] The majority involved comparisons of the conventional tablet form of sumatriptan with other triptans, including almotriptan,[19-23] eletriptan,[24-27] naratriptan,[29, 30] rizatriptan,[31-37] rizatriptan orally disintegrating tablet,[38, 39] subcutaneous sumatriptan,[42, 43] zolmitriptan,[44-46] and zolmitriptan orally disintegrating tablet.[49] In addition, 1 single-blind, crossover trial of 42 adults selected from the Headache Center (A Gemelli Hospital, Rome) compared almotriptan 12.5 mg, eletriptan 40 mg, rizatriptan 10 mg, the conventional tablet form of sumatriptan 100 mg, and zolmitriptan 2.5 mg.[50] However, we rated it poor quality due to multiple flaws, including lack of blinding of outcome assessors and exclusion of 28% of patients who failed to complete the trial for unspecified reasons. We found no head-to-head trials involving comparisons with frovatriptan or reformulated sumatriptan.

Most of the head-to-head trials have been previously analyzed in a prior systematic review, the findings of which contrasted with separate meta-analyses of placebo-controlled trials.[11, 12] Additional meta-analyses of indirect comparisons based on placebo-controlled trials of triptans were also identified.[51, 52] Only 1 of these reviews used a set of predefined, explicit criteria (the Jadad score) to assess the internal validity of trials.[52] The goal of the review was to infer the relative effectiveness of different drugs, including triptans, for the treatment of moderate to severe migraine by using pooled results from placebo-controlled trials. Thus, the authors relied mainly on studies that compared a triptan with a placebo, rather than on direct comparison studies. The investigators selected 5 efficacy measures and 3 adverse effect measures for comparison. Fifty-four trials, most of which were not head-to-head trials, were included in the meta-analysis. The inclusion criteria specified that trials had to be published in peer reviewed journals except for trials of eletriptan, for which unpublished data were obtained directly from the manufacturer.

Ferrari and colleagues used a similar approach but did not consider study quality.[11, 12] The main value of their analysis was that it included the results of all known head-to-head trials, regardless of quality and publication status. Because the analysis was based on original data, the authors were able to calculate the results for endpoints that were not reported in publications,

such as the 24-hour response rate. The investigators included 53 clinical trials of triptans, including 12 unpublished trials, all of which were identified by contacting pharmaceutical companies and investigators. Most of the included trials compared a triptan with a placebo, rather than another triptan. Using original data from the manufacturers (except for the trials of frovatriptan), the investigators compared the pooled results for each drug and dosage, using the conventional tablet form of sumatriptan 100 mg as the reference standard. This meta-analysis was comprehensive, examined important outcome measures, and applied statistical methods appropriately, but the strategy for pooling studies had important weaknesses: The investigators gave equal weight to the results of all studies without considering their quality and pooled recent studies of newer drugs with older ones that were conducted under different circumstances.

Eletriptan

Direct comparisons

We included head-to-head trials that compared eletriptan 40 mg with the encapsulated conventional oral tablet form of sumatriptan 100 mg,[24-26] encapsulated naratriptan 2.5 mg,[28] and encapsulated zolmitriptan 2.5 mg.[27]

Eletriptan 40 mg compared with the encapsulated conventional tablet form of sumatriptan 100 mg. Three fair-quality trials compared eletriptan 40 mg with the conventional tablet form of sumatriptan 100 mg.[24-26] In these studies, sumatriptan was put in a capsule to make it look like eletriptan so that the study could be double-blind. At 2 hours, a significantly greater proportion of patients were pain-free with eletriptan 40 mg than with the encapsulated conventional oral tablet form of sumatriptan 100 mg in 2 of 3 trials.[24, 26] When we pooled data from all 3 trials, the combined rates were 35% (376/1063) for eletriptan 40 mg and 25% (272/1076) for the encapsulated conventional oral tablet form of sumatriptan 100 mg, with a relative risk of 1.47 (95% CI, 1.11 to 1.94) and a number needed to treat of 10. Two-hour rates of normal function were also significantly greater for eletriptan 40 mg than the encapsulated conventional tablet form of sumatriptan 100 mg in 2 of 3 trials:[24, 26] 62% (569/913) for eletriptan 40 mg and 56% (457/819) for the encapsulated conventional tablet form of sumatriptan 100 mg, with a relative risk of 1.09 (95% CI, 0.86 to 1.38). We found rates of 24-hour sustained pain-free in only 1 trial, in which eletriptan 40 mg was superior to the encapsulated conventional tablet form of sumatriptan 100 mg (24% compared with 14%; $P<0.05$).[24] When Ferrari and colleagues[11] combined these data[24] with unpublished data for 24-hour sustained pain-free outcomes from an additional trial,[25] the resulting direct difference of –8 (95% CI, –14 to –3) still showed that eletriptan 40 mg was superior to the encapsulated conventional tablet form of sumatriptan 100 mg.

Findings from these trials engendered debate over whether encapsulation of the comparator triptan for blinding purposes suppressed their normal absorption rate and usual effectiveness. This concern has led to multiple studies comparing pharmacokinetic and clinical effects of the conventional tablet form of sumatriptan tablets with and without encapsulation.

In vitro and in vivo dissolution testing by the manufacturers of eletriptan and the conventional tablet form of sumatriptan have produced conflicting results.[53-55] In an in vitro dissolution study funded by the manufacturer of eletriptan,[54] no significant difference in dissolution rate (estimated as area under the curve) was found for the conventional tablet form of sumatriptan 100 mg, with or without encapsulation based on the ratio of geometric means of 0.99 (90% CI, 0.92 to 1.06). However, an in vivo study (Fuseau 2001), funded by the manufacturer of the conventional tablet form of sumatriptan, showed absorption was delayed between 0 to 2

hours after dosing (AUC_2) when the conventional tablet form of sumatriptan 50 mg was encapsulated compared to when it was not encapsulated in a sample of 26 healthy adults (geometric mean treatment ratio 0.79; 90% CI, 0.59 to 1.05) and in a sample of 30 adults during a migraine (n=30) (geometric mean treatment ratio 0.73; 90% CI, 0.52 to 1.02).[55] The Fuseau trial has been criticized by an investigator sponsored by the manufacturer of eletriptan for using twice as much magnesium stearate to encapsulate sumatriptan than was used in the original head-to-head trials of eletriptan and suggested that the greater quantity magnesium stearate could have hampered capsule dissolution and confounded absorption. Also, it is unclear why the Fuseau and colleagues evaluated only the 50 mg dose of the conventional tablet form of sumatriptan and not also the 100 mg dose or why they used a 90% confidence interval to evaluate statistical significance, rather than the more common and more stringent 95% confidence interval. Subsequently, in another study funded by the manufacturer of eletriptan involving 10 healthy volunteers, the conventional tablet form of sumatriptan 100 mg and encapsulated sumatriptan 100 mg were found to be similar in elapsed time to initial capsule disintegration (6 minutes compared with 5 minutes) and in mean time to complete disintegration (18 ± 14 minutes compared with 16 ± 7 minutes).[53]

Meta-analyses have also been conducted to compare the 2-hour pain relief and pain-free outcomes from head-to-head trials of eletriptan and the encapsulated conventional tablet form of sumatriptan to those from all other trials of either eletriptan or the unencapsulated conventional tablet form of sumatriptan, respectively.[11, 56, 57] But, none has conclusively found that the clinical efficacy of the conventional oral tablet form of sumatriptan 100 mg on 2-hour pain-relief or pain-free outcomes was significantly decreased in trials where it was encapsulated compared with trials where it was not encapsulated.

In their 2002 meta-analysis,[11] Ferrari and colleagues conducted a sensitivity analysis to examine how company sponsorship may have influenced results for sumatriptan and placebo comparators.[11] Because the eletriptan-encapsulated sumatriptan comparator trials were all conducted by Pfizer,[24-26] this provided an opportunity for qualitative indirect comparison of average absolute 2-hour pain-free rate for the conventional tablet form of sumatriptan 100 mg with and without encapsulation. For the outcome of 2-hour pain-free, the *overall* average absolute rate for sumatriptan 100 mg was 29% (95% CI, 27 to 31) and was 8% (95% CI, 7 to 9) for placebo. In the Pfizer-conducted eletriptan-sumatriptan comparator trials, however, Ferrari and colleagues found lower average absolute 2-hour pain-free rates for encapsulated sumatriptan 100 mg and for placebo, respectively. Although inconclusive, the findings of Ferrari and colleagues suggest the presence of heterogeneity between Pfizer-conducted and other company-conducted trials that could have influenced 2-hour pain-free results. However, because the pattern of non-encapsulated placebo was similar to that of encapsulated sumatriptan – lower efficacy in Pfizer-conducted trials – use of encapsulation for blinding could not be the only source of heterogeneity in these trials.

One meta-analysis compared the time course of response for the conventional tablet form of sumatriptan with and without encapsulation using model-based random-effects logistic regression techniques and data from 19 head-to-head and placebo-controlled trials.[56] No significant difference was found at any time point between 0 and 4 hours in proportion of patients who achieved pain relief for the conventional tablet form of sumatriptan with or without encapsulation.

In 2005, we conducted our own meta-analysis to compare the mean absolute rates of 2-hour pain relief and pain-free for eletriptan and the conventional tablet form of sumatriptan. We

compared data from head-to-head trials of eletriptan 40 mg and the encapsulated conventional tablet form of sumatriptan 100 mg[24-26] with data from all other available head-to-head trials and placebo-controlled trials involving either triptan. Pooled absolute rates of 2-hour pain relief and absence of pain are shown in Table 3. For the conventional tablet form of sumatriptan 100 mg, the mean rates of 2-hour pain relief and pain-free were numerically *lower* when it was encapsulated compared to when it was not encapsulated, but overlapping confidence intervals suggest that the difference is not statistically significant. Unexpectedly, however, for eletriptan 40 mg, the mean rate of 2-hour pain relief and pain-free were numerically *higher* in trials where the comparator was the encapsulated conventional tablet form of sumatriptan compared to when the comparator was placebo or another unencapsulated triptan. But, here again, overlapping 95% confidence intervals suggest that the difference is not statistically significant.

Table 3. Pooled absolute rates of 2-hour pain-free and pain-relief (95% confidence intervals)

Encapsulation status	Pain-free		Pain-relief	
	E40	S100	E40	S100
Encapsulated	33.2 (29.0 to 37.8)	25.1 (20.5 to 30.4)	66.3 (63.4 to 69.0)	57.6 (53.6 to 61.4)
Unencapsulated	30.9 (28.4 to 33.5)	33.2 (26.1 to 41.1)	60.1 (56.6 to 63.6)	59.4 (56.4 to 62.3)

Overall, meta-analyses have provided suggestive evidence that sumatriptan's usual efficacy was suppressed when it was encapsulated for blinding purposes in the Pfizer-conducted trials. However, because the pattern of lower efficacy was also seen for non-encapsulated placebo and a pattern of higher efficacy was seen for non-encapsulated eletriptan, our conclusion is that use of encapsulation cannot provide the entire explanation for the unexpected results in the Pfizer-conducted eletriptan-sumatriptan comparator trials.

Therefore, using meta-regression techniques, we explored the impact of potential sources of clinical heterogeneity including mean age, percentage of female subjects, and percentage with severe baseline pain. However, even after adjustment for those patient variables, we found that the modest differences persisted between 2-hour pain-relief and pain-free outcomes in the trials of eletriptan and the encapsulated conventional tablet form of sumatriptan 100 mg compared with those in other trials of either eletriptan or nonencapsulated sumatriptan. Other variables of interest were recruitment method, type of run-in period, type of prior migraine treatment, including whether the trial population had been previously exposed to triptans, and year the study was conducted, but the publications provided insufficient data to assess their effects. Other variables, such as the scientific group conducting the study, place of study, and sponsorship might contribute to the difference, but they are confounded with the effects of drug and were not included in the analysis.

We also explored the presence of unexplained post-randomization exclusions of treated patients as another possible explanation for the unexpected findings in the 3 head-to-head trials of eletriptan compared with the encapsulated conventional tablet form of sumatriptan 100 mg.[24-26] As in the majority of trials of triptans, the head-to-head trials of eletriptan and the encapsulated conventional tablet form of sumatriptan 100 mg excluded from their efficacy analyses an average

of 16% of randomized patients who took no study medication for the primary reason that they did not have a treatable migraine during the study period. However, unlike in most other trials, an additional subset (mean=7%, range=5% to 12%) of *treated* patients who were not "evaluable" due to unspecified violations of the protocol were excluded from the 2-hour efficacy analyses in the head-to-head trials of eletriptan compared to the encapsulated conventional tablet form of sumatriptan 100 mg.[24-26]

Using a "worst-case scenario" approach, we estimated pooled 2-hour pain-free rates for the *all-treated* populations which we compared for eletriptan and the encapsulated conventional tablet form of sumatriptan 100 mg based on both risk difference and relative risk meta-analyses using random-effects models (Table 4). All treated patients excluded from the eletriptan 40 mg groups were included in the "worst-case scenario" analyses as treatment failures and all treated patients excluded from the encapsulated conventional tablet form of sumatriptan 100 groups were included as if they achieved 2-hour pain-free outcomes. In contrast to published findings based on the "evaluable" populations, in our worst-case scenario analyses, the difference in rates of 2-hour pain-free between eletriptan and the encapsulated conventional tablet form of sumatriptan 100 mg was smaller and was no longer statistically significant.

It is important to note that results from our "worst-case scenario" analysis are hypothetical and, without knowledge of the real reasons for the exclusion of the treated patients, it is not possible for us to assess whether such bias exists or to what degree. Therefore, meaningful interpretation of results from the head-to-head trials of eletriptan compared with the encapsulated conventional tablet form of sumatriptan 100 mg is still not possible.

Table 4. Head-to-head trials of eletriptan compared with the encapsulated conventional tablet form of sumatriptan 100mg: Comparison of 2-hour pain-free outcomes from published analyses of per-protocol populations to estimates of all-treated populations using a worst-case scenario approach

	Evaluable population (published results)		All-treated (estimated)	
Author Year	Eletriptan n/N (% pts)	Sumatriptan n/N (% pts)	Eletriptan n/N (% pts)	Sumatriptan n/N (% pts)
Goadsby 2000	34/117 (29%)	26/115 (23%)	34/136 (25%)	40/129 (31%)
Mathew 2003	280/779 (36%)	216/799 (27%)	280/835 (34%)	266/849 (31%)
Sandrini 2002	52/169 (31%)	29/160 (18%)	52/175 (30%)	39/170 (23%)
Pooled	366/1065 (34%)	271/1074 (25%)	366/1146 (32%)	345/1148 (30%)
Risk difference	0.09 (95% CI, 0.05 to 0.13) Cochran Q=0.787234 (df=2) *P*=0.6746		0.02 (95% CI, –0.04 to +0.07) Cochran Q =3.13898 (df=2) *P*=0.2082	
Relative risk	1.36 (95% CI, 1.19 to 1.55) Cochran Q=1.33899 (df=2) *P*=0.512		1.06 (95% CI, 0.87 to 1.29) Cochran Q =3.126956 (df=2) *P*=0.2094	

Eletriptan 40 mg compared with encapsulated naratriptan 2.5 mg. We included 1 fair-quality trial of 483 adults that treated moderate to severe migraines and found eletriptan 40 mg to

be superior to encapsulated naratriptan 2.5 mg in rates of 2-hour pain-free (35% compared with 14%; $P<0.001$), 2-hour normal function (60% compared with 52%; $P=0.014$), and 24-hour sustained pain-free (22% compared with 11%; $P<0.05$).[28]

Eletriptan 40 mg compared with encapsulated zolmitriptan 2.5 mg. We included 1 fair-quality trial of 1337 adults that treated moderate to severe migraines and found eletriptan 40 mg to be similar to the lowest recommended dosage of zolmitriptan 2.5 mg (encapsulated) on rates of 2-hour pain-free (32% compared with 26%), 2-hour functional response (61% compared with 55%), and 24-hour sustained pain-free (20% compared with 17%).[27]

Placebo-controlled trials: Eletriptan

Placebo-controlled trials provided supplemental information about the efficacy of eletriptan 40 mg in the early treatment of mild migraines and improving quality of life.

Early intervention. The efficacy of eletriptan 40 mg administered while pain is mild has been demonstrated in 1 fair-quality placebo-controlled trial of 565 adults.[58] In this trial, patients were instructed to take trial medication as soon as they were sure that they were experiencing a migraine. Despite being encouraged to take the medication while the pain was still mild, almost half of patients reported pain that was moderate to severe upon treatment. Consequently, the investigators based analyses on only the subgroup of patients whose pain was still mild at baseline. In this subgroup, eletriptan 40 mg was superior to placebo in rates of 2-hour pain-free (68% compared with 25%; $P<0.0001$) and 24-hour sustained pain-free (56% compared with 18%; $P<0.01$). Based on our independent random-effects meta-analysis (Appendix D) for 2-hour pain-free, the relative risk was 2.72 (95% CI, 1.92 to 3.84) and the number-needed-to-treat was 2. For 24-hour pain-free, the relative risk was 3.21 (95% CI, 2.09 to 4.94) and the number-needed-to-treat was 3.

Work productivity. We included 2 placebo-controlled trials that evaluated the efficacy of eletriptan 40 mg in improving work productivity outcomes.[59, 60] Eletriptan 40 mg reduced total time lost (4 compared with 9 hours; *P* not reported) and work time lost (2.5 compared with 4 hours; $P=0.013$) in 1 placebo-controlled trial.[60] In the other trial, improvements on the Work Productivity Questionnaire (PQ-7) were significantly greater for eletriptan 40 mg than placebo (+22.4 compared with +11.8; $P<0.01$).[59]

Rizatriptan

Direct comparisons

Rizatriptan 10 mg compared with the conventional tablet form of sumatriptan. We included 4 fair-quality head-to-head trials comparing rizatriptan 10 mg with the conventional tablet form of sumatriptan 100 mg[36, 37] and the conventional tablet form of sumatriptan 50 mg in patients with migraine of moderate to severe pain intensity.[32, 33] Supplemental unpublished data for 3 of these trials was provided by the manufacturer.[32, 35, 36]

In terms of quality, the main limitation for both trials of rizatriptan 10 mg compared with the conventional tablet form of sumatriptan 100 mg was a randomization process that did not achieve balance between treatment groups on all baseline characteristics. In the trial conducted by Tfelt-Hansen and colleagues, patients in the rizatriptan 10 mg group were significantly younger than patients in the conventional tablet form of sumatriptan 100 mg group (37 years compared with 39 years; $P<0.01$). The age difference was adjusted for in the analysis of the primary outcome of time to pain relief, but not for other outcomes.[36] In the trial by Visser and colleagues, patients in the conventional tablet form of sumatriptan 100 mg group were

predominantly from tertiary referral centers in the Netherlands, and 62% had severe pain at baseline. In contrast, the rizatriptan 10 mg, 20 mg, and 30 mg and placebo groups consisted of patients from the Netherlands and the United States, with 47% to 51% having severe pain at baseline. The difference in proportion of patients with severe pain at baseline was statistically significant for only the comparison of the conventional tablet form of sumatriptan 100 mg (62%) with placebo (47%; *P* not reported).[37]

Findings were mixed across these trials (Table 4) and do not demonstrate a clear advantage for rizatriptan over the conventional tablet form of sumatriptan 50 mg or 100 mg. Findings were most favorable for rizatriptan 10 mg over the conventional tablet form of sumatriptan 100 mg in the Tfelt-Hansen trial, which involved 1099 adults with migraine pain of moderate to severe intensity.[36] However, this trial differed from the others in one main way: Patients with prior exposure to rizatriptan were excluded, which limits the applicability of these findings to patients who are rizatriptan-naive. In the other 3 trials, patients were enrolled regardless of prior triptan use.[32, 33, 37]

At 1 hour, rates of pain-free were generally higher in the rizatriptan 10 mg treatment groups, but only 1 difference in 1 trial reached statistical significance, a comparison with the conventional tablet form of sumatriptan 50 mg.[32] At 2 hours, rates of pain-free and normal function were again generally higher in the rizatriptan 10 mg treatment groups, but the differences reached statistical significance only in the Tfelt-Hansen trial.[36]

For the comparison of the conventional tablet form of sumatriptan 100 mg to rizatriptan 10 mg, although the difference in 2-hour pain-free reached statistical significance in only 1[36] of 2 individual trials,[36, 37] when Ferrari and colleagues[11] pooled these trials' data, the combined direct difference (–7) was statistically significant (95% CI, –13 to –1). For the comparison of the conventional tablet form of sumatriptan 50 mg to rizatriptan, even when Ferrari and colleagues pooled data from the 2 individual trials, the combined direct difference (–3) did not reach statistical significance for 2-hour pain-free outcomes (95% CI, –9 to +2).[11]

Table 5. One-hour and 2-hour outcomes in head-to-head trials comparing rizatriptan with the conventional tablet form of sumatriptan

Author Year	Triptan	Pain-free				2-hour normal function	
		1-hour	*P* value	2-hour	*P* value		*P* value
Tfelt-Hansen 1998[36]	Rizatriptan 10 mg	10%	NS	40%	<0.05	42%	<0.05
	Sumatriptan 100 mg	8%		33%		33%	
Visser 1996[37]	Rizatriptan 10 mg	NR	NR	26%	NS	27%	NS
	Sumatriptan 100 mg	NR		22%		25%	
Goldstein 1998[32]	Rizatriptan 10 mg	11%	0.04	41%	NS	48%	NS
	Sumatriptan 50 mg	8%		37%		43%	
Kolodny 2004[33]	Rizatriptan 10 mg	9%	NS	38%	NS	46%	NS
	Sumatriptan 50 mg	8%		34%		42%	

At 24 hours, the rate of recurrence was similar for rizatriptan 10 mg and the conventional tablet form of sumatriptan 50 mg[32] and 100 mg.[36, 37] Data on sustained pain-free outcomes at 24 hours were not reported in the original publications. However, based on pooled direct difference estimates for 24-hour sustained pain-free outcomes that were calculated by Ferrari and colleagues using unpublished data obtained from the drugs' manufacturers, differences between rizatriptan 10 mg and the conventional tablet form of sumatriptan 50 mg (–2; 95% CI, –7 to +3) and 100 mg (–4; 95% CI, –9 to +2) were not statistically significant.[11]

For 24-hour quality of life, there were generally no significant differences in mean scores for the 5 domains of the Migraine-Specific Quality-of-Life Questionnaire across the trials comparing rizatriptan 10 mg with the conventional tablet form of sumatriptan 50 mg[32, 33] or 100 mg.[36] The only exception was that the mean score on the Work Functioning domain was significantly greater for rizatriptan 10 mg than the conventional tablet form of sumatriptan 50 mg (12.9 compared with 12.3; P=0.029) in 1 of the 2 trials.[32] Quality-of-life outcomes were not reported in the Visser trial of rizatriptan 10 mg and the conventional tablet form of sumatriptan 100 mg.

Rizatriptan 10 mg compared with naratriptan 2.5 mg. Rizatriptan 10 mg was superior to naratriptan 2.5 mg in 1 good-quality trial (N=522).[31] However, limitations in consistency and applicability reduced the strength of the findings from this trial. Rizatriptan 10 mg was superior to naratriptan 2.5 mg on the 2-hour outcomes of time to pain relief (hazard ratio 1.62; 95% CI, 1.26 to 2.09), rates of pain-free (45% compared with 21%; P=0.001), and normal functioning (39% compared with 23%; P<0.001). At 2-hours, overall satisfaction was also measured using a 7-point scale (1=completely satisfied and 7=completely dissatisfied) and was significantly higher for rizatriptan 10 mg (3.55; P<0.001) than naratriptan 2.5 mg (4.21). But, inconsistent with 2-hour outcomes, differences between rizatriptan 10 mg and naratriptan 2.5 mg were not statistically significant on 24-hour outcomes. At 24 hours, similar numbers of patients on rizatriptan 10 mg and naratriptan 2.5 needed additional medication (40% compared with 46%; *P*

not reported), had recurrences (33% compared with 21%; *P* not reported), and had improved scores on the Migraine-Specific Quality-of-Life Questionnaire (*P* not reported), including Work Functioning (11.73 compared with 11.86), Social Functioning (12.16 compared with 11.92), Energy/Vitality (11.56 compared with 11.95), Migraine Symptoms (12.42 compared with 12.37), and Feelings/Concerns (11.55 compared with 11.79).[61] Additionally, the applicability of this trial was potentially limited due to its exclusion of patients with prior exposure to rizatriptan or naratriptan.

Rizatriptan 10 mg compared with zolmitriptan 2.5 mg. Rizatriptan 10 mg showed an advantage over the lowest recommended dose of zolmitriptan 2.5 mg on 2-hour outcomes in a fair-quality trial of 766 adults with moderate to severe migraine pain.[35] Patients were eligible for enrollment regardless of their prior triptan use, but only 30% had used any triptan within the past 30 days. Compared with zolmitriptan 2.5 mg, rizatriptan had a similar rate of 1-hour pain-free (13% compared with 10%) and superior rates of 2-hour pain-free (43% compared with 36%; $P<0.05$) and normal function (45% compared with 37%; $P<0.05$). At 24 hours, rizatriptan 10 mg and zolmitriptan 2.5 mg had similar rates of recurrence (28% compared with 29%) and similar mean scores on all 5 domains of the Migraine-Specific Quality-of-Life Questionnaire.

Placebo-controlled trials: Rizatriptan

Because head-to-head trials involving rizatriptan lacked data about consistency of effect and early treatment of migraine, we examined placebo-controlled trials that measured these outcomes.

Consistency. We found 1 fair-quality placebo-controlled trial that examined the use of rizatriptan 10 mg for treatment of 4 consecutive migraine headaches.[62] Rizatriptan showed consistently higher 2-hour response rates than placebo during headache 1 (77% [320/246] compared with 37% [30/82]; $P<0.01$), headache 2 (78% [228/291] compared with 37% [27/73]; *P* not reported), headache 3 (80% [207/259] compared with 28% [21/75]; *P* not reported), and headache 4 (74% [190/255] compared with 54% [31/57]; *P* not reported). However, it is unclear whether differences between rizatriptan and placebo groups in the number of patients excluded from the analyses of headache 2 (9% compared with 11%), headache 3 (19% compared with 8%), and headache 4 (20% compared with 30%) may have resulted in groups compared after headache 1 being dissimilar in important patient characteristics that could have biased the analyses.

Early intervention. The efficacy of rizatriptan 10 mg administered early in a migraine, while pain is mild, has been demonstrated in 2 identically designed, good-quality placebo-controlled trials named Rizatriptan TAME1 (Treat A Migraine Early) and TAME2.[63] Findings from TAME1 and TAME2 were both reported in a single publication. Eligibility criteria required a history of migraines that typically started out mild. The study plan was for patients to treat their migraines while still mild in severity and present for less than 1 hour, but not spontaneously resolving. In both trials, rizatriptan was superior to placebo in rates of 2-hour pain-free and 24-hour sustained pain-free. Rates of 2-hour pain-free for rizatriptan compared with placebo in TAME1 were 57% and 31%, respectively, and in TAME2 were 59% and 31%, respectively (*P* not reported for pairwise comparisons). Rates of 24-hour sustained pain-free for rizatriptan compared with placebo in TAME1 were 43% and 23%, respectively, and in TAME2 were 48% and 25%, respectively (*P* not reported for pairwise comparisons). Based on our independent random-effects meta-analysis (Appendix D), these findings resulted in a pooled relative risk of 1.86 (95% CI, 1.57 to 2.21) and a number-needed-to-treat of 3 for 2-hour pain-free outcomes.

For 24-hour sustained pain-free rates, we calculated a pooled relative risk of 3.52 (95% CI, 1.67 to 7.42) and a number-needed-to-treat of 5.

Rizatriptan orally disintegrating tablets

Direct comparisons

Rizatriptan orally disintegrating tablet 10 mg compared with the conventional tablet form of sumatriptan 100 mg. We found no head-to-head trials that compared rizatriptan orally disintegrating tablet 10 mg to sumatriptan 100 mg; that evaluated quality-of-life, workplace, or consistency outcomes; or that evaluated early treatment of mild migraine. Two open, fair-quality trials demonstrated rizatriptan orally disintegrating tablet 10 mg to be superior to the conventional tablet form of sumatriptan 50 mg on preference and rates of 2-hour normal function and pain-free.[39, 41] Similar numbers of patients had recurrence of migraine within 24-hours with both rizatriptan orally disintegrating tablet 10 mg and the conventional tablet form of sumatriptan 50 mg. Only 1 of the 2 trials reported 24-hour sustained pain-free outcomes, and the rate was significantly greater for rizatriptan orally disintegrating tablet 10 mg than the conventional tablet form of sumatriptan 50 mg (41% compared with 32.3%; odds ratio 1.47; 95% CI, 1.14 to 1.90).[41]

Rizatriptan orally disintegrating tablet 10 mg compared with eletriptan 40 mg. We also found 1 fair-quality, open head-to-head trial primarily designed to evaluate preference for rizatriptan orally disintegrating tablet 10 mg compared with eletriptan 40 mg in 439 adults who had no prior experience with either triptan.[38] Greater numbers of patients expressed a preference for treatment with rizatriptan orally disintegrating tablet 10 mg (61%; 95% CI, 56 to 66) than eletriptan 40 mg (39%; 95% CI, 34 to 44), with the most common reason being "relieved my headache pain faster." At 2 hours, similar numbers of patients in the rizatriptan and eletriptan groups were completely or very satisfied with study medication (45% compared with 40%), were pain-free (52% compared with 50%), or had any functional disability (43% compared with 47%). Rates of 24-hour sustained pain-free were also similar for rizatriptan orally disintegrating tablet 10 mg (43%) and for eletriptan 40 mg (47%).

Placebo-controlled trials: Rizatriptan orally disintegrating tablet

We did not find any placebo-controlled trials that evaluated rizatriptan orally disintegrating tablet 10 mg for consistency over multiple attacks. We are aware of a placebo-controlled trial of rizatriptan orally disintegrating tablet 10 mg for early treatment of migraine (N=207), for which an in-press article is pending publication in an upcoming issue of Headache. However, it was brought to our attention after our search end date of January 2009 and, consequently, a review of its findings will be postponed until the next update of this review.

Although we did not find any published quality-of-life data, the manufacturer provided unpublished data[61] for 1 published placebo-controlled trial.[64] This trial involved treatment of 555 adults with moderate to severe pain intensity and prior triptan use was allowed. The Migraine-Specific Quality-of-Life Questionnaire was used to measure quality of life at 24 hours; rizatriptan orally disintegrating tablet 10 mg was superior to placebo ($P<0.001$) in mean scores on all 5 domains: Migraine Symptoms (12.6 compared with 10.3), Feelings/Concerns (11.2 compared with 8.6), Work Functioning (12.6 compared with 10.5), Social Functioning (12.2 compared with 10.1), and Energy/Vitality (11.6 compared with 9.6).

Zolmitriptan: Oral tablet, orally disintegrating tablet, nasal spray

Direct comparisons: Oral tablet

We included head-to-head trials of oral zolmitriptan 5 mg compared with the conventional tablet form of sumatriptan 100 mg[45] and 50 mg.[44, 46] We also identified unpublished data from a trial comparing zolmitriptan 2.5 mg with naratriptan 2.5 mg (Protocol 311CIL/0099) that we accessed in the form of a summary report on the manufacturer's website (http://www.astrazenecaclinicaltrials.com). The trials involving the conventional tablet form of sumatriptan[12, 65] and naratriptan 2.5 mg[65] have been previously evaluated in meta-analyses that estimated direct differences and rate ratios. All 3 trials involved treatment of moderate to severe migraines. The trials comparing zolmitriptan 5 mg with the conventional tablet form of sumatriptan 50 mg provided data on consistency of treatment across 6 consecutive headaches.[44, 45] We found no head-to-head trials involving zolmitriptan that evaluated its effects in early treatment of mild migraines or its effects on quality of life or work productivity.

Zolmitriptan 5 mg compared with the conventional tablet form of sumatriptan. One fair-quality trial compared zolmitriptan 5 mg to the conventional tablet form of sumatriptan 100 mg in 1058 adults who had never been treated with either triptan.[45] Zolmitriptan 5 mg and the conventional tablet form of sumatriptan 100 mg had similar rates of pain-free at 1 hour (8% compared with 10%; rate ratio 0.70; 95% CI, 0.47 to 1.04)[65] and 2 hours (29% compared with 30%; rate ratio 0.98; 95% CI, 0.81 to 1.18),[65] no activity impairment at 2 hours (data not reported), recurrence at 24 hours (26% compared with 28%), and complete response at 24 hours (39% compared with 38%). In the Ferrari meta-analysis of unpublished data provided by manufacturers, the conventional tablet form of sumatriptan 100 mg and zolmitriptan 5 mg also had similar rates of 24-hour pain-free (direct difference –1; 95% CI, –5 to +6).[12]

For the comparison of zolmitriptan 5 mg to the conventional tablet form of sumatriptan 50 mg, 2-hour and 24-hour pain-free rates were published for only 1 of the 2 trials for 1522 (90%) of participants who treated at least 2 attacks.[46] Using those data and unpublished data for the other trial,[44] Ferrari and colleagues calculated pooled direct differences for 2-hour pain-free (0%; 95% CI, –4 to +4) and 24-hour sustained pain-free (–1%; 95% CI, –5 to +3), suggesting that zolmitriptan 5 mg and the conventional tablet form of sumatriptan 50 mg have similar effects on these outcomes.[12]

The 2 head-to-head trials comparing zolmitriptan 5 mg to the conventional tablet form of sumatriptan 50 mg also provided the best data on consistency. The first of these, conducted in the United States, compared zolmitriptan 2.5 mg and 5 mg to sumatriptan 25 mg and 50 mg.[44, 66] Over 6 months, each patient was treated for up to 6 consecutive headaches. Patients were recruited from primary care, neurology, and research clinics. Of 1445 patients enrolled, 1212 treated at least 2 migraine headaches and 1043 completed the study. However, this trial has been criticized because it did not exclude patients who had previously taken sumatriptan.[67] There may have been a selection bias favoring zolmitriptan, since patients who responded inconsistently to sumatriptan in the past may be more likely to enroll in an experimental trial of a newer triptan. To assess consistency, the authors calculated the proportion of patients who responded in 2 hours in 80% to 100% of headaches (Table 6). The results indicate that the 2-hour response is not a reliable indicator of consistency across multiple migraine headaches.

Table 6. Consistency of response[a] in Gallagher 2000

Triptan	2-hour pain-relief	Consistency across 6 migraine headaches
Zolmitriptan 2.5 mg	67.1%	47.1%
Zolmitriptan 5 mg	64.8%	44.3%
Sumatriptan 25 mg	59.6%	33.0%
Sumatriptan 50 mg	63.8%	39.2%

[a] Response was defined as a reduction in headache intensity from severe of moderate at baseline to mild or none.

A good-quality trial of similar design was conducted in Europe.[46] In that trial, there were essentially no differences in efficacy among zolmitriptan 2.5 mg, zolmitriptan 5 mg, and sumatriptan 50 mg. The 3 treatments also had similar consistency across attacks: about 40% of patients in each group reported a 2-hour response in 80% or more of their headaches.

Zolmitriptan 2.5 mg compared with naratriptan 2.5 mg. An unpublished trial comparing zolmitriptan 2.5 mg with naratriptan 2.5 mg consisted of 2 parts. In Part 1, 553 adults were randomized to treat 1 headache with zolmitriptan 2.5 mg, naratriptan 2.5 mg, or placebo. The 438 who treated a headache and provided efficacy data were re-randomized to either zolmitriptan 2.5 mg or naratriptan to treat up to 3 more headaches in Part 2. According to the trial's brief summary report, a higher proportion of patients in the zolmitriptan groups had headaches of severe intensity at baseline in both Parts 1 and 2. However, we could not examine the magnitude of these differences or any other baseline characteristics as their details were not provided in the trial summary report. It was noted that the baseline difference was more marked in Part 1 and was adjusted for in the analysis of 2-hour pain-relief data. The adjusted 2-hour pain-relief rate was similar for zolmitriptan 2.5 mg and naratriptan 2.5 mg (54% compared with 47%). Although the trial summary did not report 2-hour or 24-hour pain-free outcomes, Chen and colleagues obtained these data from the manufacturer and estimated risk ratios of 1.73 (95% CI, 1.10 to 2.72) and 1.04 (95% CI, 0.74 to 1.47), respectively.[65] However, as these risk ratios do not appear to have been adjusted for the above-described baseline differences in headache intensity, we interpret these risk ratios with caution.

Direct comparisons: Zolmitriptan orally disintegrating tablets and nasal spray

We included 1 head-to-head trial comparing zolmitriptan orally disintegrating tablet 2.5 mg with the conventional tablet form of sumatriptan 50 mg[49] and 2 head-to-head trials that compared different formulations of zolmitriptan.[47, 48]

Zolmitriptan orally disintegrating tablet compared with the conventional tablet form of sumatriptan 50 mg. In 1 head-to-head trial, 218 adults were randomized to open treatment with either zolmitriptan orally disintegrating tablet or the conventional tablet form of sumatriptan and were then crossed over to treat a second migraine with the alternative trial medication.[49] Results were reported for only the combined treatment periods. Patients with prior use of either trial medication within the past 3 months were excluded. The trial was designed to measure patient preference. The standard pain, associated migraine symptom, and functional capacity outcomes were not reported. Preference data were unavailable for 18 (10%) of patients. Because of these flaws, this trial was rated poor quality and its results will not be discussed here.

Comparisons of different zolmitriptan formulations. One good-quality, randomized trial (N=1372) compared double-blinded, double-dummy treatment with zolmitriptan nasal spray 0.5

mg, 1.0 mg, 2.5 mg, and 5.0 mg and oral zolmitriptan 2.5 mg.[47] Another trial used a crossover design to compare patient preference among zolmitriptan orally disintegrating tablet 2.5 mg, zolmitriptan standard oral tablet 2.5 mg, and zolmitriptan nasal spray 5 mg, but it was rated poor quality due to lack of blinding, presence of high attrition, and lack of separately reported results from the first treatment period.[48]

The good-quality trial found zolmitriptan nasal spray 5 mg to be superior to zolmitriptan standard oral tablet 2.5 mg on rate of pain-free at 30 minutes (7% compared with 2%; $P<0.05$) and 45 minutes (10% compared with 5%; $P<0.05$) and on rate of resumption of normal activities at all time points (53% compared with 45%; *P* not reported). Zolmitriptan nasal spray 5 mg and zolmitriptan standard oral tablet 2.5 mg were similar on rate of 2-hour pain-free (38% compared with 37%) and rate of recurrence at 24 hours (26% for both). Zolmitriptan nasal spray 2.5 mg was similar to zolmitriptan standard oral tablet 2.5 mg in rate of pain-free at timepoints between 30 minutes and 1 hour, but was inferior at 2 hours (26% compared with 37%; $P<0.05$) and 4 hours (43% compared with 54%; $P<0.05$).

Placebo-controlled trials: Zolmitriptan

Early intervention. The efficacy of zolmitriptan standard oral tablet 2.5 mg administered while pain is mild has been demonstrated in 1 fair-quality placebo-controlled trial.[68] In this trial, 280 patients were instructed to administer treatment when pain was still mild and within 4 hours of onset. Zolmitriptan was superior to placebo in rates of 2-hour pain-free (43% compared with 18%; $P<0.001$) and 2-hour normal function (68% compared with 51%; $P<0.01$). The only 24-hour outcome reported was need for further medication, which was significantly lower after zolmitriptan 2.5 mg (46%) than placebo (71%; $P<0.0001$). Based on our independent random-effects meta-analysis (Appendix D), these findings correspond to a pooled relative risk of 2.41 (95% CI, 1.81 to 3.20) and a number-needed-to-treat of 4 for 2-hour pain-free outcomes.

Almotriptan

Direct comparisons

We included 4 head-to-head trials of almotriptan 12.5 mg, including comparisons to the conventional tablet form of sumatriptan 100 mg[20] and 50 mg,[69] rizatriptan 10 mg,[22] and zolmitriptan 2.5 mg.[23] Three[21, 23, 69] of 4 head-to-head trials were previously evaluated in a recent meta-analysis.[70]

Almotriptan 12.5 mg compared with the conventional tablet form of sumatriptan. Both trials comparing almotriptan 12.5 mg with the conventional tablet form of sumatriptan were rated fair quality due to differences between comparison groups at baseline, and both provided data on 2-hour pain-free and 24-hour recurrence outcomes.[20, 69] Rate of 2-hour pain-free was consistently lower for almotriptan 12.5 mg in both trials. Compared with the conventional tablet form of sumatriptan 50 mg (25%), significantly fewer patients were pain-free at 2 hours after taking almotriptan 12.5 mg (18%; $P=0.005$). It is unknown, however, whether the higher mean body weight in the almotriptan group (74.5 kg compared with 72.3 kg; $P=0.003$) may have disadvantaged those patients' treatment response. Compared with the conventional tablet form of sumatriptan 100 mg, fewer patients on almotriptan 12.5 mg were pain-free at 2 hours (28% compared with 33%), but this difference was not statistically significant.[20] At 24 hours, rates of recurrence for almotriptan 12.5 mg were slightly higher than for the conventional tablet form of sumatriptan 50 mg (27% compared with 24%)[69] and slightly lower than for the conventional

tablet form of sumatriptan 100 mg (18% compared with 25%).[20] Differences in 24-hour recurrence rates were nonsignificant in both trials.

Sustained 24-hour pain-free, functional disability, and quality-of-life outcomes were not reported in either of the original trials comparing almotriptan 12.5 mg with the conventional tablet form of sumatriptan. Based on findings from a more recent review of almotriptan trials, however,[70] similar rates of patients had sustained 24-hour pain-free outcomes with almotriptan 12.5 mg and the conventional tablet form of sumatriptan 100 mg (rate ratio 0.86; 95% CI, 0.62 to 1.21).

Almotriptan 12.5 mg compared with zolmitriptan 2.5 mg. One good-quality trial provided evidence that almotriptan 12.5 and zolmitriptan 2.5 mg were similar on 2-hour and 24-hour efficacy outcomes in patients who were enrolled regardless of prior triptan use.[23] Both almotriptan and zolmitriptan tablets were encapsulated for blinding purposes. At 2-hours, almotriptan 12.5 mg and zolmitriptan 2.5 mg were similar in rates of pain-free (43% compared with 48%) and no functional impairment (47% compared with 49%). Almotriptan 12.5 mg and zolmitriptan 2.5 mg were also similar in rates of "excellent" satisfaction (16% compared with 15%) and 24-hour sustained pain-free plus no adverse events (29% compared with 32%).

Almotriptan 12.5 mg compared with rizatriptan 10 mg. One fair-quality trial was designed primarily to compare patient preference for open almotriptan 12.5 mg against open rizatriptan 10 mg in patients from Germany, Italy, and Spain who had never been treated with either triptan.[22] Among the 255 of 327 patients in the 2-attack intention-to-treat population who recorded a preference for one triptan over another, half preferred almotriptan (n=128) and the other half preferred rizatriptan (n=127). Among the secondary efficacy variables analyzed (e.g., 2-hour pain-free; 2-hour pain-relief; sustained pain-free; sustained pain-free plus no adverse events; use of rescue medications; recurrence between 2-24 hours; recurrence between 24-48 hours), the only significant difference found indicated an advantage for rizatriptan 10 mg over almotriptan 12.5 mg on 2-hour pain-free outcomes (58% compared with 52%; P=0.03). This trial did not report quality-of-life or functional disability outcomes.

Placebo-controlled trials: Almotriptan

As 24-hour pain-free outcomes were not reported in head-to-head trials of almotriptan 12.5 compared with conventional sumatriptan 100 mg, we relied on findings from the meta-analysis by Ferrari and colleagues that used data from placebo-controlled trials to enable indirect comparison between the 2 triptans.[11] We also included placebo-controlled trials of almotriptan that analyzed consistent treatment across multiple headaches[71] and early treatment of mild migraine.[72-74]

Indirect comparison of almotriptan with the conventional tablet form of sumatriptan 100 mg for 24-hour pain-free. In their meta-analysis of 53 triptan trials, Ferrari and colleagues included data from 3 abstracts of placebo-controlled trials of almotriptan 12.5 mg.[75-77] Using pooled data from the almotriptan 12.5 arms of these trials, they calculated a mean absolute rate of sustained pain-free, which they compared to the mean for the conventional tablet form of sumatriptan. The actual mean value and 95% confidence interval was not provided for almotriptan but it was described as being higher than for the conventional tablet form of sumatriptan 100 mg. However, this comparison did not assess or adjust for potential clinical or methodological heterogeneity across trials. Therefore, we suggest that this finding be interpreted with caution.

Consistency. We found 1 fair-quality, placebo-controlled trial that examined the use of almotriptan 12.5 mg for treatment of 3 consecutive headaches.[71] The results of this trial demonstrated that a significantly greater number of patients achieved 2-hour pain-free outcomes in 3 of 3 headaches with almotriptan 12.5 mg than placebo (18% compared with 5%; $P<0.05$).

Early intervention. The efficacy of almotriptan 12.5 mg administered early in a migraine, while pain is mild, has been demonstrated in 2 fair-quality placebo-controlled trials named Act when Mild ('AwM')[73] and Axert® Early Migraine Intervention Study ('AEGIS').[74] The 'AwM' trial was designed to compare early and non-early intervention and involved 4 treatment groups. For the purposes of this review, our interest was in the 2 treatment groups in which patients were randomized to administer treatment with almotriptan or placebo when pain was still mild and within 1 hour of onset. Results from the other 2 treatment groups, in which patients were randomized to administer treatment with almotriptan or placebo when pain was moderate to severe, were reported separately and will not be discussed here. In the Axert® Early Migraine Intervention Study, patients were allowed to treat pain of any intensity, as long as it was within 1 hour of onset, but outcomes for mild and moderate-to-severe headaches were reported separately. In both trials, almotriptan was superior to placebo in rates of 2-hour pain-free and 24-hour sustained pain-free. Rate of 2-hour pain-free in 'AwM' was 49% for almotriptan and 25% for placebo (odds ratio 2.93; 95% CI, 1.62 to 5.31; $P=0.0004$), and in 'AEGIS' were and 37% and 24%, respectively ($P=0.01$). Rate of 24-hour sustained pain-free was 46% for almotriptan and 16% for placebo in 'AwM', and in the 'AEGIS' trial was 25% and 16%, respectively ($P=0.040$). Based on our independent random-effects meta-analysis (Appendix D), these findings correspond to a pooled relative risk of 1.71 (95% CI, 1.32 to 2.21) and a number-needed-to-treat of 6 for 2-hour pain-free outcomes. For 24-hour sustained pain-free rates, we calculated a pooled relative risk of 2.08 (95% CI, 1.12 to 3.86) and a number-needed-to-treat of 6. Functional disability and quality-of-life outcomes were also reported in a secondary publication of the 'AEGIS' trial.[72] At 2 hours, mean functional disability scores showed that significantly more patients functioned normally with almotriptan than placebo (54% compared with 38%; $P=0.007$). At 24 hours, scores in all 5 domains of the Migraine Quality-of-life Questionnaire were consistently better for almotriptan than placebo.

Naratriptan

Direct comparisons

We included 2 head-to-head trials comparing naratriptan 2.5 mg with the conventional tablet form of sumatriptan 100 mg.[29, 30] One was good quality[30] and the other was fair.[29] In the good-quality trial, naratriptan 2.5 mg and the conventional tablet form of sumatriptan 100 mg had similar rates of 2-hour pain-relief (60% compared with 52%) and 2-hour no-or-mild disability (54% compared with 62%).[30] No statistical analyses were performed on 24-hour outcome data, but naratriptan 2.5 mg appeared to have a lower rate of recurrence (17% compared with 44%) and a similar rate of sustained relief (48% compared with 44%) compared with sumatriptan 100 mg. The fair-quality trial did not report pain outcomes at 2 hours,[29] but rates of 4-hour pain relief (76% compared with 84%) and 24-hour sustained relief (39% compared with 34%) were reported as similar for naratriptan 2.5 mg and the conventional tablet form of sumatriptan. Neither trial reported on pain-free, workplace productivity, or quality of life. Both trials looked at treatment of only 1 headache per patient and thus did not provide data on consistency of response across multiple headaches.

Placebo-controlled trials: Naratriptan

We found no placebo-controlled trials of naratriptan that reported quality of life, workplace productivity, or 2-hour or 24-hour pain-free outcomes. We also found no placebo-controlled trials that evaluated consistency of naratriptan across multiple headaches.

Reformulated (rapid-release) oral sumatriptan

Direct comparisons

We found no head-to-head trial directly comparing reformulated (rapid-release) oral sumatriptan tablet with any other triptan.

Placebo-controlled trials: Reformulated oral sumatriptan

We included placebo-controlled trials of reformulated oral sumatriptan that looked at early treatment of migraine while pain is still mild.[78, 79] We also used data from placebo-controlled trials of reformulated sumatriptan 100 mg and the conventional tablet form of sumatriptan to explore indirect comparisons between the 2 formulations on 2-hour pain-free rates.

Early intervention. The efficacy of reformulated sumatriptan 100 mg administered early in a migraine, while pain is mild, was demonstrated in a fair-quality trial of 432 adults who were instructed to administer treatment when pain was still mild and within 1 hour of onset.[78, 79] Rate of 2-hour pain-free was 66% for reformulated sumatriptan 100 mg and 20% for placebo ($P<0.001$). At 24 hours, rate of sustained pain-free also was significantly greater for reformulated sumatriptan 100 mg than placebo (40% compared with 10%; $P<0.001$). From these data, we calculated a relative risk of 3.38 (95% CI, 2.65 to 4.30) and a number needed to treat of 2 for 2-hour pain-free and a relative risk of 4.09 (95% CI, 2.83 to 5.92) and a number needed to treat of 3 for 24-hour sustained pain-free.

Function and productivity outcomes from this trial were reported.[78] Compared with placebo, rate of normal function was significantly greater for reformulated sumatriptan 100 mg at 45 minutes (29% compared with 18%; $P<0.05$), 1 hour (50% compared with 25%; $P<0.001$), and 2 hours (60% compared with 28%; $P<0.001$). At 24 hours, significantly less time was lost on activities other than paid work for reformulated sumatriptan 100 mg (2.0 hours) than placebo (3.6 hours; $P<0.05$). However, lost time in paid work was similar for reformulated sumatriptan 100 mg and placebo (2.5 and 1.9 hours, respectively).

Indirect comparison of reformulated with the conventional tablet form of sumatriptan. In the absence of head-to-head trials that directly compared reformulated and the conventional tablet form of sumatriptan, we explored indirect comparisons between formulations using data from placebo-controlled trials. Data from placebo-controlled trials of reformulated sumatriptan[80] and the conventional tablet form of sumatriptan[36, 37, 45, 81-85] were pooled, and combined relative risks and numbers needed to treat were generated for each triptan for 2-hour pain-free rates (Table 6). Estimates of relative risk were similar for the conventional tablet form of sumatriptan and reformulated sumatriptan and the large overlap of 95% confidence intervals did not suggest a clear advantage for either formulation over the other. However, the somewhat higher rate of 2-hour pain-free rates in the placebo group of the reformulated sumatriptan trial compared with those of the conventional tablet form of sumatriptan trials suggests the presence of at least some heterogeneity between the 2 sets of trials, likely in patient population or outcome assessment. Therefore, we caution against drawing firm conclusions about the comparison of reformulated and the conventional tablet form of sumatriptan until results from adjusted, quantitative, indirect comparisons, or head-to-head trials become available.

We also sought results on 24-hour sustained pain-free outcomes from placebo-controlled trials of reformulated and the conventional tablet form of sumatriptan, but insufficient data were available from trials of conventional sumatriptan.

Table 7. Pain-free at 2 hours in placebo-controlled trials: Pooled relative risk and number needed to treat for conventional and reformulated sumatriptan

Sumatriptan 100 mg	% sumatriptan group pain-free at 2 hr (n/N)	% placebo group pain-free at 2 hr (n/N)	Relative risk of 2 hr pain-free (95% confidence interval)	Number needed to treat	Heterogeneity: Q (degrees of freedom), *P*
Conventional	30% (437/1478)	8% (57/696)	3.30 (2.51 to 4.34)	4	7.36 (7) *P*=0.3923
Reformulated	47% (426/902)	15% (137/892)	3.13 (2.09 to 4.68)	3	5.38 (1) *P*=0.02

Sumatriptan injection and nasal spray

Direct comparisons

We included 2 head-to-head trials that compared injectable sumatriptan with the conventional oral formulation.[42, 43] But because the trials were poor quality, their findings will not be discussed here. We found no head-to-head trials comparing sumatriptan nasal spray with any other triptan.

Placebo-controlled trials: Sumatriptan injection

Indirect comparisons of subcutaneous sumatriptan to oral formulations of other triptans. Sumatriptan is the only triptan approved in the United States and Canada in an injectable form. Given the lack of fair-quality or good-quality head-to-head trials involving subcutaneous sumatriptan 6 mg, we examined findings of a good-quality systematic review that qualitatively evaluated indirect comparisons between subcutaneous sumatriptan 6 mg and other triptans on the basis of unadjusted estimates of relative risk calculated for each triptan using pooled data from placebo-controlled trials.[52] The main advantage of subcutaneous sumatriptan 6 mg over oral triptans is that it could potentially provide earlier pain relief. In 12 trials,[86-89 90-96] pooled rates of 1-hour pain relief were significantly greater for subcutaneous sumatriptan 6 mg than placebo (70% compared with 22%), which resulted in the largest relative benefit estimate (3.2; 95% CI, 2.8 to 3.6) and a number needed to treat of 2.[52] Benefits relative to placebo calculated for other triptans were lower, ranging from 1.6 (95% CI, 1.3 to 1.9) for oral the conventional tablet form of sumatriptan 100 mg to 2.3 (95% CI, 1.9 to 2.8) for eletriptan 40 mg.

Functional capacity, work productivity, and quality of life. Numerous fair-quality, placebo-controlled studies of subcutaneous sumatriptan reported on functional capacity, work productivity, and quality of life.[86-90, 92-106] Subcutaneous sumatriptan consistently reduced time to return to work,[86, 89, 90, 94-96, 103] degree of clinical disability,[87, 88, 93, 98, 99, 102, 105, 106] and time to emergency room discharge[98] and improved quality of life-related symptoms (contentment and vitality dimensions of the Minor Symptom Evaluation Profile).[102]

Frovatriptan

Direct comparisons

We are aware of 1 head-to-head trial that directly compared frovatriptan 2.5 mg with the conventional tablet form of sumatriptan 100 mg.[107] However, information about this trial is available only in the form of an abstract, which did not provide adequate methodological detail for assessment of internal validity. Consequently, results from this trial were excluded from our review.

Placebo-controlled trials: Frovatriptan

Indirect comparisons of frovatriptan to other oral triptans. Two-hour pain-free data from placebo-controlled trials were pooled and a combined risk difference for frovatriptan 2.5 mg and for the conventional tablet form of sumatriptan 100 mg were qualitatively compared. For the conventional tablet form of sumatriptan 100 mg, we conducted a risk difference meta-analysis of 8 placebo-controlled trials.[36, 37, 45, 81-85] Compared with placebo (8%, 57/696), rates of 2-hour pain-free were 20% higher (95% CI, 0.16 to 0.25) for the conventional tablet form of sumatriptan 100 mg (30%, 437/1478), with a number needed to treat of 4. For frovatriptan 2.5 mg, we obtained the risk difference estimate for 2-hour pain-free rates from a good-quality systematic review that pooled data from 5 placebo-controlled trials involving a total of 2866 patients.[108] Results of their risk difference meta-analysis indicate that rates of 2-hour pain-free were only 9% higher (95% CI, 0.07 to 0.10; number needed to treat of 12) for frovatriptan 2.5 mg (12%) compared with placebo (3%), indicating frovatriptan is probably inferior to the conventional tablet form of sumatriptan 100 mg.

Early intervention. One fair-quality, placebo-controlled, crossover trial of frovatriptan 2.5 mg reported results from 137 adults who took study medication in the early stage of their migraine.[109] Rate of 2-hour pain-free was better with frovatriptan 2.5 mg than placebo (28% compared with 20%; P=0.04), with a relative risk of 1.40 (95% CI, 1.11 to 1.76) and a number needed to treat of 12. Results of the comparison between frovatriptan 2.5 mg and placebo for rate of 24-hour sustained pain-free were not reported.

Key Question 1b. Fixed-dose combination tablets containing a triptan compared with triptan monotherapy

Direct comparisons

The only 2 head-to-head trials that involved Treximet® were both conducted as part of the new drug application program and were designed to meet the US Food and Drug Administration's minimum requirement for all fixed-dose combination products that the product show superiority to its individual components.[110] Although sumatriptan tablets are commercially available in only 25 mg, 50 mg, and 100 mg strengths, in order to match the dosage strength for the sumatriptan component in Treximet®, these trials used an 85 mg dose for sumatriptan monotherapy. Both trials demonstrated that Treximet® 85 mg/500 mg was superior in efficacy to its individual components, sumatriptan 85 mg and naproxen 500 mg, on the primary outcome of sustained 24-hour pain-free response.[110] Treximet® was also superior to sumatriptan 85 mg in improving patients' return to normal function, overall productivity, and satisfaction with overall effectiveness.[111] Whether Treximet® is superior to monotherapy with the commercially available 100 mg dosage of sumatriptan, or any other triptan, has not yet been directly evaluated in any known head-to-head trial.

Placebo-controlled trials: Treximet®

Placebo-controlled trials provided supplemental evidence on the efficacy of Treximet® in early treatment of migraine when pain is still mild.[112-116]

Early intervention. Treximet® is the most well-studied triptan for early treatment of mild migraine. The efficacy of Treximet® (rapid-release sumatriptan RT 85 mg/naproxen 500 mg) administered early in a migraine while the pain is still mild has been demonstrated in 6 trials (GlaxoSmithKline Protocols TRX101998, TRX101999, TRX103632, TRX103635, TRX106571, and TRX106573), enrolling a total of over 2700 adults. Methods and results for 2 pairs of protocols (TRX101998 and TRX101999; TRX103632 and TRX103635) are fully published in 2 journal articles, respectively.[116, 117] Methods and results for protocols TRX106571 and TRX106573 had not yet been published at the time of this report, but were accessed from the summary reports available on the manufacturer's clinical trial registry website (http://www.gsk-clinicalstudyregister.com). Protocols TRX101998 and TRX101999 used parallel designs and were rated good quality. Protocols TRX106571 and TRX106573 used crossover designs to specifically evaluate efficacy and harms in adults with a history of poor response or intolerance to previous triptan treatment. Protocols TRX106571 and TRX106573 were rated fair-quality mainly because the summary report only provided combined results for both crossover periods, which did not appear to be assessed or adjusted for potential order effects. Protocols TRX103632 and TRX103635 used 4-period crossover designs to evaluate consistency across 3 attacks.[117] Patients were randomized to 1 of 5 treatment sequences, 4 of which contained 1 interspersed placebo treatment period. One sequence that contained 4 consecutive treatment periods of Treximet® was included for comparison in order to assess period effects and within-subject consistency. Results for protocols TRX103632 and TRX103635 were reported separately for the first period only and were rated good quality.

Patients in all 6 trials were instructed to take trial medication within 1 hour of migraine onset and while the pain remained mild. In all 6 trials, Treximet® was superior to placebo on rates of 2-hour pain-free and 24-hour sustained pain-free. We calculated separate pooled relative risk estimates for the subgroup of 4 trials (TRX101998, TRX101999, TRX103632, TRX103635; N=1537) that enrolled patients regardless of their triptan treatment history and for the subgroup of 2 trials, which required prior poor response or intolerance (TRX106571 and TRX106573; N=535). For 2-hour pain-free outcomes, compared to the combined estimate of benefit from the 4 trials that enrolled patients regardless of their prior triptan treatment history (relative risk, 3.12; 95% CI, 2.64 to 3.69), the benefit of Treximet® over placebo was somewhat smaller in the 2 trials which required prior poor response or intolerance to triptans (relative risk, 2.62; 95% CI; 1.92 to 3.58). For 24-hour sustained pain-free outcomes, however, compared with the combined estimate of benefit from the 4 trials of patients with an unspecified triptan treatment history (relative risk, 3.21; 95% CI, 2.63 to 3.91), the benefit of Treximet® over placebo was somewhat larger in patients with a prior history of poor response or intolerance to triptans (relative risk 3.77, 95% CI, 2.38 to 5.99).

Protocols TRX103632 and TRX103635 also evaluated within-subject consistency of 2-hour pain-free and 24-hour sustained pain-free outcomes in 973 of 1135 (86%) patients who treated at least 3 attacks with Treximet®.[117] The rate of patients who were pain-free at 2 hours postdose in at least 2 of the first 3 attacks treated with Treximet® was 52% to 55% across both trials. The rates of patients with a sustained pain-free response through 24 hours postdose in at least 2 of the first 3 attacks treated with Treximet® ranged from 14% to 15% across the 2 trials. Subgroup analyses of the patients randomized to the sequence with no interspersed placebo

treatment found similar rates of 2-hour pain-free and 24-hour sustained pain-free, which suggests against significant period effects. In patients randomized to the sequence that contained 4 consecutive treatment periods of Treximet®, 21% (18/84) in TRX103635 and 28% (27/95) in TRX103632 had 2-hour pain-free outcomes in all 4 attacks.

Open-label studies: Treximet®

The effect of Treximet® on quality of life was evaluated in one 12-month open-label study using the Migraine-Specific Quality of Life Questionnaire.[118] Of the 600 patients enrolled, 565 (94%) treated at least 1 migraine and 362 (64%) completed the 12-month trial and were included in the quality of life analyses. Measurement of clinically relevant improvement was based on changes of +6.80 points for the Role Restrictive domain score, +8.72 points for the Role Preventive domain score, and +5.76 points for the Emotional Function domain score. Proportions of patients who achieved clinically relevant improvements at 12 months were 60% for the Role Restrictive domain, 56% for the Role Preventive domain, and 64% for the Emotional Function domain.

Key Question 1c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic component agents

We found no evidence on the comparison of Treximet® and co-administration of its individual components, reformulated, rapid-release sumatriptan 85 mg and naproxen 500 mg.

Key Question 2. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different triptans in adult patients being treated for migraine?

Key Question 2a. Monotherapy compared with monotherapy

There are no comparative studies concerning serious, life-threatening events associated with triptan use. But data on rare or life-threatening complications is available for the various forms of sumatriptan. A published review of the safety of sumatriptan examined adverse events in clinical trials and postmarketing surveillance data.[119] In 1998, 16 serious cardiovascular events following use of subcutaneous sumatriptan and 11 following use of conventional oral sumatriptan were reported to the voluntary postmarketing surveillance system. In 1993, 103 serious cardiovascular events were reported for subcutaneous sumatriptan and 38 for conventional oral sumatriptan. The review concluded that "serious events including myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of sumatriptan. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low."

Data on rates of overall and specific adverse events from head-to-head trials—chest pain and central nervous system symptoms including dizziness, paresthesia, somnolence, and fatigue/asthenia—are summarized in Appendix E; there were no consistent differences between triptans. In most cases, descriptions of the methods used to assess intensity, duration, seriousness, and relationship to study medication were unclear or were not provided. Investigators generally described the adverse events as predominantly of mild to moderate severity and transient in nature.

Chest pain/tightness

Head-to-head trial results suggest a few differences among triptans in chest pain/tightness. In 1 trial,[36] chest pain was more frequent in patients taking sumatriptan 100 mg than rizatriptan 5 mg (6% compared with 1%; $P<0.05$) but did not differ from rizatriptan 10 mg (6% compared with 3%). Incidence of treatment-emergent chest pain was also significantly greater for the conventional oral form of sumatriptan 50 mg compared with almotriptan 12.5 mg (2.2% compared with 0.3%; $P=0.004$).[69] Subcutaneous sumatriptan 6 mg was associated with higher rates of mild to moderate chest pain than eletriptan 80 mg in 1 open trial of 1696 migraine headaches.[120]

Central nervous system symptoms

No significant between-group differences were reported by the trials that assessed dizziness, paresthesias, or somnolence. In 1 trial, fatigue/asthenia was more frequent in patients using sumatriptan 100 mg than those using rizatriptan 5 mg (8% compared with 2%; $P<0.05$), but no difference was found between sumatriptan 100 mg and rizatriptan 10 mg (8% compared with 8%).[36]

Key Question 2b. Fixed-dose combination tablets containing a triptan compared with triptan monotherapy

In Brandes 2007, adverse event rates that were reported in 2% or more patients in any treatment group were provided separately for the 2 trials comparing Treximet® with monotherapy consisting of reformulated sumatriptan, naproxen 500 mg, or placebo.[110] There was no significant difference between Treximet® and monotherapy with reformulated sumatriptan 85 mg on rate of any adverse event, only dizziness, only paresthesia, or only somnolence. We pooled data from the trials and also found no significant difference in rate of any adverse event between Treximet® and monotherapy with reformulated sumatriptan 85 mg (27% [197/737] of patients using Treximet and 26% [194/735] or patients using reformulated sumatriptan 85 mg). We also found no significant difference in rates of the adverse events dizziness, paresthesia, and somnolence, which were reported by 4% (28/737), 2% (18/737), and 3% (24/737), respectively, of patients using Treximet and 2% (16/735), 2% (17/735), and 2% (17/735), respectively, of patients using sumatriptan. In Study 1, rate of chest discomfort was 2% for Treximet® and 1% for reformulated sumatriptan 85 mg monotherapy. In Study 2, rate of chest discomfort was below 2% in both groups; thus, data was not reported.

Key Question 2c. Fixed-dose tablets containing a triptan compared with co-administration of its individual triptan and analgesic components

We found no evidence comparing Treximet® with co-administration of its components, reformulated, rapid-release sumatriptan RT 85 mg and naproxen 500 mg.

Key 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 adverse effects?

There is no evidence that any ethnic or racial group has a higher risk of adverse events from triptans or that one triptan has a particular advantage over others in any of these groups. Migraine is more common among women than men and in whites than blacks, and peaks in prevalence around age forty.[121] We found no trials that included primarily men, blacks, or the elderly. However, the manufacturer of rizatriptan provided unpublished data on subgroups based on gender, age (< 40 years compared with ≥ 40 years), race (Caucasian or other), prophylactic treatment (any, beta-blockers, calcium channel blockers, tricyclic antidepressants, or valproate), and association with menstruation for 5 head-to-head trials comparing rizatriptan 10 mg with the conventional tablet form of sumatriptan,[32, 33, 36] naratriptan 2.5 mg,[31] and zolmitriptan 2.5 mg.[35] No statistical analyses were performed due to small sample sizes in these subgroups, so these findings should be considered exploratory and interpreted with caution.

Age

Unpublished data from head-to-head trials[32, 33] provided by the manufacturer of rizatriptan suggested that 2-hour pain relief was higher for rizatriptan 10 mg than the conventional tablet form of sumatriptan 50 mg only in the subgroup of patients who were below 40 years in age, not in the subgroup age 40 and above. In other head-to-head trials rates of 2-hour pain relief were superior for rizatriptan regardless of age.[31, 35, 36]

Gender

Unpublished data from head-to-head trials[31-33, 35, 36] provided by the manufacturer of rizatriptan suggest that rate of 2-hour pain relief was higher for rizatriptan 10 mg than the conventional tablet form of sumatriptan 50 mg and 100 mg, naratriptan 2.5 mg, and zolmitriptan 2.5 in subgroups separating men and women.

Race

Unpublished data from head-to-head trials[31-33, 35, 36] provided by the manufacturer of rizatriptan suggest that rates of 2-hour pain relief were higher for rizatriptan 10 mg than the conventional tablet form of sumatriptan 50 mg and 100 mg, naratriptan 2.5 mg, and zolmitriptan 2.5 in subgroups separating Caucasian and non-Caucasian adults.

In a 12-headache randomized placebo-controlled trial, subcutaneous sumatriptan was equally effective in whites, blacks, Hispanics, and others in relieving headache, reducing disability, and in adverse event rates.[100]

Two placebo-controlled trials published in 2002[122, 123] reported results of eletriptan and zolmitriptan in Japanese migraineurs. The trials enrolled samples similar in age, sex, and migraine history. Eletriptan and zolmitriptan had similarly better 2-hour pain relief, pain-free, and relief of associated symptoms (nausea, photophobia, phonophobia, vomiting); 24-hour recurrence; use of escape medication; and rate of adverse events (asthenia, paresthesia, somnolence) when each was compared with placebo. Outcome rates were within the ranges for eletriptan and zolmitriptan reported in head-to-head trials of predominantly white patients in otherwise similar samples.

Use of migraine prophylaxis

Results of pharmacokinetic trials, mostly in healthy volunteers, have been used to make recommendations for or against dosage adjustment in patients taking propranolol and other antimigraine drugs.

Unpublished data from head-to-head trials comparing rizatriptan 10 mg with the conventional tablet form of sumatriptan 50 mg or 100 mg[32, 36] provided by the manufacturer of rizatriptan suggest that in migraineurs rate of 2-hour pain-relief may be affected by whether or not patients use prophylactic migraine medication, especially tricyclic antidepressants or valproate. Rate of 2-hour pain-relief for rizatriptan 10 mg was greater than for the conventional tablet form of sumatriptan 100 mg in patients who were not using any prophylactic migraine treatments. However, in those who were using prophylactic migraine treatments, 2-hour pain-relief was lower for rizatriptan 10 mg.

Other

Trials of triptans have generally excluded patients who have cardiovascular disease, uncontrolled hypertension, liver disease, and several other conditions.

In general, triptans have proved to be as effective for migraine associated with menstruation as for other attacks. A double-blind, placebo-controlled randomized controlled trial demonstrated the effectiveness of subcutaneous sumatriptan in menstrual migraine.[91] Retrospective meta-analysis of randomized controlled trials of rizatriptan, zolmitriptan, and subcutaneous sumatriptan support the view that triptans are equally effective for headache during menstruation as in other migraine headches.[124-126]

We identified 1 double-blind randomized controlled trial of a triptan to prevent migraines associated with menses.[127] In this trial, across 4 menstrual periods, more patients treated with naratriptan 1 mg were headache-free than with placebo (23% compared with 8%). An earlier pilot study by the same investigator used sumatriptan for prophylaxis of menstrual migraine, but that study was uncontrolled.[128]

In small subgroups of adults with menstruation-associated migraines from 2 head-to-head trials, both rizatriptan 10 mg and the conventional tablet form of sumatriptan 50 mg were superior to placebo in improving rate of 2-hour pain relief. But, in the menstruation-associated migraine subpopulations, rizatriptan 10 mg was no longer statistically superior to sumatriptan 50 mg as it was in the study population overall.[32, 33]

SUMMARY

The main findings of this review are summarized in Table 8.

Table 8. Summary of the evidence

	Comparison: Overall strength of evidence	Conclusion
Key Question 1. Comparative effectiveness		
a. Monotherapy vs. monotherapy	Eletriptan vs. other triptans: Fair	Evidence from 5 head-to-head trials insufficient for conclusions about comparative efficacy of eletriptan, encapsulated sumatriptan, naratriptan, and zolmitriptan due to the differential effects associated with use of unilateral encapsulation in these trials Fair evidence from 3 placebo-controlled trials suggests that eletriptan is at least equivalent in efficacy to the conventional tablet form of sumatriptan 100 mg
	Rizatriptan 10 mg vs. the conventional tablet form of sumatriptan 50 mg or 100 mg: Fair	Rizatriptan 10 mg at least comparable to the conventional tablet form of sumatriptan 50 mg and 100 mg in rates of 2-hour and 24-hours pain-free and 24-hour quality-of-life Superiority of rizatriptan 10 mg on 2-hour pain-free is possible but unclear due to mixed findings across trials
	Rizatriptan 10 mg vs. naratriptan 2.5 mg: Fair	Rizatriptan 10 mg superior to naratriptan 2.5 mg at 2 hours in rates of pain-free, presence of normal function, and satisfaction and comparable at 24 hours in recurrence and quality of life
	Rizatriptan 10 vs. zolmitriptan 2.5 mg: Fair	Rizatriptan 10 mg superior to zolmitriptan 2.5 mg at 2 hours in rates of pain-free and presence of normal functioning and comparable on 24-hour recurrence and quality of life
	Rizatriptan orally disintegrating tablets 10 mg vs. the conventional tablet form of sumatriptan 50 mg: Fair	Rizatriptan orally disintegrating tablet 10 mg superior on preference and 2-houroutcomes of pain-free and normal function and comparable on 24-hour outcomes in 2 open trials
	Rizatriptan orally disintegrating tablets 10 mg vs. eletriptan 40 mg	Comparable on satisfaction, pain-free, and functional disability Patient preference favors rizatriptan orally disintegrating tablet 10 mg
	Zolmitriptan 5 mg vs. the conventional tablet form of sumatriptan 100 mg and 50 mg: Fair	Comparable efficacy in pain outcomes Zolmitriptan 5 mg and the conventional tablet form of sumatriptan 50 mg were consistently comparable across 6 headaches
	Zolmitriptan 2.5 mg vs. naratriptan 2.5 mg: Poor	Comparable in adjusted rates of 2-hour pain-relief Unadjusted outcomes cannot be

	Comparison: Overall strength of evidence	Conclusion
		meaningfully interpreted.
	Zolmitriptan 2.5 mg and 5 mg nasal spray vs. zolmitriptan 2.5 mg oral tablet: Fair	Zolmitriptan 5 mg nasal spray superior to zolmitriptan 2.5 mg oral tablet in pain-free at 30 and 45 minutes and in normal function at all time points and comparable for later outcomes Zolmitriptan 2.5 mg had no advantage over zolmitriptan 2.5 oral tablet at early times and was inferior on later outcomes
	Almotriptan 12.5 mg vs. other triptans: Fair	Almotriptan 12.5 mg similar to the conventional tablet form of sumatriptan 50 mg and 100 mg and zolmitriptan 2.5 mg on 2-hour pain-free, 24-hour recurrence, and 24-hour pain-free Almotriptan 12.5 mg compared with rizatriptan 10 mg: Patient preference was almost identical, but 2-hour pain-free rates were superior for rizatriptan
	Naratriptan 2.5 vs. mg the conventional tablet form of sumatriptan 100 mg: Fair	Similar for 2-hour and 24-hour sustained pain relief Pain-free outcomes not reported
	Reformulated sumatriptan (rapid-release): Poor	No head-to-head trials Indirect comparisons from placebo-controlled trials suggests that reformulated sumatriptan is at least similar in efficacy to the conventional tablet form of sumatriptan 100 mg
	Sumatriptan nasal spray and injection: Poor	Head-to-head trials comparing subcutaneous sumatriptan with other triptans were poor quality No head-to-head trials were found for sumatriptan nasal spray
	Frovatriptan: Poor	No fully published head-to-head trials 5 placebo-controlled trials (N=2866) suggest frovatriptan is probably inferior to the conventional tablet form of sumatriptan 100 mg
b. Fixed-dose combination tablet vs. monotherapy	Treximet® (reformulated sumatriptan 85 mg/naproxen 500 mg) vs. reformulated sumatriptan 85 mg: Good	Treximet® superior in pain-free at 2 hours and 24 hours and in normal function, overall productivity, and patient satisfaction
c. Fixed-dose combination tablet vs. co-administration of individual components	Treximet® (reformulated sumatriptan 85 mg/naproxen 500 mg) vs. co-administration of individual components: Poor	No trials found

	Comparison: Overall strength of evidence	Conclusion
Key Question 2: Comparative safety		
a. Monotherapy vs. monotherapy	Almotriptan, eletriptan, naratriptan, rizatriptan oral tablet, rizatriptan orally disintegrating tablet, the conventional tablet form of sumatriptan, zolmitriptan oral tablet, zolmitriptan orally disintegrating tablet, zolmitriptan nasal spray: Good	Comparable overall tolerability and no consistent differences in chest pain/tightness or central nervous system effects
	Frovatriptan, reformulated sumatriptan, the conventional tablet form of sumatriptan injection and nasal spray: Poor	None or poor-quality head-to-head trials
b. Fixed-dose combination tablet vs. triptan monotherapy	Treximet® (reformulated sumatriptan 85 mg/naproxen 500 mg) vs. reformulated sumatriptan 85 mg: Good	No consistent difference in rates of overall adverse events, dizziness, paresthesia, or somnolence
c. Fixed-dose combination tablet vs. co-administration of individual components	Treximet® (reformulated sumatriptan 85 mg/naproxen 500 mg) vs. co-administration of individual components: Poor	No head-to-head trials
Key Question 3: Subgroups		
	All triptans: Poor	No evidence that any one triptan has a particular advantage or disadvantage over others in any subgroups based on age, gender, race, use of prophylactic treatment, or association with menstruation

This review indicates several concrete suggestions for improving the quality of future head-to-head trials. First, studies should compare currently recommended doses. Second, rather than defining a single primary endpoint and selectively reporting others, studies should prespecify a range of endpoints that encompass several aspects of single-headache efficacy at 1 hour, 2 hours, and 24 hours, as well as consistency, satisfaction, function, and quality of life for 6 months or more. Third, more comparisons among triptans other than sumatriptan are needed. Fourth, better evidence concerning the efficacy of triptans for early and mild migraine would improve the applicability of research to everyday practice and could provide a stronger basis for future practice guidelines.

Selection bias in head-to-head trials is a more difficult issue to address. It is increasingly difficult to find triptan-naive patients. We make a few observations: First, there is a role for trials in comparing the efficacy of triptans among patients who are unsatisfied with their current triptan therapy. As long as the studies are clearly described, studies that recruit patients who have been on triptan therapy can be informative. Studies that do recruit such patients need to assess patients' reasons for wanting to enroll in a trial and their complaints about their current triptan therapy. Second, trials could compare more than 2 triptans and could randomize patients among triptans new to them. The size of the effect of previous triptan use within a particular trial could also be measured. Finally, studies could make greater efforts to draw from the larger denominator of migraineurs who do not seek specialty or even primary medical care and who are less likely to have used triptans.

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Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a

participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results

as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug’s adverse effects impact the patient’s ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to “effect size”. Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategy

Update 4

Database: Ovid MEDLINE(R) <1996 to August Week 1 2008>
Search Strategy:
---
1 almotriptan.mp. (168)
2 eletriptan.mp. (202)
3 frovatriptan.mp. (93)
4 naratriptan.mp. (229)
5 rizatriptan.mp. (325)
6 sumatriptan.mp. or exp Sumatriptan/ (1623)
7 zolmitriptan.mp. (394)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2162)
9 limit 8 to yr="2005 - 2008" (490)
10 limit 9 to (english language and humans) (388)
11 limit 10 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or randomized controlled trial) (171)
12 from 11 keep 1-171 (171)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2nd Quarter 2008>
Search Strategy:
---
1 triptans.mp. (5)
2 sumatriptan.mp. or exp Sumatriptan/ (7)
3 almotriptan.mp. (1)
4 frovatriptan.mp. (0)
5 naratriptan.mp. (1)
6 rizatriptan.mp. (3)
7 zolmitriptan.mp. (2)
8 eletriptan.mp. (3)
9 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5 (10)
10 5-hydroxytryptamine.mp. (12)
11 migraine$.mp. (73)
12 11 and 9 (10)
13 11 and 10 (2)
14 13 or 12 (11)
15 from 14 keep 1-11 (11)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2008>
Search Strategy:
---
1 triptans.mp. (52)

2 sumatriptan.mp. or exp sumatriptan/ (420)
3 almotriptan.mp. (39)
4 frovatriptan.mp. (14)
5 naratriptan.mp. (42)
6 rizatriptan.mp. (80)
7 zolmitriptan.mp. (84)
8 eletriptan.mp. (38)
9 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5 (625)
10 5-hydroxytryptamine.mp. (408)
11 migraine$.mp. (2077)
12 11 and 9 (490)
13 11 and 10 (20)
14 13 or 12 (497)
15 from 14 keep 1-497 (497)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2008>
Search Strategy:
---
1 triptans.mp. (7)
2 sumatriptan.mp. or exp Sumatriptan/ (15)
3 almotriptan.mp. (3)
4 frovatriptan.mp. (2)
5 naratriptan.mp. (5)
6 rizatriptan.mp. (5)
7 zolmitriptan.mp. (4)
8 eletriptan.mp. (4)
9 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5 (16)
10 5-hydroxytryptamine.mp. (6)
11 migraine$.mp. (59)
12 11 and 9 (16)
13 11 and 10 (0)
14 13 or 12 (16)
15 from 14 keep 1-11 (11)
16 from 15 keep 1-11 (11)

Database: Ovid MEDLINE(R) <1996 to January Week 4 2009>
Search Strategy:
---
1 almotriptan.mp. (175)
2 eletriptan.mp. (204)
3 frovatriptan.mp. (96)
4 naratriptan.mp. (230)
5 rizatriptan.mp. (329)
6 sumatriptan.mp. or exp Sumatriptan/ (1656)

7 zolmitriptan.mp. (401)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2215)
9 limit 8 to (english language and humans) (1686)
10 (200808$ or 200809$ or 20081$ or 2009$).ed. (332752)
11 10 and 9 (42)
12 from 11 keep 1-42 (42)

Appendix C. Quality assessment for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination criteria. This appendix lists questions that are posed for each included study in order to assess study quality. These quality-assessment questions differ for systematic reviews, controlled trials, and nonrandomized trials.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of "good," "fair," or "poor." Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria that may indicate the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only probably valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies?
   A good-quality review should focus on a well-defined question or set of questions. These questions ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the 4 components of study design: indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, such as how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?
   If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, dates, and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only Medline was searched for a review looking at proton pump inhibitors then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed?
   A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, how randomization was done, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors

may use a published checklist or scale or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?
   The review should demonstrate that the studies included are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample sizes, patient characteristics, interventions, settings, outcome measures, follow-up periods, drop-out rates (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?
   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis). For reviews that provide a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual studies should be weighted in some way (for example, according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of internal validity

1. Was the assignment to treatment groups really random?
   Adequate approaches to sequence generation:
   - Computer-generated random numbers
   - Random-numbers table

   Inferior approaches to sequence generation:
   - Use of alternation, case record number, birth date, or day of week

   Not reported

2. Was the treatment allocation concealed?
   Adequate approaches to concealment of randomization:
   - Centralized or pharmacy-controlled randomization
   - Serially numbered identical containers
   - On-site computer-based system with a randomization sequence that is not readable until allocation

   Inferior approaches to concealment of randomization:
   - Use of alternation, case record number, birth date, or day of week
   - Open random-numbers list

Serially numbered envelopes (Even sealed opaque envelopes can be subject to manipulation.)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup (giving numbers for each group)?

Assessment of external validity (applicability)

1. How similar is the population to the population to which the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of follow-up? (Give numbers at each stage of attrition.

Nonrandomized Studies

Assessment of internal validity

1. Was the selection of patients for inclusion unbiased? In other words, was any group of patients systematically excluded?

2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)

3. Were the investigated events specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (independent ascertainers and validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of follow-up correlate with reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of external validity

1. Was the description of the population adequate?

2. How similar is the population to the population to which the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)

5. What was the funding source and role of funder in the study?

References:

Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews.* CRD Report Number 4. 2nd ed. University of York, UK; 2001.

Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* Apr 2001;20(3 Suppl):21-35.

Appendix D. Excluded studies

Study	Reason for exclusion
Adelman JU, Mannix LK and Von Seggern RL. Rizatriptan tablet versus wafer: Patient preference. *Headache.* 2000;40(5):371-372.	Wrong Drug or Comparison
Anonymous. Investigational 'triptan' improves 2-hour headache response compared with oral sumatriptan. *Formulary.* 1999;34(10):819-820.	Wrong Drug or Comparison
Ashford E, Salonen R, Saiers J, et al. Consistency of response to sumatriptan nasal spray across patient subgroups and migraine types. *Cephalalgia.* 1998;18(5):273-277.	Wrong Outcome
Bahra A, Gawel MJ, Hardebo JE, et al. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology.* 2000;54(9):1832-1839.	Wrong Population
Burke-Ramirez P, Webster C, Laurenza A, et al. Efficacy of sumatriptan injection for the acute treatment of migraine in a primarily non-caucasian group of patients. *Functional Neurology.* 1998;2(13):182.	Wrong Publication Type-ABSTRACT ONLY
Cabanas A and Rodriguez RRFCA. Subcutaneous sumatriptan comparative study versus placebo in migraine attacks. *Journal of the Neurological Sciences.* 1997;150(Suppl):S303.	Wrong Publication Type-ABSTRACT ONLY
Cabarrocas X and Almotriptan Study G. Efficacy and tolerability of subcutaneous almotriptan for the treatment of acute migraine: a randomized, double-blind, parallel-group, dose-finding study. *Clinical Therapeutics.* 2001;23(11):1867-75.	Wrong Drug or Comparison
Cabarrocas X, Zayas JM and Suris M. Equivalent efficacy of oral almotriptan, a new 5-HT1B/1D agonist, compared with sumatriptan 100mg. *40th Annual Scientific Meeting of the American Association for the Study of Headache.* 1998.	Wrong Publication Type-ABSTRACT ONLY
Cady R, Martin V, Adelman J, et al. Migraine treatment with rizatriptan and non-triptan usual care medications: a pharmacy-based study. *Headache.* Oct 2004;44(9):900-7.	Wrong Outcome
Cady RC, Ryan R, Jhingran P, et al. Sumatriptan injection reduces productivity loss during a migraine attack: results of a double-blind, placebo-controlled trial. *Neurology.* 1997;48(3):A121.	Wrong Publication Type
Cittadini E, May A, Straube A, et al. Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo-controlled, double-blind crossover study. *Archives of Neurology.* Nov 2006;63(11):1537-42.	Wrong Population
Cutler NR, Claghorn J, Sramek JJ, et al. Pilot study of MK-462 in migraine. *Cephalalgia.* 1996;16(2):113-116.	Wrong Drug or Comparison
Dahlof CG, Lipton RB, McCarroll KA, et al. Within-patient consistency of response of rizatriptan for treating migraine. *Neurology.* 2000;55(10):1511-6.	Wrong Design
Di Monda V, Nicolodi M, Aloisio A, et al. Efficacy of a fixed combination of indomethacin, prochlorperazine, and caffeine versus sumatriptan in acute treatment of multiple migraine attacks: a multicenter, randomized, crossover trial. *Headache.* 2003;43(8):835-44.	Wrong Drug or Comparison

Study	Reason for exclusion
Diener HC, Pascual J and Vega P. Comparison of rizatriptan 10mg versus zolmitriptan 2.5mg in migraine. *Headache.* 1999;39:351.	Wrong Publication Type-ABSTRACT ONLY
Disability in Strategies of Care Study g. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) Study: A randomized trial. *JAMA : the journal of the American Medical Association.* 2000;284(20):2599-605.	Wrong Design
Dowson A. Can oral 311C90, a novel 5-HT(1D) agonist, prevent migraine headache when taken during an aura? *European Neurology.* 1996;36(SUPPL. 2):28-31.	Wrong Outcome
Dowson AJ, Charlesworth BR, Purdy A, et al. Tolerability and consistency of effect of zolmitriptan nasal spray in a long-term migraine treatment trial. *Cns Drugs.* 2003;17(11):839-51.	Wrong Design
Eletriptan Steering C. Efficacy, safety, and tolerability of oral eletriptan for treatment of acute migraine: a multicenter, double-blind, placebo-controlled study conducted in the United States. *Headache.* 2003;43(3):202-13.	Wrong Outcome
Elkind AH, Satin LZ, Nila A, et al. Frovatriptan use in migraineurs with or at high risk of coronary artery disease. *Headache.* 2004;44(5):403-10.	Wrong Outcome
Encarnacion JR, Ellis MR and Lindbloom EJ. Is oral zolmitriptan efficacious in the acute treatment of cluster headache? *Journal of Family Practice.* 2000;49(9):784, 849.	Wrong Population
Fernandez FJ, Cabarrocas X, Zayas JM, et al. Oral almotriptan in the treatment of migraine: a dose finding study. *Cephalalgia.* 1999;19:362.	Wrong Publication Type-ABSTRACT ONLY
Ferrari MD. Treatment of migraine attacks with sumatriptan. *New England Journal of Medicine.* 1991;325(5):316-321.	Wrong Outcome
Fleishaker JC, McEnroe JD, Azie NE, et al. Cardiovascular effect of almotriptan in treated hypertensive patients. *Clinical Pharmacology & Therapeutics.* 2002;71(3):169-75.	Wrong Outcome
Gallagher RM. Comparison of zolmitriptan and sumatriptan for the acute treatment of migraine. *Cephalalgia.* 1999;19:358.	Wrong Publication Type-ABSTRACT ONLY
Goadsby PJ, Zagami AS, Donnan GA, et al. Oral sumatriptan in acute migraine. *Lancet.* 1991;338(8770):782-3.	Wrong Outcome
Goldstein DJ, Roon KI, Offen WW, et al. Selective seratonin 1F (5-HT(1F)) receptor agonist LY334370 for acute migraine: a randomised controlled trial. *Lancet.* 2001;358(9289):1230-4.	Wrong Drug or Comparison
Goldstein J, Keywood C and Hutchison J. 24-hour migraine recurrence was low during treatment with frovatriptan. *European Journal of Neurology.* 1999;6(Supplement 3).	Wrong Publication Type-ABSTRACT ONLY
Hardebo JE and Dahlof C. Sumatriptan nasal spray (20 mg/dose) in the acute	Wrong Drug or

Study	Reason for exclusion
treatment of cluster headache. *Cephalalgia.* 1998;18(7):487-489.	Comparison
Hutchinson J, Pfaffenrath V and Geraud G. A randomized, placebo-controlled, parallel-group trial of frovatriptan and sumatriptan for a single acute migraine attack [abstract]. *European Journal of Neurology.* 2007;14(suppl 1)(144):P1458.	Wrong Publication Type
Katsarava Z, Fritsche G, Muessig M, et al. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology.* 2001;57(9):1694-8.	Wrong Outcome
Kozma CM and Reeder CE. Comparison of the economic, clinical, and humanistic attributes of dihydroergotamine and sumatriptan. *Clinical Therapeutics.* 1995;17(2):315-319.	Wrong Drug or Comparison
Lipton RB, Stewart WF, Cady R, et al. 2000 Wolfe Award. Sumatriptan for the range of headaches in migraine sufferers: results of the Spectrum Study. *Headache.* 2000;40(10):783-91.	Wrong Population
Loder E, Brandes JL, Silberstein S, et al. Preference comparison of rizatriptan ODT 10-mg and sumatriptan 50-mg tablet in migraine. *Headache.* 2001;41(8):745-53.	Wrong Drug or Comparison
Massiou and H. A comparison os sumatriptan nasal spray and intranasal dhiydroergotamine (DHE) in the acute treatment of migraine. *Functional Neurology.* 1996;2/3(11):151.	Wrong Publication Type-ABSTRACT ONLY
Mathew NT, Kailasam J, Gentry P, et al. Treatment of nonresponders to oral sumatriptan with zolmitriptan and rizatriptan: a comparative open trial. *Headache.* 2000;40(6):464-5.	Wrong Publication Type-ABSTRACT ONLY
Milton KA, Scott NR, Allen MJ, et al. Pharmacokinetics, pharmacodynamics, and safety of the 5-HT(1B/1D) agonist eletriptan following intravenous and oral administration. *Journal of Clinical Pharmacology.* 2002;42(5):528-39.	Wrong Population
O'Quinn S and Salonen R. Sumatriptan nasal spray compared with intranasal dihydroergotamine in the acute treatment of migraine: results of a comparator trial. *Headache.* 1998;38:396.	Wrong Publication Type-ABSTRACT ONLY
Oral Sumatriptan International Multiple-Dose Study G. Evaluation of a multiple-dose regimen of oral sumatriptan for the acute treatment of migraine. *European Neurology.* 1991;31(5):306-13.	Wrong Design
Pascual J, Bussone G, Hernandez JF, et al. Comparison of preference for rizatriptan 10-mg wafer versus sumatriptan 50-mg tablet in migraine. *European Neurology.* 2001;45(4):275-283.	Wrong Drug or Comparison
Pradel FG, Subedi P, Varghese AA, et al. Does earlier headache response equate to earlier return to functioning in patients suffering from migraine? *Cephalalgia.* Apr 2006;26(4):428-35.	Wrong Drug or Comparison
Pryse-Phillips W. Oral eletriptan (40-80 mg) versus oral sumatriptan (50-100 mg) for the treatment of acute migraine in sumatriptan-na[spacing acute]ve patients. *European Journal of Neurology.* 1999;6(Supplement 3):7-11.	Wrong Publication Type-ABSTRACT ONLY

Study	Reason for exclusion
Pryse-Phillips W and Committee ES. Comparison of oral eletriptan (40-80mg) and oral sumatriptan (50-100mg) for the treatment of acute migraine: a randomised, placebo-controlled trial in sumatriptan-naive patients. *Cephalalgia.* 1999;19:355.	Wrong Publication Type-ABSTRACT ONLY
Reches A. Comparison of the efficacy, safety and tolerability of oral eletriptan and cafergot(r) in the acute treatment of migraine. *European Journal of Neurology.* 1999;6(Supplement 3):7-11.	Wrong Design
Robbins L. Triptans versus analgesics. *Headache.* 2002;42(9):903-7.	Wrong Design
Robert M, Cabarrocas X, Fernandez FJ, et al. Efficacy and tolerabilty of oral almotriptan in the treatment of migraine. *Cephalalgia.* 1998;18:406.	Wrong Publication Type-ABSTRACT ONLY
Russell MB, Holm TOE, Nielsen MR, et al. Subcutaneous sumatriptan in general practice: A randomized double- blind placebo-controlled cross-over study. *Ugeskrift for Laeger.* 1995;157(16):2320-2323.	Non-English Language
Saiers J, Jones M, Kane K, et al. Naratriptan tablets 2.5 Mg exhibit prolonged action and are well-tolerated in non-severe migraine attacks: data from a comparator study with sumatriptan. *European Journal of Neurology.* 1999;6(Supplement 3).	Wrong Publication Type-ABSTRACT ONLY
Sakai F. Safety and tolerability of rizatriptan. *Cephalalgia, Supplement.* 2000;20(1):16-18.	Wrong Outcome
Salonen R, Petricoul O, Sabin A, et al. Encapsulation delays absorption of sumatriptan tablets. *Cephalalgia.* 2000;20:423-4.	Wrong Outcome
Savani N, Pfaffenrath V, Rice L, et al. Efficacy, tolerability, and patient satisfaction with 50- and 100-mg sumatriptan tablets in those initially dissatisfied with the efficacy of 50-mg sumatriptan tablets. *Clinical Therapeutics.* 2001;23(2):260-71.	Wrong Design
Schoenen J, Jones M, Kane K, et al. Naratriptan 2.5mg tablets have similar efficacy in the acute treatment of migraine as zolmitriptan 2.5mg tablets, but exhibit a longer duration of action and are better tolerated: results of a comparator study [abstract]. *Neurology.* 1999;52(6 Suppl 2):A257-258.	Wrong Publication Type
Schoenen J, Pascual J, Rasmussen S, et al. Patient preference for eletriptan 80 mg versus subcutaneous sumatriptan 6 mg: results of a crossover study in patients who have recently used subcutaneous sumatriptan. *European Journal of Neurology.* Feb 2005;12(2):108-17.	Wrong Drug or Comparison
Silberstein SD. Rizatriptan versus usual care in long-term treatment of migraine. *Neurology.* 2000;55(9 SUPPL. 2):S25-S28.	Wrong Design
Steiner TJ and Eletriptan Steering Committee. Efficacy, safety and tolerability of oral eletriptan (40mg and 80mg) in the acute treatment of migraine: results of a phase III study. *Cephalalgia.* 1999;18:385.	Wrong Publication Type-ABSTRACT ONLY

Study	Reason for exclusion
Tfelt-Hansen P and Steiner TJ. Sumatriptin vs dihydroergotamine: Patient preference [1]. *International Journal of Clinical Practice.* 2001;55(2):151.	Wrong Design
The S2MB11 Study Group. Patients preference between 25, 50 and 100mg oral doses of sumatriptan. *European Journal of Neurology.* 1996;3(1):86.	Wrong Publication Type-ABSTRACT ONLY
Visser WH and Jiang K. Effect of rizatriptan versus sumatriptan on migraine-associated symptoms. *Headache.* 1998:409.	Wrong Publication Type
Wilding I, Clark D, Wray H, et al. Disintegration Profiles of Encapsulated And Non-Encapusulated Sumatriptan: Gamma Scientography in Healthy Volunteers. *Journal of Clinical Pharmacology.* 2005;45.	Wrong Outcome-Included for Background

Appendix E. Pooled relative risks (95% confidence interval) for pain-free outcomes in placebo-controlled trials of early treatment with triptans

Triptan dose	Triptan n/N (%)	Placebo n/N (%)	Relative risk (95% CI) NNT	Cochrane Q (degrees of freedom), *P* value
2-hour pain-free				
Frovatriptan 2.5 mg	67/241 (28%)	48/241 (20%)	1.40 (1.11, 1.76) NNT=12	N/A
Almotriptan 12.5 mg	110/265 (41%)	64/262 (24%)	1.71 (1.32, 2.21) NNT=6	0.67 (df=1) *P*=0.41
Rizatriptan 10 mg	395/682 (60%)	107/334 (31%)	1.86 (1.57, 2.21) NNT=3	0.03 (df=1) *P*=0.86
Zolmitriptan 5 mg	58/136 (43%)	25/141 (18%)	2.41 (1.81, 3.20) NNT=4	N/A
Eletriptan 40 mg	37/55 (68%)	14/57 (25%)	2.72 (1.92, 3.84) NNT=2	N/A
Treximet 85 mg/500 mg	400/826 (48%)	131/820 (16%)	3.12 (2.64, 3.69) NNT=3	1.12 (df=3) *P*=0.77
S-RT 100 mg	94/142 (66%)	30/153 (20%)	3.38 (2.65, 4.30) NNT=2	N/A
24-hour sustained pain-free				
Almotriptan 12.5 mg	87/265 (33%)	42/262 (16%)	2.08 (1.12, 3.86) NNT=6	3.49 (df=1) *P*=0.06
Treximet 85 mg/500 mg	313/826 (38%)	92/820 (11%)	3.21 (2.63, 3.91) NNT=4	1.18 (df=3) *P*=0.76
Eletriptan 40 mg	34/55 (56%)	10/57 (18%)	3.21 (2.09, 4.94) NNT=3	N/A
Rizatriptan 10 mg	310/682 (45%)	83/344 (24%)	3.52 (1.67, 7.42) NNT=5	7.39 (df=1) *P*=0.01
S-RT 100 mg	57/142 (40%)	15/153 (10%)	4.09 (2.83, 5.92) NNT=3	N/A

Appendix F. Adverse events in head-to-head trials of triptans

Author Year	P	% Patients Reporting Any Adverse Event													
		A12.5	E40	N2.5	R5	R10	R10-ODT	S50	S100	S6-inj	Z2.5	Z5	Z2.5-ODT	Z2.5-nasal	Z5-nasal
Dowson 2002	<0.001	9%	-	-	-	-	-	-	22%	-	-	-	-	-	-
Spierings 2001	NS	15%	-	-	-	-	-	19%	-	-	-	-	-	-	-
Diez 2007	NS	17%	-	-	-	18.5%	-	-	-	-	-	-	-	-	-
Goadsby 2007	NS	19%	-	-	-	-	-	-	-	-	21%	-	-	-	-
Goadsby 2000	NS	-	47%	-	-	-	-	-	52%	-	-	-	-	-	-
Mathew 2003	NS	-	31%	-	-	-	-	-	37%	-	-	-	-	-	-
Steiner 2003	NS	-	30%	-	-	-	-	-	-	-	34%	-	-	-	-
Garcia-Ramos 2003	NS	-	31%	28%	-	-	-	-	-	-	-	-	-	-	-
Gobel 2000	NS	-	-	22%	-	-	-	-	33%	-	-	-	-	-	-
Havanka 2000	NS	-	-	24%	-	-	-	-	26.5%	-	-	-	-	-	-
Bomhof 1999	<0.05	-	-	29%	-	39%	-	-	-	-	-	-	-	-	-
Goldstein 1998	NS	-	-	-	44%	45%	-	-	46%	-	-	-	-	-	-
Kolodny 2004	NS	-	-	-	38%	47%	-	49.5%	-	-	-	-	-	-	-
Lines 1997	NS	-	-	-	33%	-	-	37%	-	-	-	-	-	-	-
Pascual 2000	NS	-	-	-	-	31%	-	-	-	-	39%	-	-	-	-
Tfelt-Hansen 1998	NS	-	-	-	-	47%	-	-	52%	-	-	-	-	-	-
Tfelt-Hansen 1998	<0.01	-	-	-	39%	-	-	-	52%	-	-	-	-	-	-
Visser 1996	NS	-	-	-	-	48%	-	-	46%	-	-	-	-	-	-
Lainez 2006	NS	-	27%	-	-	-	22%	-	-	-	-	-	-	-	-
Loder 2001	NS	-	-	-	-	-	28%	31%	-	-	-	-	-	-	-
Pascual 2001	NS	-	-	-	-	-	31.5%	34%	-	-	-	-	-	-	-
Carpay 1997	NS	-	-	-	-	-	-	-	60%	66%	-	-	-	-	-
Gallagher 2000	NS	-	-	-	-	-	-	52%	-	-	51%	57%	-	-	-
Geraud 2000	NS	-	-	-	-	-	-	-	57%	-	-	58%	-	-	-
Gruffyd-Jones 2001	NS	-	-	-	-	-	-	34%	-	-	35%	38%	-	-	-
Charlesworth 2003	NS	-	-	-	-	-	-	-	-	-	39.5%	-	-	44%	49%
Dowson 2003	NS	-	-	-	-	-	-	33%	-	-	-	-	42%	-	-

Author Year	P	% patients experiencing chest pain/tightness									
		A12.5	E40	N2.5	R5	R10	S6-inj	S50	S100	Z2.5	Z5
Bomhof 1999	NS	-	-	2	-	3	-	-	-	-	
Dowson 2002	NS	0	-	-	-	-	-	-	1	-	-
Gallagher 2000	NS	-	-	-	-	-	-	2.7	-	2.1	1
Geraud 2000	NS	-	-	-	-	-	-	-	2	-	-
Goadsby 2000	NS	-	7	-	-	-	-	-	7	-	-
Goadsby, 2007	NR	1.1	-	-	-	-	-	-	-	0.6	-
Gruffyd-Jones 2001	NS	-	-	-	-	-	-	3.1	-	3.4	5.0
Kolodny	NR	-	-	-	1.7	3.4	-	4.5	-	-	-
Lainez, 2006	NR	-	1.8	-	-	1.2	-	-	-	-	-

Author Year	P	% patients experiencing chest pain/tightness									
		A12.5	E40	N2.5	R5	R10	S6-inj	S50	S100	Z2.5	Z5
Lines 1997	NS	-	-	-	2	-	-	5	-	-	-
Mathew, 2003	NS	-	1.6	-	-	-	-	-	2	-	-
Pascual 2000	NS	-	-	-	-	2	-	-	-	4	-
Sandrini 2002	NS	-	1	-	-	-	-	2	1	-	-
Spierings 2001	0.004	0.3	-	-	-	-	-	2.2	-	-	-
Steiner, 2003	NR	-	2.3	-	-	-	-	-	-	0.2	-
Tfelt-Hansen 1998	<0.05	-	-	-	1	3	-	-	6	-	-

Author Year	P	% patients experiencing dizziness									
		A12.5	E40	N2.5	R5	R10	S6-inj	S50	S100	Z2.5	Z5
Bomhof 1999	NS	-	-	5	-	8	-	-	-	-	-
Diez, 2007	NR	0.3	-	-	-	2.8	-	-	-	-	-
Dowson 2002	NS	0	-	-	-	-	-	-	2.1	-	-
Gallagher 2000	NS	-	-	-	-	-	-	5	-	6.1	8
Garcia-Ramos, 2003	NS	-	6.3	2.5	-	-	-	-	-	-	-
Geraud 2000	NS	-	-	-	-	-	-	-	9	-	9
Goadsby 2000	NS	-	4	-	-	-	-	-	4	-	-
Goadsby, 2007	NR	1.3	-	-	-	-	-	-	-	2.5	-
Gruffyd-Jones	NS	-	-	-	-	-	-	5	-	3.4	5.7
Kolodny 2004	NR	-	-	-	6.6	8.5	-	10.5	-	-	-
Lainez, 2006	NR	-	3.8	-	-	1.9	-	-	-	-	-
Lines 1997	NS	-	-	-	5	-	-	5	-	-	-
Pascual 2000	NS	-	-	-	-	5	-	-	-	6	-
Sandrini 2002	NS	-	7	-	-	-	-	7	5	-	-
Spierings 2001	NS	2.0	-	-	-	-	-	1.7	-	-	-
Steiner, 2003	NR	-	1.5	-	-	-	-	-	-	1.7	-
Tfelt-Hansen 1998	NS	-	-	-	6	8	-	-	9	-	-

Author Year	P	% patients experiencing paresthesia					
		A12.5	E40	R10	S50	S100	Z5
Dowson 2002	NS	0.5	-	-	-	3.1	-
Gallagher 2000	NS	-	-	-	4.4	-	7.4
Geraud 2000	NS	-	-	-	-	7	6
Goadsby 2000	NS	-	2	-	-	5	-
Gruffyd-Jones 2001	NS	-	-	-	5.4	-	5.2
Kolodny 2004	NS	-	-	4.4	-	3.5	-
Mathew, 2003	NS	-	1.1	-	-	2.4	-
Spierings 2001	NS	1.2	-	-	0.9	-	-

Author Year	*P*	% patients experiencing somnolence								
		A12.5	**E40**	**N2.5**	**R5**	**R10**	**S50**	**S100**	**Z2.5**	**Z5**
Bomhof 1999	NS	-	-	<1	-	5	-	-	-	-
Diez 2007	NS	0.3	-	-	-	2.5	-	-	-	-
Dowson 2002	NS	0.5	-	-	-	-	-	2.1	-	-
Gallagher 2000	NS	-	-	-	-	-	-	-	4.3	7.7
Garcia-Ramos, 2003	NS	-	5.2	4.5	-	-	-	-	-	-
Geraud 2000	NS	-	-	-	-	-	-	6	-	8
Goadsby, 2007	NR	1.1	-	-	-	-	-	-	1.3	-
Gruffyd-Jones 2001	NS	-	-	-	-	-	-	-	3.1	5
Kolodny 2004	NR	-	-	-	5.9	7.8	-	-	-	-
Lainez, 2006	NR	-	2	-	-	3.9	-	-	-	-
Lines 1997	NS	-	-	-	4	-	-	-	-	-
Pascual 2000	NS	-	-	-	-	6	-	-	4	-
Sandrini 2002	NS	-	7	-	-	-	-	3	-	-
Spierings 2001	NS	1.4	-	-	-	-	1.9	-		
Steiner, 2003	NR	-	2.3	-	-	-	-	-	1.2	-
Tfelt-Hansen 1998	NS	-	-	-	7	9	-	7	-	-

Author Year	*P*	% patients experiencing fatigue/asthenia							
		A12.5	**E40**	**N2.5**	**R5**	**R10**	**S100**	**Z2.5**	**Z5**
Bomhof 1999	NS	-	-	5	-	7	-	-	-
Diez, 2007	NR	2.0	-	-	-	2.0	-	-	-
Dowson 2002	NS	0.5	-	-	-	-	5.7	-	-
Garcia-Ramos, 2003	NS	-	3.6	1.9	-	-	-	-	-
Geraud 2000	NS	-	-	-	-	-	11	-	11
Goadsby 2000	NS	-	3	-	-	-	3	-	-
Goadsby, 2007	NR	2.1	-	-	-	-	-	4	-
Gruffyd-Jones	NS	-	-	-	-	-	-	5.3	6.6
Kolodny 2004	NR	-	-	-	5.2	3.7	-	-	-
Lainez, 2006	NR	-	5.3	-	-	2.7	-	-	-
Lines 1997	NS	-	-	-	7	-	-	-	-
Pascual 2000	NS	-	-	-	-	6	-	5	-
Sandrini 2002	NS	-	7	-	-	-	8	-	-
Steiner, 2003	NR	-	3.3	-	-	-	-	2.5	-
Tfelt-Hansen	<0.05	-	-	-	2	8	8	-	-

Abbreviations: A, almotriptan; E, eletriptan; N, naratriptan; R, rizatriptan; S, sumatriptan; Z, zolmitriptan; inj, injection; ODT, orally disintegrating tablet; NS, not significant; NR, not reported; '-' not applicable.