Drug Class Review
on
Triptans

Final Report

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INTRODUCTION

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

The first triptan, sumatriptan, was introduced in 1991. As of January 2003, seven triptans were available in the U.S. (Table 1). Triptans may be taken subcutaneously; orally as pills or capsules; sublingually as quick-dissolving wafers; or intranasally as a spray.

Table 1. Triptans

Triptans	Forms available in U.S.	Dosages of oral form* (mg)
Almotriptan (Axert)	Oral	**12.5** (6.25), may repeat once after 2 hours
Alniditan	not available**	
Avitriptan	not available**	
Donitriptan	not available	
Eletriptan	Oral	**20** or **40**, may repeat once after 2 hours, maximum 80 mg per day†
Frovatriptan (Frova)	Oral	**2.5,** may repeat after 2 hours, maximum 7.5 mg per day
Naratriptan (Amerge)	Oral	**2.5**,1, 5, may repeat after 4 hours, maximum 5 mg per day
Rizatriptan (Maxalt)	oral, orally dissolving wafer	**10**, 5, may repeat after 2 hours, maximum 30 mg per day
Sumatriptan (Imitrex)	oral, S.C., intranasal	**50** or **100** 25, may repeat after 2 hours, maximum 200 mg per day.
Zolmitriptan (Zomig)	Oral, orally dissolving wafer, intranasal	**2.5** or **5**, may repeat after 2 hours, maximum 10 mg per day

*** Usual recommended dose** is bold. For sumatriptan, maker now states that 100 mg is the recommended oral dose.
** Development ceased.
† Eletriptan is being marketed in 20 mg, 40 mg, and 80 mg tablets, but the maximum recommended single dose of the drug is 40 mg.

Drugs for migraine are often classified by whether they are taken to prevent migraine attacks (prophylaxis) or to shorten (abort) an attack. All of the triptans available in the U.S. are approved by the FDA for use during a migraine attack. None are approved for prophylaxis of migraine or for hemiplegic or basilar migraine. Sumatriptan is the only approved for cluster headache.

Comparing the clinical effectiveness and adverse effects of the different triptans has been an area of considerable interest to researchers and patients, and several review articles[2-7] and meta-analyses[8-11] have compared them.

Comparing triptans is complex, however, because of the large variety of outcome measures 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 two 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 two-hour pain relief measure has been criticized. As mentioned earlier, the main criticism is that a two-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" 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 (i.e., 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."[12]

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.[13] 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 two-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 two-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 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.[14] Other experts argue that "preference" is the best measure: that is, a patient should try several different triptans, eventually settling on the one that offers the best combination of pluses and minuses for that individual.[3]

Table 2. Outcome Measures

Component of effect	Commonly used measures of effect
Short-term effects	
Headache response	Headache relief within 2 hours or another time period
Freedom from pain	Pain-free within 2 hours or another time period
Speed of headache response	Headache relief or pain-free within 1 hour, or other measures of speed (e.g., hazard rate, survival curves)
Sustained headache response	Recurrence of headache within 24 hours, sustained headache relief for 24 hours, or 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 time 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	e.g., "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	Measured in studies in which patients take a triptan for 2 or 3 distinct headaches on different days.
Need for rescue medication	Use of non-triptan medications, which may indicate inadequate or unsustained relief from the triptan
Adverse effects	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 effects	
Reliability or consistency of response	Over several months, does the triptan *consistently* relieve pain or other symptoms?
Functional status/disability	Migraine Disability Assessment Scale (MIDAS) and various others

Finally, if a patient responds well to a triptan, consistently, and without experiencing disabling side effects, she 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 one has the highest overall response rate or overall rate of adverse events.

Within the research literature, what kinds of studies provide the best evidence by which to compare different triptan drugs? It is widely agreed that well-designed, double-blind, randomized controlled trials that directly compare two 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.[15] 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 to a nontriptan

drug or to a placebo can provide information on which triptans have been demonstrated to improve certain outcomes and which have not.

Scope and Key Questions

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 their constituencies. Initially, 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, revised, and approved by representatives of organizations participating in the Drug Effectiveness Review Project. It is the representatives' responsibility to ensure that the questions reflect public input or input from their members. The participating organizations approved the following key questions to guide this review.

Key Question 1. What are the comparative effectiveness and duration of response of different oral triptans in reducing the severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?

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 3. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

METHODS

Eligibility Criteria

We used the following criteria to select studies for inclusion in the systematic review:

1. Studies of adult patients with migraine were included. Migraine must be defined explicitly to exclude other types of headache (e.g. tension headache). Subgroups of interest included different races, ages (older adult vs younger adult), or genders, pregnant or lactating women, patients with coronary artery disease, persons taking prophylactic migraine medication, and women who have migraine headaches associated with menses.

2. Studies comparing an eligible oral triptan with another triptan, another anti-migraine drug (such as ergotamine), or placebo were included. The eligible triptans were almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Treatment could be for any level of migraine (during aura, or when pain was mild, moderate, or severe), but studies had to specify the timing of treatment.

3. For short-term efficacy, we included studies that reported one or more of the following outcomes: reduction or resolution of symptoms (pain, nausea, vomiting, photophobia), reduction of duration of symptoms, duration of improvement, consistency of effectiveness (proportion of headaches successfully treated per patient), functional outcome, quality of life, or adverse effect (including drug interactions). Eligible pain measures included pain relief and pain-free response at various times after taking medication, sustained response, sustained pain-free response, and use of rescue medications. For long-term efficacy, we included studies that reported consistency, patient satisfaction, and workplace productivity.

4. For short-term efficacy we included published, double-blind, randomized controlled trials conducted in an outpatient setting (including emergency department). For the long-term endpoints we also sought longitudinal cohort studies. We also included systematic reviews of these efficacy trials. To be considered for possible inclusion as a systematic review, a systematic search had to be done to identify trials, and explicit criteria for inclusion in the review had to be used.

5. For safety and adverse effects, we included controlled clinical trials that reported the frequency of withdrawals or the frequency or severity of specific adverse events. We also included long-term observational studies of the tolerability or of withdrawals for one or more triptans.

We excluded studies that were unpublished, had no original data, or evaluated complex interventions in which the effect of the triptan could not be determined (e.g., a triptan plus an analgesic as initial therapy). We also excluded studies that had poor internal validity as judged by explicit criteria for quality (see below). As discussed below, we also excluded studies that used encapsulated sumatriptan in a control group.

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Central Register of Controlled Trials (1st Quarter 2004), Medline (1966- March Week 2 2004), EMBASE (1980-March 24, 2004), and reference lists of review articles. In electronic searches, we combined terms for the triptan class and the individual triptan drugs with disease terms (migraine, cluster) (see Appendix A for the complete search strategy). We invited pharmaceutical manufacturers and subcommittee members to provide additional citations. We used authors' names to search for articles related to abstracts identified in our searches or in a previous meta-analysis.[11, 16] All citations were imported into an electronic database (EndNote™ 6.0).

Data Abstraction

One reviewer abstracted the following data from included head-to-head 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 (e.g., scales used), and results for each outcome. After the first reviewer tabulated the results, a second reviewer verified the data in the tables. Data from the active-control trials were abstracted by one reviewer only.

Validity Assessment

We assessed the internal validity of systematic reviews, randomized trials, and longitudinal cohort studies using prespecified criteria (Appendix B). For trials, the criteria were appropriate randomization, blinding, and allocation concealment; similarity of groups at baseline and maintenance of comparable groups, adequate reporting of dropouts, attrition, crossover, adherence, and contamination. In most short-term studies of triptans, patients who do not take the medication during the study period are excluded from further analysis. The most common reason for not taking the medication is that the patient did not experience a headache during the short period of study. Excluding these patients violates the "intention-to-treat" principle, but it does not introduce bias between the compared groups. (It introduces a selection bias, in that the subjects with milder or less frequent headaches are more likely to be dropped from the study.)

External validity refers to the applicability of a study's results to patients who are prescribed triptans in practice. Trial characteristics that are potential threats to external validity are listed in Table 3. In our review, we recorded those characteristics that can be extracted with reasonable accuracy from published studies, such as the adequacy of description of the study population; the study's inclusion and exclusion criteria; whether triptan-naive subjects or patients who have taken triptans were recruited; doses; use of other medications; and the funding source and role of the funder. However, in contrast to our ratings of internal validity, we did not rate external validity as good, fair, or poor. This is because (1) many of the listed characteristics cannot be reliable ascertained from published reports and (2) assessing the importance of potential selection biases, and deciding to whom study results should be applied, is a clinical judgment that should be made by those who will use this report.

Table 3. Trial Characteristics Potentially Related to External Validity

Characteristics	Potential Effect
Selection biases	
Strict inclusion criteria for migraine	Results may not apply to migraine patients who use triptans but do not meet International Headache Society criteria for case definition or study criteria for severity and frequency of attacks
Exclusion of subgroups of migraine sufferers, e.g., those who have comorbid diseases	Results may not apply to many patients who take triptans
Run-in periods before randomization	May select for more compliant patients
Inclusion of patients who use other triptans	Patients who are unsatisfied with their current triptan may be more willing to enroll than those who are satisfied. This could bias the study against the previous triptan
Restriction to "triptan-naive" patients	Excludes the majority of patients who use triptans
Intervention-related biases	
Doses of compared drugs are not equivalent	May exaggerate the comparative efficacy or safety of one of the drugs
Patients are required to wait until pain is moderate to severe before taking triptan	May not represent results for patients who take the triptan earlier in the course of a migraine
Form, route, appearance, taste, or delivery system of drug is altered	May affect the speed or efficacy of the altered preparation relative to use in actual practice
Bias in reporting results	
Not all prespecified endpoints are reported	May indicate that the investigators selectively reported results favorable to one of the compared drugs
Not all completed trials are published	Studies that have more dramatic or statistically significant results may be more likely to be submitted or accepted for publication (publication bias)

Data Synthesis

Characteristics of included head-to-head trials are presented in Evidence Table 1 and also described in the narrative. For each outcome measure, we recorded and tabulated the absolute rate of response for each triptan/dose used and whether the differences were statistically significant. Within a study, the difference between the absolute rates of response for a particular outcome indicates the clinical significance of the effect. For example, if a particular study found that 28% of patients taking Triptan 1 and 33% of patients taking Triptan 2 had pain relief by two-hours, the absolute difference would be 5%, indicating that, if 100 patients took Triptan 2 instead of Triptan 1, 5 more of them, or 1 in 20, would experience pain relief.

There are two main ways to summarize the results of the trials: by outcome and by study. Both are important to gain a full understanding of the results. In this report, results are summarized by outcome, with reference to results by study when appropriate.

RESULTS

Overview

Searches identified 1,340 citations: 106 from Cochrane Central Register of Controlled Trials, 429 from Medline, 695 from EMBASE, 50 from manufacturer dossiers and 60 from hand searching and reference lists. We received dossiers from the makers of almotriptan, rizatriptan, sumatriptan and zolmitriptan during the second update process. We excluded 280 randomized controlled trials because they examined the wrong population (e.g. healthy volunteers, non-adults, or not migraine or cluster headache), excluded drugs (non-triptans or excluded triptans), the wrong outcomes (that is, none of the outcomes listed in Table 2.) or were abstracts that did not provide sufficient detail to rate results and quality. The process of exclusion of these and 997 other publications are detailed in Figure 1.

Key Question 1. What are the comparative effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?

Systematic Reviews

We found two Cochrane reviews, one comparing rizatriptan to placebo[17] and the other, eletriptan to placebo.[18] Neither of these systematic reviews provided comparative information about triptans.

We also found three self-described systematic reviews[8, 19, 20] and one meta-analysis[10, 11] of the comparative efficacy of different triptans.

Only one of these reviews used a set of predefined, explicit criteria (the Jadad score) for assessing the internal validity of the trials.[20] The goal of the review was to compare all treatments, including triptans, for the treatment of moderate to severe migraine. 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 review journals except for trials of eletriptan, for which unpublished data were obtained directly from the manufacturer. The main results of the study are summarized in Appendix C.

A meta-analysis that used a similar approach, but which did not consider study quality, was published in the *Lancet* in 2001.[10] The investigators included 53 clinical trials of triptans, including 12 unpublished trials (Appendix D), all of which were identified by contacting pharmaceutical companies and investigators. Most of the included trials compared a triptan to placebo rather than to 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 sumatriptan 100 mg as the reference standard (Appendix E). This meta-analysis was comprehensive, examined important outcome measures, and applied statistical methods appropriately, but the strategy for pooling studies also 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.

Both of these publications relied primarily on studies that compared a triptan to a placebo, rather than on direct comparison studies. Both of these meta-analyses pooled results from

placebo-controlled trials in an effort to make inferences about the relative effectiveness of different triptans. Whether trials that do not compare triptans directly can be used to compare the efficacy of different triptans is controversial. The validity of these comparisons, and their ability to predict the results of head-to-head trials, has not been established.

A second publication from the authors of the *Lancet* paper included a table and several paragraphs summarizing the results of 22 head-to-head trials.[21] The main value of this analysis was that it included the results of all known head-to-head trials, regardless of quality or publication status. Because it was based on original data, the authors were able to calculate the results for endpoints, such as the 24-hour response rate, that were not reported in publications. The authors' conclusions about these trials are summarized in Appendix F.

Randomized, Controlled Head-to-Head Trials

Of the 30 randomized, controlled head-to-head trials of various triptans, 13 met the inclusion criteria for this key question. As summarized in Appendix G, many of the excluded head-to-head trials were reported only in abstract form[22-25] or were of poor internal validity.[26-33]

Evidence Table 1 summarizes the design characteristics of the included trials. In general, the trials recruited subjects who were similar with respect to age, sex, and migraine history, and most recruited patients who were not pregnant and had no major coexisting medical conditions. There was more variation among the trials in the use of triptans prior to enrollment in the study and in the use of other migraine medications during the study period. Only two of the trials were rated as having good internal validity. The most common reason for a "fair-quality" rating was a baseline difference in the compared groups. These differences, while they did not in themselves confound the study results, increased uncertainty about the success of the randomization methods in distributing other confounding factors equally among the compared groups. Two studies were rated fair-to-poor quality because they did not adequately describe the baseline characteristics of the compared groups.

In five trials[34-38], sumatriptan or another comparator was put in a gelatin capsule to ensure that patients did not know what medications they received. Data about the effects of encapsulation on pharmacokinetics are conflicting.[39-41] Some argue that the gelatin capsule can slow the release of a triptan so that it performs less well than it does in its native form. Others argue that encapsulation has no effect on triptan kinetics.

We conducted a meta-analysis to examine how encapsulation affects the results of head-to-head trials. We focused on the effect of encapsulation on pain relief and pain-free response at two-hours. Table 4 shows the combined estimates of triptan efficacy with or without encapsulation. Whenever the number of studies is more than 1, the overall estimate is obtained by using random effects model (DerSimonian and Laird, 1986) to incorporate variation among studies into account.

For all triptans, encapsulation was consistently associated with decreased efficacy. Paradoxically, the efficacy of eletriptan tended to increase in studies using encapsulated sumatriptan. Put differently, trials that compared eletriptan to encapsulated versions of other triptans had larger effect sizes than would be expected from the results of other trials, because encapsulated sumatriptan was less effective than expected, and eletriptan was more effective than expected.

It is important to note that, while encapsulation was associated with decreased efficacy, it is not possible to determine whether encapsulation was the *cause* of decreased efficacy. In the meta-regression, these findings persisted after adjustment for mean age, percentage of female

subjects, and percentage with severe baseline pain. The publications provided insufficient data to assess the effects of other variables of interest, including the year of conduct, recruitment method, type of run-in period, and the type of prior migraine treatment, including whether the trial population was "triptan-naïve." 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 not included in the analysis.

Table 4. Comparison of Triptan Efficacy in Trials With or Without Use of Encapsulated Comparators

	2 hours pain relief (Percent, 95% CI)					
	Overall		Studies using encapsulated comparator		Studies without use of an encapsulated comparator	
Drug & Dose	No. of Studies	Percentage (95% CI)	No. of Studies	Percentage (95% CI)	No. of Studies	Percentage (95% CI)
Sumatriptan 50	7*	60.1 (54.7, 65.3)	2	54.3 (47.3, 61.3)	5	62.4 (56.1, 68.4)
Sumatriptan 100	17	58.9 (56.5, 61.2)	5	57.6 (53.6, 61.4)	12	59.4 (56.4, 62.3)
Almotriptan 12.5	4	60.4 (55.4, 65.3)	2	57.806 (54.3, 61.2)	2	63.295 (54.7, 71.1)
Rizatriptan 10	8	66.2 (60, 71.8)	1	46.1 (36.0, 56.4)	7	68.4 (63.0, 73.3)
Naratriptan 2.5	4	47.6 (43.4, 51.8)	1	41.9 (35.1, 49)	3	49.7 (45.3, 54.1)
Zolmitriptan 2.5	5	63.5 (60.7, 66.3)	1	60 (54.5, 64.4)	4	64.6 (61.9, 67.2)
Eletriptan 40	8	62.1 (60, 65.2)	3	66.3 (63.4, 69.0)	5	60.1 (56.6, 63.6)
Eletriptan 80	6	68.0 (62.8, 72.8)	2	71.9 (60.8, 80.8)	4	66.5 (60.2, 72.3)

	2 hours pain free (Percent, 95% CI)					
	Overall		Studies using encapsulated comparator		Studies without use of an encapsulated comparator	
Drug & Dose	No. of Studies	Percentage (95% CI)	No. of Studies	Percentage (95% CI)	No. of Studies	Percentage (95% CI)
Sumatriptan 50	6	27.5 (22.4, 33.4)	2	22.2 (17.0, 28.459)	4	30.5 (24.6, 37.3)
Sumatriptan 100	9	28.7 (24.4, 33.3)	5	25.1 (20.5, 30.4)	4	33.2 (26.1, 41.1)
Almotriptan 12.5	4	29.7 (19.5, 42.3)	2	22.2 (14.1, 33.1)	2	38.4 (34.3, 42.6)
Rizatriptan 10	8	39.8 (36.2, 43.4)	1	25.8 (17.8, 35.9)	7	41.0 (38, 44.2)
Naratriptan 2.5	2	19.3 (15.8, 23.4)	1	17.8 (13.0, 23.9)	1	20.7 (15.7, 26.6)
Zolmitriptan 2.5	4	29.2 (24.2, 34.9)	1	26.3 (22.1, 31.0)	3	30.2 (23.8, 37.4)
Eletriptan 40	8	31.8 (29.4, 34.3)	3	33.2 (29, 37.8)	5	30.9 (28.4, 33.5)
Eletriptan 80	6	40.6 (31.4, 50.7)	2	52.4 (24.9, 78.4)	4	35.4 (28.8, 42.6)

* Whenever the number of studies is more than 1, the overall estimate is obtained by using DerSimonian and Laird (1986) method.

Appendix H summarizes the results of the included trials by outcome measure. Portions of Appendix H are repeated in the following sections, which describe the results for each reported endpoint. Nine of the 13 trials had a sumatriptan comparator. In these trials, sumatriptan was compared with eletriptan (3 trials), naratriptan (1 trial), rizatriptan (2 trials), and zolmitriptan (3 trials). The four other trials compared rizatriptan to naratriptan and to zolmitriptan[42, 43] and eletriptan to naratriptan and zolmitriptan.[37, 38] None of the included studies evaluated frovatriptan.

Pain Relief by Two-Hours

All included trials reported two-hour headache response rates, which was usually the primary study endpoint.

Naratriptan Versus Sumatriptan

One trial compared various doses of naratriptan to sumatriptan 100 mg and to placebo.[44] In this trial, participants came to the clinic during a migraine attack, were randomized and treated there, and stayed there for four-hours. Approximately 85 to 98 patients were in each group. Similar two-hour pain relief rates were reported for naratriptan 2.5 mg and sumatriptan 100 mg (52% vs 60%). However, four-hours after dosing, headache relief was reported by significantly more patients treated with sumatriptan 100 mg (80%) than with naratriptan 2.5 mg (63%) or 5 mg (65%) ($P < 0.05$).

Naratriptan Versus Rizatriptan

One single-dose trial in 522 patients with migraine compared naratriptan 2.5 mg with rizatriptan 10 mg.[43] In this trial, a significant higher percentage of patients taking rizatriptan 10 mg (68.7%) reported two-hour pain relief than those taking naratriptan 2.5 mg (48.4%) ($p<0.001$).

A detailed examination of this trial illustrates the need to consider many different aspects of effectiveness, however. Rizatriptan was more likely to relieve pain at one-hour (38.7% versus 27.8%) and at two-hours (68.7% versus 48.7%). Also at two-hours, rizatriptan was more likely to result in a pain-free response (44.8% and 20.7%) and in normal function (39.3% versus 22.6%). More patients had a sustained pain-free response for 24-hours with rizatriptan (29% versus 17%).[45] All of these comparisons were statistically significant. The two drugs had similar effectiveness in relieving nausea and photophobia; rizatriptan was better at relieving phonophobia. Patients were significantly more satisfied with rizatriptan than with naratriptan after two-hours (33% were "completely" or "very" satisfied with rizatriptan versus 19% with naratriptan),[46] but 24-hour satisfaction was not measured.

Despite the superior speed of action of rizatriptan, and the higher rates of sustained response, there was no difference between rizatriptan and naratriptan in overall quality of life for 24-hours. Patients completed the MSQOL Questionnaire, which asks about 5 aspects of quality of life (work/social/energy/symptoms/feelings). None of the five differed between the two drugs. Rizatriptan had a significantly higher rate of adverse events (39% versus 29%, $p<0.05$). The article does not address whether the severity of these events differed for the two drugs. The most common adverse events were asthenia/fatigue, dizziness, nausea, and somnolence, but the study was not of sufficient size to assess differences in specific adverse events.

Rizatriptan Versus Sumatriptan

In one fair-quality trial[47] 1099 patients took either rizatriptan 5 mg (164), rizatriptan 10 mg (387), or sumatriptan 100 mg (388). After two-hours, 60%, 67%, and 62% of patients, respectively, had pain relief (not significant). This trial provides the only direct comparison between the most efficacious doses of rizatriptan and sumatriptan.

Rizatriptan Versus Zolmitriptan

A trial of zolmitriptan 2.5 versus rizatriptan 10 mg[42] found no difference in two-hour pain relief. No trials comparing zolmitriptan 5 mg versus rizatriptan 10 mg were identified.

Sumatriptan Versus Zolmitriptan

Three trials have compared zolmitriptan 5 mg to sumatriptan 50 mg[48, 49] or sumatriptan 100 mg.[50] All reported only insignificant differences in headache relief at two-hours. When evaluating a lower and less commonly used dosage of sumatriptan (25 mg), however, zolmitriptan 2.5 mg and 5 mg were superior (67.1%, 64.8% versus 59.6%; $p<0.001$).[49]

Eletriptan

Five trials compared eletriptan to encapsulated sumatriptan[34-36], naratriptan[38], and zolmitriptan.[37] Significantly more patients taking eletriptan 40 mg experienced two-hour pain relief than those taking encapsulated sumatriptan 100 mg in two[35, 36] of three trials and those taking encapsulated naratriptan 2.5 mg.[38]

Pain Outcomes at One-Half Hour

Seven included head-to-head trials reported headache relief and pain-free responses at 0.5-hour (see tables 5 and 6 below). These trials found no differences between any triptans studied.

Table 5. 0.5-Hour Pain Relief (% of Patients)

Trial	p value	E40	E80	N2.5	R5	R10	S50	S100	Z2.5
Bomhof	NS	-	-	11	-	14	-	-	-
Pascual	NS	-	-	-	-	14	-	-	14.9
Tfelt-Hansen	NS	-	-	-	12	13	-	11	-
Goadsby	NS	5	12	-	-	-	-	10	-
Sandrini	n/a	nr	nr	-	-	-	nr	nr	-
Garcia-Ramos, 2003	NS	12	-	5	-	-	-	-	-
Steiner, 2003	NS	-	12	-	-	-	-	-	7

Table 6. 0.5-Hour Pain Free (% of Patients)

Trial	p value	E40	E80	N2.5	R5	R10	S50	S100	Z2.5
Bomhof	NS	-	-	1	-	1.5	-	-	-
Pascual	NS	-	-	-	-	2.7	-	-	0.7
Tfelt-Hansen	NS	-	-	-	1	2	-	1	-
Goadsby	NS	nr	nr	-	-	-	-	nr	-
Sandrini	n/a	nr	nr	-	-	-	nr	nr	-

Pain Outcomes at One-Hour

Significant differences between triptans are evident at one-hour. Twelve head-to-head trials reported headache relief at one-hour. The results of these trials are shown in table 7 below. (In

the table, as in Appendix H, statistically significant comparisons are indicated by bold type.) Patients who took rizatriptan 10 mg were more likely to have pain relief at one-hour than patients taking naratriptan 2.5 mg,[43] zolmitriptan 2.5 mg,[42] and sumatriptan 100 mg;[47] but in the fourth study, the results for rizatriptan 10 mg and sumatriptan 50 mg were similar. No study compared rizatriptan 10 mg to a comparable dose of zolmitriptan (i.e., 5 mg.)

Sumatriptan 100 mg was similar to naratriptan 2.5 mg and to zolmitriptan 5 mg. Two good-quality studies that compared zolmitriptan 5 mg to sumatriptan 50 mg had conflicting results.[48, 49]

Eletriptan 40 mg was superior to encapsulated sumatriptan 100 mg in 2 of 3 studies and to encapsulated naratriptan 2.5 mg for pain relief at one-hour. The 80 mg dose of eletriptan was superior in three of three comparisons to other encapsulated triptans (sumatriptan 50 and 100 mg, zolmitriptan 2.5 mg).

Table 7. One-Hour Pain Relief (% of Patients)

Trial	p value	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Havanka	NS	-	-	30	-	-	-	-	35	-	-
Bomhof	p<0.029	-	-	**27.8**	-	**38**	-	-	-	-	-
Pascual	p<0.05	-	-	-	-	**42.5**	-	-	-	**35.3**	-
Tfelt-Hansen	p<0.05	-	-	-	30	**37**	-	-	**28**	-	-
Geraud	NS	-	-	-	-	-	-	-	35	-	34
Gallagher	p=0.014	-	-	-	-	-	39.2	**41.7**	-	43.4	**45.5**
Gruffyd-Jones	NS	-	-	-	-	-	-	38	-	36.9	39.5
Goadsby	<0.01	**38**	**41**	-	-	-	-	-	**20**	-	-
Sandrini	<0.05	30	**37**	-	-	-	-	**24**	27	-	-
Mathew	<0.01	**34**	-	-	-	-	-	-	**27**	-	-
Garcia-Ramos	<0.05	**34**	-	**25**	-	-	-	-	-	-	-
Steiner	<0.0001	-	**40**	-	-	-	-	-	-	**25**	-

Ten trials reported the proportion of patients who were pain-free at one-hour (see table below). Significantly more patients were pain free at one- hour in the eletriptan 40 mg and rizatriptan 10 mg groups compared to the naratriptan 2.5 mg groups in two trials. The naratriptan was encapsulated in the eletriptan comparison. Eletriptan 80 mg was superior for one-hour pain-free when compared to encapsulated sumatriptan 50 mg and encapsulated zolmitriptan 2.5 mg.

Table 8. One-Hour Pain-Free (% of Patients)

Trial	p value	E40	E80	N2.5	R5	R10	S50	S100	Z2.5	Z5
Bomhof	<0.05	-	-	**3.3**	-	**9.5**	-	-	-	-
Pascual	NS	-	-	-	-	12.7	-	-	10.4	-
Tfelt-Hansen	NS	-	-	-	7	10	-	8	-	-
Geraud	NS	-	-	-	-	-	-	11	-	8
Gruffyd-Jones	NS	-	-	-	-	-	11.4	-	9.1	12
Goadsby	NS	8	17	-	-	-	-	6	-	-
Sandrini	<0.05	6	**13**	-	-	-	**5**	7	-	-
Mathew	NS	7	-	-	-	-	-	5	-	-
Garcia-Ramos	0.05	**12**	-	**6**	-	-	-	-	-	-
Steiner	<0.01	-	**12**	-	-	-	-	-	**6**	-

Pain-free at Two- Hours

The table below reflects the trials that reported the proportion of patients who were pain-free after two-hours. Compared with naratriptan 2.5 mg, sumatriptan 100 mg, and zolmitriptan 2.5 mg, more patients taking rizatriptan 10 mg were pain-free at two- hours. Sumatriptan 100 mg and zolmitriptan 5 mg had similar efficacy.[42, 43, 47] Eletriptan 40 mg was superior to encapsulated sumatriptan 100 mg in two of three studies and encapsulated naratriptan 2.5 mg and encapsulated zolmitriptan 2.5 mg in eliminating pain at two-hours. Eletriptan 80 mg was superior to encapsulated sumatriptan 100 mg in all three studies and to encapsulated zolmitriptan 2.5 mg for this outcome.

Table 9. Two-Hour Pain-Free (% of Patients)

Trial	p value	E40	E80	N2.5	R5	R10	S50	S100	Z2.5	Z5
Bomhof	<0.001	-	-	**20.7**	-	**44.8**	-	-	-	-
Pascual	<0.05	-	-	-	-	**43.2**	-	-	**35.6**	-
Tfelt-Hansen	<0.05	-	-	-	25	**40**	-	**33**	-	-
Lines	NS	-	-	-	22	**-**	28	-	-	-
Geraud	NS	-	-	-	-	**-**	**-**	30	-	29
Gruffyd-Jones	NS	-	-	-	-	**-**	35.3	-	32.4	36
Goadsby	<0.05	29	**37**	-	-	-	-	**23**	-	-
Sandrini	<0.05	**31**	37	-	-	-	19	**18**	-	-
Sandrini	<0.0005	31	**37**	-	-	-	19	**18**	-	-
Mathew, 2003	<0.0001	**36**	-	-	-	-	-	**27**	-	-
Garcia-Ramos, 2003	<0.001	**35**	-	**18**	-	-	-	-	-	-
Steiner, 2003	<0.0001	**32**	**44**	-	-	-	-	-	**26**	-

Satisfaction

Five trials reported two-hour satisfaction. Patients in two of these trials rated overall satisfaction utilizing a 7-point scale (1=completely satisfied, couldn't be better; 2=very satisfied; 3=somewhat satisfied; 4=neither satisfied nor dissatisfied; 5=somewhat dissatisfied; 6=very dissatisfied; 7=completely dissatisfied). Results from one trial suggest that a greater percentage of patients taking rizatriptan 10 mg were completely, very or somewhat satisfied with treatment than those taking zolmitriptan 2.5 mg (62.7% versus 54.6%; p=0.045). One trial reported a higher mean satisfaction score for patients taking rizatriptan 10 mg than those taking naratriptan 2.5 mg (3.55 versus 4.2; p<0.001).

Patients in two trials graded satisfaction using the terms "poor", "fair", "good", or "excellent". The time endpoints used in these trials were unclear. These trials reported that the satisfaction of patients taking sumatriptan 100 mg did not differ significantly from those taking naratriptan 2.5 mg. The two-hour satisfaction of patients taking sumatriptan 50 mg didn't differ from those taking zolmitriptan 2.5 mg, either.

A higher proportion of patients rated their study medication as "excellent" or "good" (7 or 6 on 7-point Likert scale) when taking eletriptan 40 or 80 mg compared to encapsulated zolmitriptan 2.5 mg (64% vs 66% vs 55%; p<0.01).

Return to Normal Function

Six trials reported results of patients' records of their functional disability at 1, 1.5, and two-hours. These ratings were made using a 4-point scale (0=normal; 1=mildly impaired; 2=severely impaired; 3=unable to do activities, requires bed rest). Three trials compared rizatriptan 10 mg

to other triptans. At one-hour, one trial[47] cited superiority of rizatriptan 10 mg in percent of patients with a return to normal function to sumatriptan 50 mg (no data; p<0.05) and 100 mg (14% versus 9%; p=0.031). At 1.5-hours, one trial[47] demonstrated superiority of rizatriptan 10 mg to sumatriptan 100 mg (27% versus 19%; p=0.017). Finally, at two- hours, four trials[32, 42, 43, 47] showed continued superiority of rizatriptan 10 mg over sumatriptan 50 mg (47% vs 42%; p=0.033) and 100 mg (42% versus 33%; p=0.015), naratriptan 2.5 mg (39.3% versus 22.6%; p<0.001) and zolmitriptan 2.5 mg(45.4% versus 37%; p=0.025). Significantly greater proportions of patients in eletriptan 40 mg groups reported a return to normal or near-normal levels of functioning after two- hours than those taking encapsulated sumatriptan 100 mg in the Sandrini (63% vs 46%; p<0.005) and Mathew (68% vs 61%; p<0.01) studies. Goadsby et al (2000) reported that significantly fewer patients taking eletriptan 40 mg remained at a moderate-to-severe level of functional impairment at two-hours than those taking encapsulated sumatriptan 100 mg (32% vs 42%; p-value not reported).

Endpoints at 24-Hours

The trials used inconsistent methods to measure outcomes at 24-hours (see Appendix H). To make comparisons across studies, Ferrari and colleagues, the authors of one of the recent meta-analyses summarized in Appendix B, used a composite measure of "sustained pain free," which they defined as "the proportion of patients who are pain free by two- hours post-dose and who do not experience a recurrence of moderate or severe headache and who do not use any rescue medication 2-24 h post-dose."[16] Using this definition, they were able to measure sustained pain free responses using original data provided by the manufacturers for all but one of the trials included in our review. By their data, there were no differences in the 24-hour sustained pain free endpoint between sumatriptan 100 mg and almotriptan 12.5 mg, (Cabarrocas,[51] Colman),[28] zolmitriptan 5 mg [50] or rizatriptan 10 mg.[47] There were also no differences between sumatriptan 50 mg and zolmitriptan 2.5 mg [48, 49] or rizatriptan 5 mg.[52] Rizatriptan 10 mg was superior to zolmitriptan 2.5 mg (Pascual, NNT=11)[45] and naratriptan 2.5 mg (Bomhof, NNT=8.3),[43] and zolmitriptan 2.5 mg and zolmitriptan 5 mg were superior to sumatriptan 25 mg. Eletriptan 40 mg was superior to encapsulated sumatriptan across the two studies included in the Ferrari meta-analysis.[34, 36] The remaining study (Havanka)[44] defined a sustained response as no worsening of headache, recurrence, or use of rescue medication from 4 to 24-hours;[44] by this measure, there was no difference between sumatriptan 100 mg and naratriptan 2.5 mg or naratriptan 5 mg.

Escape Medication Use

Eight trials reported use of rescue medication from 2 to 24-hours. The results are shown in table 10 below. Significantly fewer patients in eletriptan 40 mg groups used rescue medication than in encapsulated naratriptan 2.5, sumatriptan 100 mg and zolmitriptan 2.5 groups.

Table 10. Use of Rescue Medications (% Patients)

Trial	P value	E40	N2.5	R5	R10	S50	S100	Z2.5	Z5
Bomhof[43]	NS		46.5	-	40.3	-	-	-	-
Pascual[42]	NS		-	-	39.4	-	-	43.6	-
Gruffyd-Jones[48]	NS		-	-	-	23	-	23.6	22.2
Goadsby[34]	NS	29					29		
Sandrini[36]	nr	15					25		
Mathew[35]	<0.01	20					27		
Steiner[37]	<0.05	20						26	
Garcia-Ramos[38]	<0.05	15	27						

Relief of Migraine-Related Symptoms

Twelve trials reported the percentage of patients at two-hours without migraine-related symptoms including nausea, vomiting, photophobia, and phonophobia. With regard to nausea, two trials indicated significant differences between rizatriptan 10 mg and sumatriptan 100 mg (75% versus 67%; $p<0.05$)[47] and zolmitriptan 2.5 mg (74.8% versus 67.5%; $p=0.046$).[42] Eletriptan 40 mg was superior to encapsulated sumatriptan 100 mg in 2 of 3 trials and encapsulated zolmitriptan 2.5 and similar to encapsulated naratriptan 2.5 in treating nausea after two-hours. Five trials reported insignificant differences in relief of nausea between rizatriptan 10 mg and naratriptan 2.5 or between sumatriptan 25-100 mg and any other triptan studied.

Results of photophobia relief assessment are similar. Two trials reported significant superiority of rizatriptan 10 mg compared to naratriptan 2.5 (59.2% versus 47.2; $p<0.05$) and zolmitriptan 2.5 mg (64.4% versus 56.5%; $p=0.029$) in providing patients with photophobia relief at two-hours.[42, 43] Rizatriptan 10 mg was found to be equal to sumatriptan 100 mg[47] with regard to photophobia relief at two-hours, however. Relief of photophobia rates also did not differ between sumatriptan 100 mg and naratriptan 2.5 mg and zolmitriptan 5 mg. Eletriptan 40 mg was superior to encapsulated sumatriptan 100 mg in one of three trials and the 80 mg dose was similar to encapsulated zolmitriptan 2.5 mg in treating photophobia at two-hours.

Six trials reported on phonophobia relief at two-hours. One trial reported that significantly more patients experienced relief of phonophobia while taking rizatriptan 10 mg (65%) than naratriptan 2.5 (51.9%) ($p<0.05$).[43] Eletriptan 40 mg was superior in both trials of encapsulated sumatriptan 100 mg and the 80 mg dose was similar to encapsulated zolmitriptan 2.5 mg in treating phonophobia at two-hours. Results from the remaining trials were insignificant.

Only five trials included results of vomiting relief. No significant differences between any dosages of any of the triptans studied were reported.

Consistency Over Multiple Attacks

Most head-to-head trials report results for one to three attacks of migraine. A single experience with a drug does not necessarily represent the experience of using the drug repeatedly over time. For example, a patient who responds to a drug once may not respond the next time, and a patient who has no adverse events the first time may experience one with the next use. For this reason, multiple-attack studies in which patients report their experience while using a drug over time (usually, 6 months) provides information about the consistency of response and general satisfaction with a drug that single-dose studies cannot.

The two trials comparing zolmitriptan to sumatriptan provided the best data on consistency. The first of these, conducted in the U.S., compared zolmitriptan 2.5 mg and 5 mg to sumatriptan

25 mg and 50 mg.[49, 53] Over 6 months, each patient was treated for up to 6 attacks. Patients were recruited from primary care offices, neurology offices, and research clinics. Of 1445 patients enrolled, of whom 1212 treated at least 2 migraine attacks, 1043 completed the study. To measure consistency, the authors calculated the proportion of patients who responded at two-hours in 80% to 100% of attacks (see table 11 below). The results indicate that the two-hour response is not a reliable indicator of consistency across multiple attacks.

Table 11. Consistency

DRUG	2-hour response	Consistency across 6 attacks
zolmitriptan 2.5	67.1%	47.1%
zolmitriptan 5	64.8%	44.3%
Sumatriptan 25	59.6%	33%
Sumatriptan 50	63.8%	39.2%

This trial has been criticized because it did not exclude patients who had previously taken sumatriptan.[54] 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.

A good-quality trial with a similar design was conducted in Europe.[48] In that trial, there were essentially no differences in efficacy between zolmitriptan 2.5 mg, zolmitriptan 5 mg, and sumatriptan 50 mg. The three treatments also had similar consistency across attacks: about 40% of patients in each group reported a two-hour headache response in 80% or more of their attacks.

Open-label and Uncontrolled Studies

Several open-label studies have been done to evaluate patients' preferences between triptans, the consistency of relief, functional status, and health-related quality of life. Such trials may be randomized or non-randomized.

Preferences

As a body of evidence, these preference studies provide very weak evidence about comparative effectiveness. Although randomization can ensure that similar groups begin the study taking the alternative drugs, it cannot correct the lack of blinding or the selection bias that is likely to occur in these studies: namely, that patients who want to try something new are more likely than other patients to respond poorly to the older drug. Moreover, many people might prefer a new drug simply because it is new. Blinding would prevent this bias as well.

A randomized, open-label crossover trial found that more patients preferred rizatriptan wafer than sumatriptan 50 mg tablets (64.3 versus 35.7%, $p <= 0.001$)[55] In another randomized, open-label, crossover trial,[56] 213 of 386 patients who took both drugs expressed a preference for rizatriptan ODT and 161 preferred sumatriptan 50 mg.

In another type of preference study, patients are given different medications and asked to use them at different times, comparing the results. In one such study, 42 of 94 migraine patients (44%, 95% CI 34-58%) preferred zolmitriptan 2.5 mg over sumatriptan 50 mg tablets, 27 (29%, 20-38%) preferred sumatriptan 50 mg, and 25 had no preference. In another preference study, patients were given samples of 4 different triptans when they came to see the doctor. Preferences for sumatriptan, zolmitriptan, rizatriptan, and naratriptan were similar overall, but younger patients tended to prefer the rizatriptan orally dissolving form.[57] In another study, patients who had responded before to rizatriptan were given a choice of tablet or orally

dissolving forms. Of the 367 patients studied, 188 selected the oral disintegrating tablet, while 179 preferred the conventional tablet.[58]

Consistency

Because there are so few data from head-to-head trials and active-control trials about the consistency of effect and the long-term impact of triptan use, we examined uncontrolled studies that measured these outcomes. Table 12 below summarizes selected uncontrolled, open-label studies of triptans. The main value of these studies is that they demonstrate that many patients get consistent relief from the same medicine over time, do not necessarily experience an increasing risk of adverse events, and seldom withdraw due to complications. It is important to note that these studies include only selected patients who responded initially to these drugs and tolerated them well. The response rates in these trials are not generalizable to migraine patients generally, nor do they indicate how effective different triptans are in patients who have not been on them previously.

Table 12. Uncontrolled Studies of Long-Term Repeated Use of Triptans

Author, date	Drug, dose, study design	N	Duration	2-hour attacks, % relieved	Consistent over time	Adverse effects
Cabarrocas, 2001[51]	Almotriptan, 12.5 mg, open study	806	1 year	81%	Yes	51.3% of patients
Gerth, 2001[59] Mathew, 2002[60]	Almotriptan, 12.5 mg, open study	582	6 months	76%	Yes	Drug-related chest pain 1.5%
Pascual, 2001[61]	Almotriptan, 12.5 mg, open study	762	1 year	84.2%	Yes	51.3%
Heywood, 2000[62]	Naratriptan, 2.5 mg, open study	417	1 year	70%	Yes	16% of attacks
Cady, 2001[63]	Rizatriptan wafer, various doses, open study	458	6 months	82%	Yes	
Tansey, 1993[64]	Sumatriptan, 100 mg, open study	288	1 year	84%	Yes	16%
Tepper, 1999[65]	Zolmitriptan, 2.5 and 5 mg, open study	2,499	9 months	~85%	Yes	65.7%
Cady, 1998[66]	Zolmitriptan	2,058	1 year	81%	Yes	26%

* Article states "83% were mild or moderate."

Function, Work Productivity, and Quality of Life

A large body of research has assessed improvements in patients' health-related quality of life and work productivity and reductions in their health care utilization after starting subcutaneous sumatriptan.[67-72] Compared with oral triptans, subcutaneous sumatriptan has higher efficacy and a faster onset of action.

Less research has been conducted for some of the oral triptans, and no long-term studies have compared different triptans' ability to produce these improvements. A four-attack placebo-controlled, double-blinded randomized controlled trial demonstrated reductions in self-reported work and productivity loss among patients taking oral rizatriptan.[73] Productivity was also an outcome measure in a trial of stratified versus stepped care for migraine that involved zolmitriptan.[74] Open-label, nonrandomized study data also supports the view that use of oral sumatriptan improves work attendance, productivity, and quality of life.[69, 75, 76] and reduces disability and health care utilization.[77, 78] Other improved outcomes evaluated in observational studies include health-related quality of life (rizatriptan[69] and zolmitriptan[79]).

Trials of Triptans versus Active Controls

Twenty-one trials of triptans versus other treatments to shorten a migraine attack met the inclusion criteria.[59, 67, 70, 71, 80-97] These trials are summarized in Evidence Tables 2a and 2b. All but 6[59, 93-96] of the 20 trials compared sumatriptan, the first triptan, to other treatments for migraine. For this reason, these trials do not provide very much information that would be useful in comparing one triptan to another.

Approximately two-thirds of the trials were conducted outside the United States. Most observed 1 to 3 attacks. Most of the trials used IHS criteria to determine eligibility.

In general, these trials indicate that triptans are as effective or more effective than other treatments, but can be associated with higher rates of recurrence within 24-hours and higher rates of adverse events.

One trial[80] comparing sumatriptan 100 mg to cafergot (2 mg ergotamine tartrate, 200 mg caffeine) and one trial[95] comparing zolmitriptan 2.5 mg to acetylsalicylic acid 900 mg plus metoclopramide 10 mg reported pain relief after ½ hour. At 30 minutes, no significant differences between either triptan or the other treatments were noted. In one fair-quality, single-attack trial, sumatriptan 100 mg was more likely to relieve pain within one-hour than cafergot (26% versus 18%; $p<0.001$).

Nine trials reported pain relief at two-hours. Three of these trials noted significant findings.[80, 93, 94] Eletriptan 40 mg (54% vs 33%; $p<0.01$), rizatriptan 10 mg (75.9% vs 47.3%; $p\leq0.001$) and sumatriptan 100 mg (66% vs 48%; $p<0.001$) were superior to ergotamine 200 mg/caffeine 2 mg across three trials. The percentage of patients with two-hour headache relief was 90 % with rizatriptan 10 mg and 70% with standard care ($p<0.05$) in another trial. The other six trials found no significant differences between either sumatriptan (50 mg and 100 mg), naratriptan 2.5 mg or zolmitriptan 2.5 mg vs metoclopramide combinations, domperamol, tolfenamic acid, or naproxen.

Seven trials reported two-hour pain free endpoints. Data from four of these trials show that triptans (eletriptan 40 mg, rizatriptan 10 mg, sumatriptan 100 mg, zolmitriptan 2.5 mg) were significantly better at providing patients with a pain-free response at two-hours than the active-control comparators (all p-values <0.05).[80, 93, 94, 96] The remaining trial found no significant difference between sumatriptan 100 mg and tolfenamic acid in two-hour pain free effectiveness.[88]

In two trials,[80, 83] higher proportions of patients taking sumatriptan 100 mg regarded the therapy as good-excellent when compared to an ergot alkaloid or an NSAID. More patients taking rizatriptan 10 mg than those taking ergotamine/caffeine (69.8% vs 38.6%; $p\leq0.001$) were completely, very or somewhat satisfied with medication at two-hours in a 2003 trial.[93]

However, an additional two trials[89, 91] reported that patients taking an NSAID or diclofenac were more likely to be satisfied than patients taking oral sumatriptan 100mg.

With regard to functional disability, four trials[84, 85, 89, 98] demonstrated an earlier restoration of ability to resume activities of daily living in patients taking various preparation types of sumatriptan. One trial[87] was notable because it demonstrated improvements in health-related quality of life over standard treatments—an advantage that had been repeatedly demonstrated earlier for sumatriptan. A 2003 trial[93] reported that more patients taking rizatriptan 10 mg were functioning normally at two-hours than in the ergotamine/caffeine group (57% vs 27.8% $p\leq0.001$).Eletriptan 40 mg (52% vs 31%; $p\leq0.001$) and rizatriptan 10 mg (57% vs 27.8% $p\leq0.001$) were similarly superior to ergotamine 200 mg/caffeine 2 mg in relieving functional impairment across two trials.

A significant proportion of the active-control trials reported safety and tolerability information. Four trials presented clear data indicating that a greater proportion of patients taking oral or subcutaneous sumatriptan or oral rizatriptan withdrew due to intolerable adverse events when compared to those undergoing standard migraine treatments.[83, 85, 91, 99] However, in three additional trials,[80, 82, 95] small between-groups differences in withdrawals due to adverse events favored the triptans.

Placebo-Controlled Trials of Triptans

We reviewed a limited number of placebo-controlled trials of eletriptan and reformulated sumatriptan because we found the body of head-to-head evidence to be insufficient to make strong conclusions about comparative efficacy for these triptans.

Almotriptan

Fair evidence from two placebo-controlled trials (n=685) suggests that almotriptan is at least equivalent in efficacy to conventional sumatriptan 100 mg and other similar triptans.[16, 100, 101]

Eletriptan

Fair evidence from three placebo-controlled trials (n=3076) suggests that eletriptan is at least equivalent in efficacy to conventional sumatriptan 100 mg and other similar triptans.[16, 94, 102, 103]

Reformulated Sumatriptan

As of January 2004, sumatriptan has been reformulated as a fast-disintegrating, rapid-release tablet. This will replace the conventional tablet that was studied in six of the 13 head-to-head trials. One placebo-controlled trial (n=432) of reformulated sumatriptan has been published.[104] Results of this trial are summarized in Evidence Tables 3a and 3b and suggest that sumatriptan rapid release 50 and 100 mg dosages are at least similar to conventional sumatriptan in pain-free efficacy.

Use of Triptans in Mild or Early Migraine Attacks

Triptans are approved for the treatment of moderate to severe migraine attacks. The great majority of controlled trials of triptans, and all of the included head-to-head trials, require that patients wait until a headache is moderate or severe before taking the triptan. In trials that require patients to wait until headache is moderate or severe, patients who take them while pain is mild are violating the protocol. Some investigators have looked back at the results of treatment in these protocol violators; they find that mild headaches often went away and did not recur when treated early in their course. These studies provide very weak evidence, however, because mild headaches would be expected to go away more often than moderate or severe ones. Retrospective analyses of this kind provide very weak evidence that triptans may be effective in mild headache.[105, 106]

It is clear from large, uncontrolled cohort studies of patients who use triptans regularly that patients often take them while the headache is still mild, and physicians often instruct them to do so. Nevertheless, results of placebo-controlled studies of the early use of triptans are mixed. In a 1994 double-blind, placebo-controlled single-attack trial, injection of sumatriptan sc during the migraine aura had no beneficial effects.[107] In a small 1996 pilot study, 3 of 16 patients who gave themselves zolmitriptan during the aura did not develop a migraine headache, versus 0 of 16 for placebo.[108] In a small randomized trial, 50% of patients who took a rizatriptan sublingual wafer at the onset of headache experienced complete relief by one-hour—but so did 50% of patients who took a placebo.[109] Placebo response rates may be higher in early migraine because it is less likely that a headache will persist if it is just beginning than after it has progressed for some time. Several larger trials designed to examine (and, in some cases, compare) the efficacy of triptans in mild headaches are underway.[110]

Cluster Headache

Cluster headaches cause unilateral excruciating pain associated with autonomic disturbances. Episodes usually last from 15 minutes to two-hours. Patients can be classified as having "episodic" or "chronic" cluster headaches, depending on the pattern of repeated attacks.

Randomized trials have evaluated sumatriptan in three forms (subcutaneous, oral, and nasal spray) and zolmitriptan tablets in the treatment of cluster headaches. One double-blind crossover trial (n=49) and one other crossover trial (n=134), both in inpatients and both limited to treatment of 2 attacks, found that sumatriptan sc reduced the duration of cluster headaches.[111-113] From 50% to 75% of patients experienced relief within 15 minutes, versus 26% to 35% for placebo. In a subsequent uncontrolled study, 138 patients treated a total of 6,363 attacks with sumatriptan 6 mg sc.[114] This uncontrolled study demonstrated that patients continued to obtain headache relief with repeated use over 2 years, but was not designed to determine whether use of sumatriptan improved function or quality of life compared with other treatments.

There are no trials of oral sumatriptan to shorten a cluster headache. One randomized trial of oral sumatriptan to reduce the frequency of cluster headache attacks had negative results.[115] The only published trial of sumatriptan nasal spray found that it is much less effective than sumatriptan given subcutaneously.[116]

Oral zolmitriptan was evaluated for cluster headache in one double-blind, randomized crossover trial.[117] After 30 minutes, patients who had episodic cluster headaches were more likely to have pain relief (mild or no pain) if they took zolmitriptan 10 mg or 5 mg than if they took placebo (60%, 57%, and 42%, both $p <= 0.01$ versus placebo). Zolmitriptan was ineffective in patients who had chronic cluster headaches.

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?

There are no comparative studies concerning serious, life-threatening events. Data on rare or life-threatening complications is available for the various forms of sumatriptan, which have been used to treat more than 200 million migraine attacks worldwide. A recent review of the safety of sumatriptan examined both adverse events in clinical trials and post-marketing surveillance data.[118] In 1998, 16 serious cardiovascular events following use of sumatriptan sc, and 11 following oral sumatriptan use, were reported to the voluntary postmarketing surveillance system. In 1993, 103 serious cardiovascular events were reported for sumatriptan sc and 38 for 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 specific adverse events—chest pain and central nervous system symptoms including dizziness, parasthesia, somnolence and fatigue/asthenia—are summarized in Appendix H. In most cases, descriptions of the methods used to assess intensity, duration, seriousness and relationship to study medication were unclear or not provided. Generally, investigators described the intensity of the adverse events experienced as predominantly of mild to moderate severity and transient in nature.

Chest Pain/Tightness

No significant differences were found in any of the included trials. In one trial,[47] chest pain was more frequent in patients taking sumatriptan 100 mg than those taking rizatriptan 5 mg (6% versus 1%; $p<0.05$), but was not different for sumatriptan 100 mg and rizatriptan 10 mg (6% versus 3%).

Central Nervous System Symptoms

No significant between group differences were reported by the trials that assessed dizziness, paresthesias, or somnolence. In one trial, fatigue/asthenia was more frequent in patients taking sumatriptan 100 mg than those taking rizatriptan 5 mg (8% versus 2%; $p<0.05$), but was not different for sumatriptan 100 mg and rizatriptan 10 mg (8% versus 8%).[47]

Key Question 3. Are there subgroups of patients based on demographics, other medications, or co-morbidities 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 in Blacks, and peaks in prevalence around age forty.[119] We found no trials that included primarily men, blacks, or the elderly. In a 12-attack 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.[120]

Two placebo controlled trials published in 2002[121, 122] (Evidence Tables 3a and 3b) reported results of eletriptan and zolmitriptan in Japanese migraineurs. The trials enrolled samples similar in age, sex and migraine history. Eletriptan and zolmitriptan had similar pain relief and pain-free response at two-hours, 24-hour recurrence, escape medication use, relief of associated symptoms at two-hours (nausea, photophobia, phonophobia, vomiting) and adverse events (asthenia, paresthesia, somnolence) when each were compared to placebo. Outcome rates reported were within the ranges for eletriptan and zolmitriptan in the head-to-head trials of similar samples of predominantly white patients.

Trials of triptans have generally excluded patients who have cardiovascular disease, uncontrolled hypertension, liver disease, and several other conditions. Information on contraindications is available from the package insert for each triptan. For example, certain triptans are contraindicated in patients with particular conditions, such as hepatic disease.

Pharmacokinetic trials, mostly in healthy volunteers, have been used to make recommendations about dosage adjustment in patients taking propranolol and other anti-migraine drugs.[123-127] Results of such trials have been used in making recommendations for or against dosage adjustments. No clinical trials have evaluated how the use of other antimigraine therapies affects the actual incidence of adverse events.

In general, triptans have proved to be as effective in migraine associated with menstruation as in other attacks. A double-blind, placebo controlled RCT demonstrated the effectiveness of sumatriptan sc in menstrual migraine.[128] Retrospective meta-analysis of RCTs of sumatriptan sc, rizatriptan, and zolmitriptan support the view that triptans are equally effective in attacks during menstruation and in other attacks.[129-131]

We identified one double-blind RCT of a triptan to prevent migraines associated with menses.[132] In this trial, across 4 menstrual periods, more patients treated with naratriptan, 1 mg, were headache-free compared with placebo (23% versus 8%). An earlier pilot study by the same investigator used sumatriptan for prophylaxis of menstrual migraine, but that study was uncontrolled.[133]

SUMMARY

Although a large number of head-to-head trials of the triptans have been done, relatively few have been published in peer-reviewed journals and are of fair or better quality using standard criteria for internal validity. The main findings of this review are summarized in table 13 below:

Table 13. Summary of the Evidence

Key Question	Overall Quality of the Evidence*	Conclusion
1:Comparative Effectiveness What is the comparative effectiveness and duration of response of different oral triptans in reducing the severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?	Rizatriptan 10 mg vs sumatriptan 100 mg: Fair+	Rizatriptan 10 mg is superior to sumatriptan 100 mg in the following efficacy outcomes: **Outcome** — **NNT** 1-hour pain relief — 12 2-hour pain free — 15 Return to normal function at 1-hour — 21 Return to normal function at 2 hours — 12 2-hour nausea-free — 13 The available head-to-head trials do not examine other important outcomes, such as 24 hour sustained relief and long-term consistency. Therefore, evidence is insufficient to judge the overall balance of advantages and disadvantages of rizatriptan vs. sumatriptan.
VURSES	Rizatriptan 10 mg vs naratriptan 2.5 mg: Fair+	Rizatriptan 10 mg is superior to naratriptan 2.5 in the following efficacy outcomes: **Outcome** — **NNT** 1-hour relief — 10 1-hour pain free — 17 2-hour relief — 6 2-hour pain free — 5 24-hour sustained relief — 9 2-hour photophobia-free — 9 2-hour phonophobia-free — 9
	Zolmitriptan 5 mg vs sumatriptan 100 mg: Fair+	Fair quality evidence that there are no differences in efficacy
	Naratriptan 2.5 and sumatriptan 100 mg: Fair	Naratriptan 2.5 and sumatriptan 100 provide similar 1-hour, 2-hour and 24-hour sustained pain relief. Sumatriptan 100 was superior to naratriptan 2.5 (NNT=7) for 4-hour pain relief.

Table 13. Summary of the Evidence Continued

Key Question	Overall Quality of the Evidence*	Conclusion
	Eletriptan vs other triptans: Fair-	Evidence from 5 head-to-head trials 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. Fair evidence from 3 placebo-controlled trials suggests that eletriptan is at least equivalent in efficacy to conventional sumatriptan 100 mg and other similar triptans
	Reformulated sumatriptan (rapid release): Poor	No head-to-head trials One placebo-controlled trials suggests that sumatriptan rapid release appears similar to conventional sumatriptan in pain-free efficacy
	Almotriptan: Fair-	Two head to head trials had poor internal validity and were not analyzed in this review Fair evidence from 2 placebo-controlled trials suggests that almotriptan is at least equivalent in efficacy to conventional sumatriptan 100 mg and other similar triptans
	Frovatriptan: Poor	No head-to-head trials
2: Safety/Adverse Effects 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?	Eletriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan: Good	There is good evidence from 13 head-to-head trials that there are no differences in chest pain/tightness and central nervous system effects for these triptans
	Almotriptan: Poor	Data from two head to head trials of poor internal validity were not analyzed in this review
	Frovatriptan: Poor	No head-to-head trials
3: Subgroups Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?	All triptans: Poor	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

The review suggests 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-attack 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. A few observations can be made. 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 they are clearly described, studies which recruit patients who have been on triptan therapy can be informative. It is important that studies that do recruit such patients 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 those they haven't taken before. Methods to measure the size of the effect of previous triptan use within a particular trial could also be used. Finally, studies could make greater efforts to draw from the larger denominator of migraine sufferers who do not seek specialty or even primary medical care and who are less likely to have used triptans.

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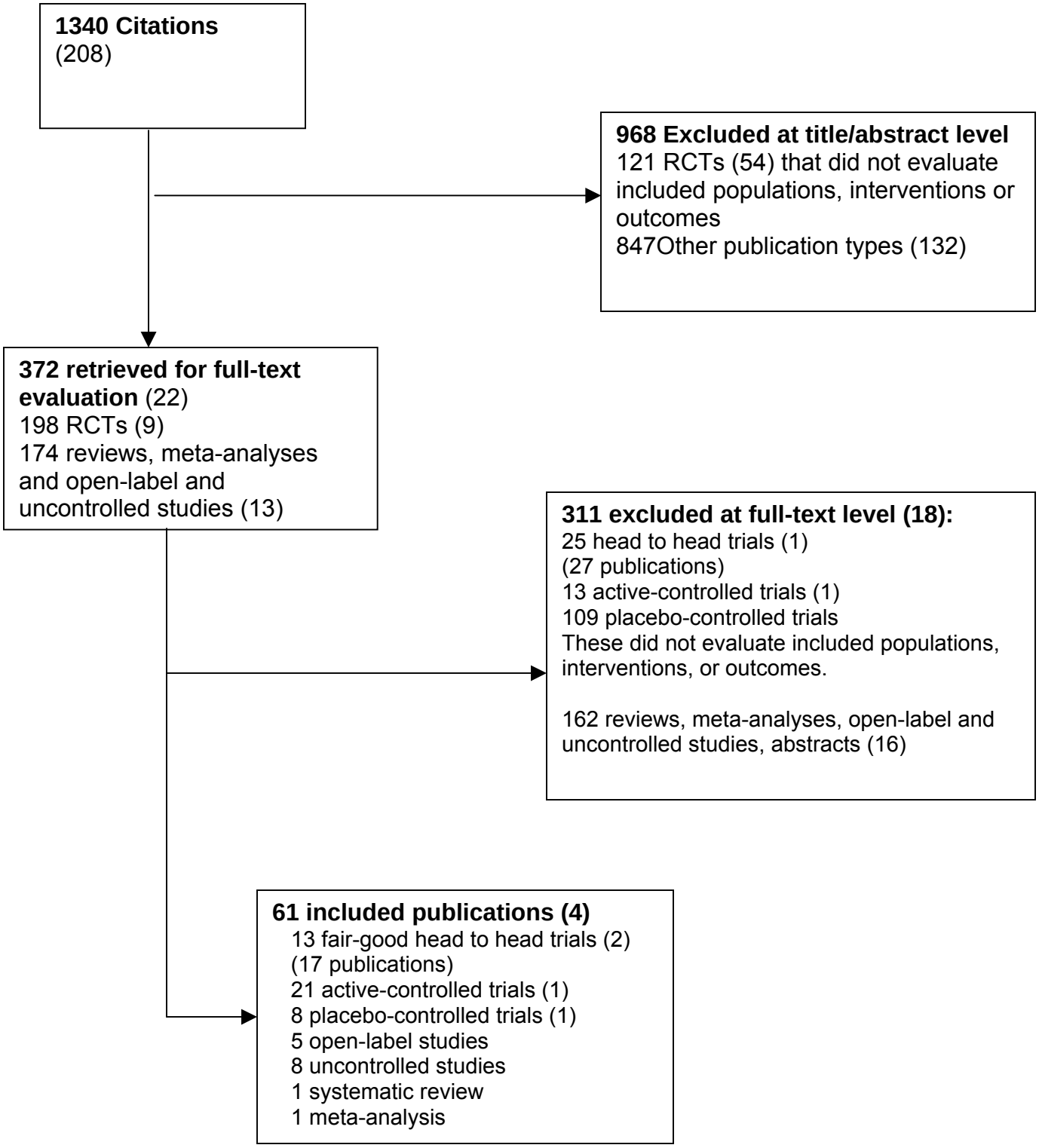
Figure 1: Triptans drug class review flow diagram (new publications from update 2)



Appendix A. Search Strategies

Ovid Technologies, Inc. Email Service

Search for: 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11
Citations: 1-454

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2004>
Search Strategy:
---
1 triptans.mp. (15)
2 sumatriptan.mp. or exp SUMATRIPTAN/ (333)
3 almotriptan.mp. (20)
4 frovatriptan.mp. (9)
5 naratriptan.mp. (30)
6 rizatriptan.mp. (52)
7 zolmitriptan.mp. (53)
8 eletriptan.mp. (20)
9 5-hydroxytryptamine.mp. (341)
10 MIGRAINE/dt [Drug Therapy] (503)
11 9 and 10 (7)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11 (454)
13 from 12 keep 1-454 (454)

Ovid Technologies, Inc. Email Service

Search for: 19 and (200308$ or 200309$ or 20031$ or 2004$).ed.
Citations: 1-47

Database: Ovid MEDLINE(R) <1996 to March Week 2 2004>
Search Strategy:
---
1 triptans.mp. (247)
2 sumatriptan.mp. or exp SUMATRIPTAN/ (1161)
3 almotriptan.mp. (78)
4 frovatriptan.mp. (49)
5 naratriptan.mp. (156)
6 rizatriptan.mp. (183)
7 zolmitriptan.mp. (257)
8 eletriptan.mp. (98)
9 5-hydroxytryptamine.mp. (3532)
10 MIGRAINE/dt [Drug Therapy] (1599)

11 9 and 10 (31)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11 (1526)
13 limit 12 to (human and english language) (1159)
14 limit 13 to (clinical trial or clinical trial, phase i or clinical, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial or review, multicase) [Limit not valid in: Ovid MEDLINE(R); records were retained] (323)
15 exp clinical trials/ or randomi$.tw. or cohort studies.mp. or observational stud$.mp. (165315)
16 Meta-analysis/ or meta analysis.mp. (8552)
17 15 or 16 (169449)
18 13 and 17 (346)
19 14 or 18 (492)
20 19 and (200308$ or 200309$ or 20031$ or 2004$).ed. (47)
21 from 20 keep 1-47 (47)

Ovid Technologies, Inc. Email Service

Search for: limit 24 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]
Citations: 1-62

Database: Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) In-Process, Other Non-Indexed Citations
Search Strategy:
---
1 triptans.mp. (41)
2 sumatriptan.mp. or exp SUMATRIPTAN/ (41)
3 almotriptan.mp. (11)
4 frovatriptan.mp. (7)
5 naratriptan.mp. (11)
6 rizatriptan.mp. (10)
7 zolmitriptan.mp. (13)
8 eletriptan.mp. (11)
9 5-hydroxytryptamine.mp. (169)
10 MIGRAINE/dt [Drug Therapy] (3)
11 9 and 10 (0)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 11 (95)
13 limit 12 to (human and english language) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained] (84)
14 limit 13 to (clinical trial or clinical trial, phase i or clinical, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study or practice guideline or randomized controlled trial or review,

multicase) [Limit not valid in: Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained] (1)
15 exp clinical trials/ or randomi$.tw. or cohort studies.mp. or observational stud$.mp. (5968)
16 Meta-analysis/ or meta analysis.mp. (504)
17 15 or 16 (6278)
18 13 and 17 (20)
19 14 or 18 (21)
20 19 and (200308$ or 200309$ or 20031$ or 2004$).ed. (1)
21 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (95)
22 migraine.mp. [mp=ti, ab, rw, sh] (358)
23 21 and 22 (70)
24 limit 23 to english language (63)
25 limit 24 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained] (62)
26 randomized controlled trial.mp. [mp=ti, ab, rw, sh] (281)
27 25 and 26 (0)
28 from 25 keep 1-62 (62)

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are 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 the true difference between the compared drugs.

For Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - 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
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
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 (i.e., 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 follow-up or overall high loss to follow-up? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom 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.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (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 events investigated specified and defined?

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

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; 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 to 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 whom 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?

Systematic Reviews

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four 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,

i.e., 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?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date 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, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been 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 (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either 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 (i.e. how many reviewers 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 judgement 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 size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (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 use 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 evaluations should be weighted in some way (e.g., 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.

Appendix C. Oldman, 2002 meta-analysis

Outcome	Summary of results
Headache relief at 2 hours	E80 and R10 significantly superior to R5, S50 and N2.5. No differences between E40, Z5, S100, Z2.5.
Headache relief at 1 hour	E80 and R10 significantly superior to S50. No differences between E40, N2.5, R5, S50, S100, Z5 and Z2.5.
Pain-free at 2 hours	E80 and R10 significantly superior to N2.5 and S50 No significant differences between N2.5, R5, S50, S100 and Z2.5
Sustained relief over 24 hours	E80 significantly superior to R5, R10, S50 and S100. No significant differences between R5, R10, S50 and S100
Pain-free over 24 hours	Not calculated due to inadquate information
Adverse events	Not calculated due to inadquate information

Appendix D. Ferrari, 2001 meta-analysis unpublished trials

Trial code	Design	Placebo	R5	R10	S25	S50	S100	Z2.5	Z5	A12.5	N2.5	E20	E40	E80	Other
0070	P/MA	-	-	-	-	537	-	538	553	-	-	-	-	-	-
0071	P/MA	-	-	-	327	330	-	313	317	-	-	-	-	-	-
0073	P	-	-	-	-	-	-	322	-	-	-	-	-	-	336*
S2WB2004	P	91	-	-	-	-	97	-	-	-	86	-	-	-	-
S2WB3002	P	104	-	-	-	-	229	-	-	-	199	-	-	-	-
S2WB4003	P	27	-	-	-	-	-	75	-	-	79	-	-	-	-
052	CO/MA	288	288	296	290	285	-	-	-	-	-	-	-	-	-
039(wafer)	P	98	100	113	-	-	-	-	-	-	-	-	-	-	-
102	P/MA	276	-	-	-	-	-	-	-	-	-	273	281	290	-
103	CO/MA	122	-	-	-	-	-	-	-	-	-	-	492	-	-
104	P/MA	86	-	-	171	175	-	-	-	-	-	-	175	170	-
302	P	89	-	-	-	-	-	-	-	-	-	97	-	-	-

R=rizatriptan; S=sumatriptan; Z=zolmitriptan; A=almotriptan; N=naratriptan; E=eletriptan

P=parallel; MA=multiple attack; CO=cross-over

*Aspirin+metoclopromide

Appendix E. Summary table of Ferrari, 2001 meta-analysis

	Efficacy
Response at 2 hours	E80, R10 and Z2.5 significantly superior E20, F2.5 and N2.5 significantly inferior Not significantly different from R5, S50, Z5 or any other triptan dosages
Pain free at 2 hours	A12.5, E80 and R10 significantly superior E20, N2.5 and S25 significantly inferior No significant differences between other triptan dosages
Recurrence of headache 2-24 hours	Recurrence rates lower for E40 and E80 Recurrence rates higher for R5 and R10 No significant differences between other triptan dosage recurrence rates that were based on 2 hour response rates
Sustained pain free	Significantly higher rates for A12.5, E80 and R10 Significantly lower rates for E20, N2.5 and S25 No significant differences reported for other triptan dosages
Consistency rates	R10 and A12.5 superior S25, N2.5E20 inferior No significant differences reported for other triptan dosages
Tolerability	S25, N2.5, A12.5 superior E80 inferior No significant differences reported for other triptan dosages

A=almotriptan; E=eletriptan; F=frovatriptan; N=naratriptan; R=rizatriptan; Z=zolmitriptan

Appendix F. Summary table of Ferrari, 2002 meta-analysis (head-to-head trials)

	Efficacy	Adverse events
Sumatriptan 100 mg	Equivalent to A12.5 and Z5. Superior to N2.5. Inferior to E40 and E80 and R10.	Equivalent to E40, R10 and Z5. Caused fewer adverse events than E80. Caused more adverse events than A12.5 and N2.5.
Sumatriptan 50 mg	Comparison to A12.5 and N2.5 nr. Equivalent to R5, R10, Z2.5 and Z5 on all standard parameters. Inferior to E40 and E80 on standard parameters and R10 on time to response.	Comparison to A12.5 and N2.5 nr. Equivalent to R10, Z2.5 and Z5. Caused less adverse events than E40, E80, and R5.
Sumatriptan 25 mg	Comparison to A12.5 and N2.5 nr. Equivalent to E40. Inferior to E80, R5, R10, Z2.5 and Z5.	Comparison to A12.5 and N2.5 nr. Caused less adverse events than R5 on all parameters and less than R10 and Z2.5 in *overall* and *chest* AE incidences. Caused less adverse events than E40, E80 and Z5 on all AE parameters and less incidence of CNS AE's than R10 and Z2.5.

A=almotriptan; E=eletriptan; N=naratriptan; R=rizatriptan; Z=zolmitriptan
nr--not reported
AE--adverse event

Appendix G. Excluded head-to-head trials

Trial	Reason for exclusion
Alderman, 2000[1]	Wrong Drug
Bates, 1998[2]	Abstract only (naratriptan)
Cabarrocas, 1998,[3] Dowson, 2002[4]	Poor quality (almotriptan) **(Note 1)**
Carpay 1997[5]	Wrong Drug
Colman, 2001,[6], Spierings, 2001[7]	Poor quality (almotriptan) **(Note 1)**
Dahlof, 1998[8]	Wrong drug (subcutaneous sumatriptan)
Diener, 2001[9]	Wrong drug (alniditan)
Dowson 2003[10]	Poor quality (Zolmitriptan orally disintegrating tablet vs sumatriptan)
Evers, 2003[11]	Wrong population (healthy subjects)
Gobel, 2000[12]	Poor quality (discrepancy in group #'s) (naratriptan) **(Note 2)**
Goldstein, 1998[13]	Poor quality (rizatriptan) **(Note 3)**
Gruffydd-Jones, 1997[14]	Compared 2 forms of sumatriptans
Hardebo 1998[15]	Wrong Drug
Jhee, 1999[16]	Wrong drug (avitriptan)
Loder, 2001[17]	Wrong drug (rizatriptan orally dissolving tablet)
Longmore, 1997[18]	Wrong outcomes (not in vivo)
Mannix 2002[19]	Wrong outcoomes
Pascual, 2001[20]	Wrong preparation of rizatriptan (wafer)
Schoenen, 1999[21]	Abstract only (naratriptan vs. zolmitriptan)
Scriberras, 1997[22]	Wrong outcome (autonomic function)
Visser, 1996[23]	Poor quality (Encapsulated sumatriptan vs rizatriptan) Encapsulation of sumatriptan; baseline results not reported for entire sample; problems with randomization methods suggested by higher proportion of sumatriptan patients with severe baseline pain and all sumatriptan patients came only from the Netherlands
Visser, 1998[24]	Abstract only (rizatriptan)
Wells, 2001[25]	Wrong outcomes
Wells, 2003[26]	Wrong outcome (cost-effectiveness)
Williams, 2003[27]	Wrong outcome (cost-effectiveness

Notes

1. **Almotriptan studies**

Cabarracas 1998, Dowson 2002.

Almotriptan 12.5 and 25 mg and encapsulated sumatriptan 100 mg were directly compared in single attack trial of 668 patients (84.9% female; mean age of 41.8).(Dowson 2002) The 668 subjects were randomized to almotriptan 12.5 (n=184), almotriptan 25 mg (191), sumatriptan 100 mg (194), or placebo (99). Significantly more patients in the almotriptan groups of this trial suffered severe pain at baseline. This baseline difference suggests flaws in randomization

methods and reduces the quality of the trial to fair. Similar proportions of patients taking almotriptan 12.5 mg (56.8%), 25 mg (56.5%) and sumatriptan 100 mg (63.7%) reported pain relief at 2 hours. There were no differences between almotriptan 12.5 mg and sumatriptan 100 mg on any efficacy measure, rates of fatigue and overall adverse events were lower for patients taking almotriptan 12.5 mg.(Dowson 2002)

Colman, 2001 and Spierings 2001.

In this trial, patients were treated with either almotriptan 12. 5 mg (591) or sumatriptan 50 mg (582) for one attack. This trial appears to have been published twice, in different journals, with the two manuscripts accepted in November, 2000[6] and in December, 2000[7]. Colman and colleagues state that their study was part of a larger trial but do not cite Spierings in making this point. Elsewhere in its text, the Colman article cites the other article (Spierings) as "in press" but does not say that both articles are reporting data from the same trial. The Spierings article does not refer to the Colman article. The two articles had 3 authors in common, all employees of the manufacturer of almotriptan, but the first authors of each paper were not co-authors of the other one.

We based our conclusion that these were the same trial on the numbers of subjects who enrolled and completed them. Specifically, both articles reported that (1) 632 patients were randomized to almotriptan 12.5, of whom 591 took the medicine and were included in the analysis; and (2) 623 patients were randomized to sumatriptan 50 mg, of whom 582 were included. Similarly, both articles reported that there were 65 men in the almotriptan group and 64 in the sumatriptan group, and both reported the same mean age, percentage of white patients, etc.

There were also discrepancies between the two articles: for example, one reported that adults 18-65 years of age were included, while the other reported that adults 18-71 were included. Spierings states that "(patients…) were randomized in blocks of 4…" while Colman states "patients were randomly assigned by a blinded investigator…" but does not mention blocks.

More importantly, the two studies had different descriptions of the baseline characteristics of the almotriptan and sumatriptan groups. Spierings et al reported that the groups were similar in gender and race, but that almotriptan-treated patients were significantly heavier in weight (74.5 kg vs. 72.3 kg, p=0.003). Colman and colleagues reported that

> "The populations in the 2 treatment groups were comparable at baseline with respect to patient demographic and clinical characteristics, including age, sex, race, severity of headache at baseline, paid employment, marital status, highest level of education, and household income."

Colman and colleagues recorded these baseline characteristics in a full-page table, which also omitted weight. Spierings noted that the almotriptan group were more likely to have nausea at baseline (72.3% vs. 66.9%, p value not given but described as "just above the level of statistical significance.") Colman and colleagues did not report this comparison either.

In the trial, the drugs were provided in "identical-looking capsules to ensure blinding." As discussed in the main article, this method of blinding is flawed, because one cannot be sure that an encapsulated triptan enters the bloodstream at the same speed as the usual tablets do.

2. Naratriptan studies

Gobel, 2000.

This trial concentrated on the claim that naratriptan is associated with a lower rate of recurrence than other triptans [12]. It was a randomized, double-blind, two-attack crossover trial in patients who had experienced recurrence of migraine headache pain in at least 50% of attacks (treated with any drugs) during the 6 months before enrollment in the trial.[12] The authors state that 225 of the 264 patients randomized took both drugs and were included in the efficacy analysis, but there are discrepancies in the reported results. The authors report that 164 patients comprised 76% of the naratriptan 2.5 mg patients; if this is correct, the number of naratriptan patients was 216, not 225. They report that 181 patients comprised 84% of sumatriptan 100 mg patients; if this is correct, the number of sumatriptan patients was 215 or 216, not 225. We did not understand the sentence: "…migraine-related symptoms, that is, headache, nausea, vomiting, photophobia, and phonophobia, were not recorded as health problems and, therefore, not as adverse events unless they were worse than usual."

The headache response rates 4 hours after treatment were 76% (corrected rate, 72%) for naratriptan 2.5 mg and 84% (corrected rate, 80%) for sumatriptan 100 mg. Of the 164 patients who responded to naratriptan, and 181 who responded to sumatriptan, 135 responded to *both* medications. Response rates 1 and 2 hours after treatment and pain-free rates at any interval were not reported. Twenty-four hour sustained headache relief was reported by 83 patients given naratriptan and 74 patients given sumatriptan (39% vs. 34%, not statistically significant). The results regarding recurrence of headache appear to be:

GROUP	total number*	responded	recurred
naratriptan 2.5 mg	215 (225?)	164	74
sumatriptan 100 mg	215 (225?)	181	101

* Unclear from article.

Among the 135 patients who responded to both medications, 55 had a recurrence when using naratriptan and 77 had a recurrence when using sumatriptan (41% vs. 57%, odds ratio 1.97, p=0.005).

This trial has been criticized because it did not exclude patients who had previously taken sumatriptan.[28] There may have been a selection bias favoring naratriptan, since patients who responded well to sumatriptan in the past are less likely to enroll in an experimental trial than those who responded poorly.

Two other trials comparing naratriptan to other triptans were excluded. One was reported only in abstract form, and was never completed.[21].

Another was completed but was also reported in abstract form only[2]. It compared sumatriptan 100 mg to 4 doses of naratriptan (0.1 mg, 0.25 mg, 1 mg, and 2.5 mg).[2] The naratriptan 1 mg group (n=208) had a lower response rate than the naratriptan 2.5 mg group (n=199) and sumatriptan 100 mg group (n=229). Focusing on the latter two groups, headache response at 2 hours was 50% for naratriptan 2.5 mg and 59% for sumatriptan 100 mg (difference –9%, CI –18 to +1%).

3. Rizatriptan Studies

Goldstein, 1998.

This trial was re-rated poor-quality by consensus after independent review by a hird reviewer. It was a crossover trial compared rizatriptan 5 mg to sumatriptan 25 mg and rizatriptan 10 mg to sumatriptan 50 mg.[13] In this trial, patients treated 2 migraine attacks in one of 5 ways: rizatriptan 5 mg then sumatriptan 25 mg; sumatriptan 25 mg then rizatriptan 5 mg; rizatriptan 10 mg then sumatriptan 50 mg; sumatriptan 50 mg then rizatriptan 10 mg; or placebo then placebo. The trial is described as "randomized, placebo-controlled," but not as masked or blinded. The term "placebo-controlled" apparently refers to the inclusion of a group of patients who took placebo for both attacks, but not to masking patients or investigators to the order the active drugs were given. A total of 1329 patients treated one attack, 1316 recorded at least one rating of pain severity after dosing, and 1187 treated 2 attacks. The analysis included only the 1187 patients who treated one attack with each drug. Baseline characteristics of the 1329 patients in the 5 treatment groups were similar, but baseline characteristics of the 1187 included in the 2-attack analyses was not reported. The results of the first treatment assignments alone were not reported.

Rizatriptan 5 mg vs. sumatriptan 25 mg. Of the 1187 patients included in the 2-attack analysis, 557 took rizatriptan 5 mg (for the first or second attack) and 563 took sumatriptan 25 mg; it is not clear why the numbers of patients taking rizatriptan 5 mg and sumatriptan 25 mg were not equal. A higher proportion of patients taking rizatriptan 5 mg had pain relief at 2 hours (68% vs. 62%, $p<0.05$), were pain-free at 2 hours (33% vs. 28%, $p<0.05$), and had no nausea at 2 hours (78% vs. 71%). There were no statistically significant differences in use of additional medications, presence of other associated symptoms, or functional disability after 2 hours. More sumatriptan 25 mg patients were pain-free at ½ hour (1.6% vs. 0.4%, $p<0.05$) but more rizatriptan 5 mg patients were pain-free at 1 hour (11% vs. 6%, $p<0.05$). There was no difference in satisfaction at 2 and 4 hours.

At 2 hours, rizatriptan 10 mg and. sumatriptan 50 mg were similar in pain relief (72% vs 68%), pain-free (41% vs. 37%), use of additional medications (19%), presence of associated symptoms, and functional disability. At one hour, rizatriptan 10 mg was superior to sumatriptan 50 mg in the proportion of patients who were pain-free (11% vs. 8%). Rizatriptan 10 mg was superior to sumatriptan 50 mg in satisfaction at 2 and 4 hours. Rizatriptan 10 mg and sumatriptan 50 mg were similar in 4 of the 5 measures of 24-hour functional status; rizatriptan 10 mg was superior in the work-related measure (12.9 vs. 12.3, on a scale from 3 to 23). Rates of adverse events were nearly identical (45% vs. 46%).

A total of seven trials have compared two-hour headache response rates of rizatriptan to other triptans. In addition to Goldstein, discussed above, one was excluded because it used an encapsulated form of sumatriptan..[24]

Another (Merck Study #052) has never been published. Because this study has not been published, the adequacy of randomization and of other aspects of the study design cannot be assessed. Some results from this trial were reported in a meta-analysis.[29] Sumatriptan 50 mg and rizatriptan 5 mg were similar in pain relief and pain-free responses at 2 hours. Sumatriptan had a small advantage in 24-hour sustained response which did not reach statistical significance (6%, CI –1 to 13), Rizatriptan 5 mg was associated with significantly fewer adverse events (12%, CI 4 to 20). In the same trial, sumatriptan 25 mg was indistinguishable from rizatriptan 10

mg on all efficacy measures, and was indistinguishable from rizatriptan 5 mg on all measures except for time to relief.

Other information

Frovatriptan.

One unpublished head-to-head study (VML 251/96/09) of frovatriptan versus sumatriptan was evaluated in a meta-analysis[30] that did not include efficacy results.

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Appendix H. Results of triptan head-to-head trials

0.5-Hour Pain Relief % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	NS	-	-	-	-	11	-	14	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	14	-	-	-	14.9	-
Tfelt-Hansen	NS	-	-	-	-	-	12	13	-	-	11	-	-
Goadsby	NS	-	-	5	12	-	-	-	-	-	10	-	-
Sandrini	n/a	-	-	nr	nr	-	-	-	-	nr	nr	-	-
Garcia-Ramos, 2003	NS	-	-	12	-	5	-	-	-	-	-	-	-
Steiner, 2003	NS	-	-	-	12	-	-	-	-	-	-	7	-

0.5-Hour Pain Free % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	NS	-	-	-	-	1	-	1.5	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	2.7	-	-	-	0.7	-
Tfelt-Hansen	NS	-	-	-	-	-	1	2	-	-	1	-	-
Goadsby	NS	-	-	nr	nr	-	-	-	-	-	nr	-	-
Sandrini	n/a	-	-	nr	nr	-	-	-	-	nr	nr	-	-

1 Hour Pain Relief % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Havanka	NS	-	-	-	-	30	-	-	-	-	35	-	-
Bomhof	p<0.029	-	-	-	-	**27.8**	-	**38**	-	-	-	-	-
Pascual	p<0.05	-	-	-	-	-	-	**42.5**	-	-	-	**35.3**	-
Tfelt-Hansen	p<0.05	-	-	-	-	-	30	**37**	-	-	**28**	-	-
Geraud	NS	-	-	-	-	-	-	-	-	-	35	-	34
Gallagher	p=0.014	-	-	-	-	-	-	-	39.2	**41.7**	-	43.4	**45.5**
Gruffyd-Jones	NS	-	-	-	-	-	-	-	-	38	-	36.9	39.5
Goadsby	<0.01	-	-	**38**	**41**	-	-	-	-	-	**20**	-	-
Sandrini	<0.05	-	-	30	37	-	-	-	-	24	27	-	-
Mathew, 2003	<0.01	-	-	34	-	-	-	-	-	-	27	-	-
Garcia-Ramos, 2003	<0.05	-	-	**34**	-	**25**	-	-	-	-	-	-	-
Steiner, 2003	<0.0001	-	-	-	**40**	-	-	-	-	-	-	**25**	-

Appendix H. Results of triptan head-to-head trials

1 Hour Pain Free % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	<0.05	-	-	-	-	**3.3**	-	**9.5**	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	12.7	-	-	-	10.4	-
Tfelt-Hansen	NS	-	-	-	-	-	7	10	-	-	8	-	-
Geraud	NS	-	-	-	-	-	-	-	-	-	11	-	8
Gruffyd-Jones	NS	-	-	-	-	-	-	-	-	11.4	-	9.1	12
Goadsby	NS	-	-	8	17	-	-	-	-	-	6	-	-
Sandrini	<0.05	-	-	6	**13**	-	-	-	-	**5**	7	-	-
Mathew, 2003	NS	-	-	7	-	-	-	-	-	-	5	-	-
Garcia-Ramos, 2003	0.05	-	-	**12**	-	**6**	-	-	-	-	-	-	-
Steiner, 2003	<0.01	-	-	-	**12**	-	-	-	-	-	-	**6**	-

2 Hour Pain Relief % of patients

Trial	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Havanka (4-hr)	NS	-	-	-	-	52	-	-	-	-	60	-	-
Bomhof	<0.001	-	-	-	-	**48.4**	-	**68.7**	-	**-**	-	-	-
Pascual	NS	-	-	-	-	-	-	70.5	-	**-**	-	66.8	-
Tfelt-Hansen	NS	-	-	-	-	-	60	67	-	**-**	62	-	-
Lines	NS	-	-	-	-	-	63	**-**	-	67	-	-	-
Geraud	NS	-	-	-	-	-	-	-	-	-	61	-	59
Gallagher	<0.001	-	-	-	-	-	-	-	**66.2**	67.9	-	**72.2**	**72.2**
Gruffyd-Jones	NS	-	-	-	-	-	-	-	-	66.6	-	62.9	65.7
Goadsby	<0.01	-	-	65	**77**	-	-	-	-	-	**55**	-	-
Sandrini	<0.05	-	-	**64**	**67**	-	-	-	-	50	**53**	-	-
Mathew, 2003	<0.0001	-	-	**67**	-	-	-	-	-	-	**59**	-	-
Garcia-Ramos, 2003	<0.01	-	-	**56**	-	**42**	-	-	-	-	-	-	-
Steiner, 2003	<0.0001	-	-	-	**74**	-	-	-	-	-	-	**60**	-

Appendix H. Results of triptan head-to-head trials

2 Hour Pain Free % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	<0.001	-	-	-	-	**20.7**	-	**44.8**	-	-	-	-	-
Pascual	<0.05	-	-	-	-	-	-	**43.2**	-	-	-	**35.6**	-
Tfelt-Hansen	<0.05	-	-	-	-	-	25	**40**	-	-	**33**	-	-
Lines	NS	-	-	-	-	-	22	**-**	-	28	-	-	-
Geraud	NS	-	-	-	-	-	-	**-**	-	**-**	30	-	29
Gruffyd-Jones	NS	-	-	-	-	-	-	**-**	-	35.3	-	32.4	36
Goadsby	<0.05	-	-	29	**37**	-	-	-	-	-	**23**	-	-
Sandrini	<0.05	-	-	**31**	**37**	-	-	-	-	19	**18**	-	-
Sandrini	<0.0005	-	-	31	**37**	-	-	-	-	19	**18**	-	-
Mathew, 2003	<0.0001	-	-	36	-	-	-	-	-	-	27	-	-
Garcia-Ramos, 2003	<0.001	-	-	**35**	-	**18**	-	-	-	-	-	-	-
Steiner, 2003	<0.0001	-	-	-	**44**	-	-	-	-	-	-	**26**	-

24-Hour Sustained Relief % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Havanka	nr	-	-	-	-	48	-	-	-	-	44	-	-
Bomhof	nr	-	-	-	-	21	-	33	-	-	-	-	-
Pascual	nr	-	-	-	-	-	-	28	-	-	-	29	-
Gallagher	<0.001	-	-	-	-	-	-	**-**	**33.1**	**-**	-	**40.7**	**42.5**
Gruffyd-Jones	nr	-	-	-	-	-	-	**-**	-	30.6	-	30.3	29.9
Goadsby	NS	-	-	34	32	-	-	-	-	-	33	-	-
Sandrini	0.005	-	-	50	**54**	-	-	-	-	34	**38**	-	-
Mathew, 2003	<0.0003	-	-	34	-	-	-	-	-	-	43	-	-
Garcia-Ramos, 2003	<0.05	-	-	**38**	-	**27**	-	-	-	-	-	-	-
Steiner, 2003	<0.001	-	-	-	**47**	-	-	-	-	-	-	**35**	-
Steiner, 2003	<0.01	-	-	**44**	-	-	-	-	-	-	-	**35**	-

Appendix H. Results of triptan head-to-head trials

Satisfaction % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Pascual	0.045	-	-	-	-	-	-	**62.7**	-	-	-	**54.6**	-
Havanka	NS	-	-	-	-	49	-	-	-	-	51	-	-
Bomhof	<0.001	-	-	-	-	**4.2**		**3.55**	-	-	-	-	-
Gruffyd-Jones	NS	-	-	-	-	**-**	-	**-**	-	65.9	-	65.8	69.7
Steiner	<0.01	-	-	-	**66**	-	-	-	-	-	-	**55**	-
Steiner	<0.01	-	-	**64**	-	-	-	-	-	-	-	**55**	-

Return to Normal Function % of patients

Ref.	p value	A12.5	N2.5	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5	
Pascual	0.025	-	-	-	-	-	-	**45.4**	-	-	-	**37**	-	2 hr
Tfelt-Hansen	0.031	-	-	-	-	-	-	**14**	-	-	**9**	-	-	1 hr
Tfelt-Hansen	0.017	-	-	-	-	-	-	**27**	-	-	**19**	-	-	1.5 hr
Tfelt-Hansen	0.015	-	-	-	-	-	-	**42**	-	-	**33**	-	-	2 hr
Bomhof	<0.001	-	-	-	-	**22.6**	-	**39.3**	-	-	-	-	-	2 hr
Goadsby*	nr	-	-	**32**	**23**	-	-	-	-	-	**42**	-	-	2 hr
Sandrini	<0.005	-	-	**63**	55	-	-	-	-	**46**	**46**	-	-	2 hr
Mathew, 2003	<0.01	-	-	**68**	-	-	-	-	-	-	**61**	-	-	2 hr

*Reporting moderate to severe functional impairment at 2 hours

Appendix H. Results of triptan head-to-head trials

Treatment emergent adverse events

Cardiovascular system

Chest pain/tightness % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	NS	-	-	-	-	2	-	3	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	2	-	-	-	4	-
Tfelt-Hansen	<0.05	-	-	-	-	-	**1**	3	-	-	**6**	-	-
Lines	NS	-	-	-	-	-	2	-	-	5	-	-	-
Geraud	NS	-	-	-	-	-	-	-	-	-	2	-	1
Gallagher	NS	-	-	-	-	-	-	-	0.9	2.7	-	2.1	6.5
Gruffyd-Jones	NS	-	-	-	-	-	-	-	-	3.1	-	3.4	5
Goadsby	NS	-	-	7	7	-	-	-	-	-	7	-	-
Sandrini	NS	-	-	1	5	-	-	-	-	2	1	-	-
Mathew, 2003	NS	-	-	1.6	-	-	-	-	-	-	2	-	-
Steiner, 2003	nr	-	-	2.3	3.3	-	-	-	-	-	-	0.2	-

Central Nervous System

Dizziness % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	NS	-	-	-	-	5	-	8	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	5	-	-	-	6	-
Tfelt-Hansen	NS	-	-	-	-	-	6	8	-	-	9	-	-
Lines	NS	-	-	-	-	-	5	-	-	5	-	-	-
Geraud	NS	-	-	-	-	-	-	-	-	-	9	-	9
Gallagher	NS	-	-	-	-	-	-	-	4.5	5	-	6.1	8
Gruffyd-Jones	NS	-	-	-	-	-	-	-	-	5	-	3.4	5.7
Goadsby	NS	-	-	4	4	-	-	-	-	-	4	-	-
Sandrini	NS	-	-	7	12	-	-	-	-	7	5	-	-
Garcia-Ramos, 2003	NS	-	-	6.3	-	2.5	-	-	-	-	-	-	-
Steiner, 2003	nr	-	-	1.5	4.3	-	-	-	-	-	-	1.7	-

Appendix H. Results of triptan head-to-head trials

Paresthesia % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Geraud	NS	-	-	-	-	-	-	-	-	-	7	-	6
Gallagher	NS	-	-	-	-	-	-	-	3.6	4.4	-	4.9	8
Gruffyd-Jones	NS	-	-	-	-	-	-	-	-	5.4	-	5.3	5.2
Goadsby	NS	-	-	2	8	-	-	-	-	-	5	-	-
Sandrini	n/a	-	-	nr	nr	-	-	-	-	nr	nr	-	-
Mathew, 2003	NS	-	-	1.1	-	-	-	-	-	-	2.4	-	-

Somnolence % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	NS	-	-	-	-	<1	-	5	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	6	-	-	-	4	-
Tfelt-Hansen	NS	-	-	-	-	-	7	9	-	-	7	-	-
Lines	NS	-	-	-	-	-	4	-	-	5	-	-	-
Geraud	NS	-	-	-	-	-	-	-	-	-	6	-	8
Gallagher	NS	-	-	-	-	-	-	-	3.6	3.8	-	4.3	7.7
Gruffyd-Jones	NS	-	-	-	-	-	-	-	-	4.5	-	3.1	5
Goadsby	n/a	-	-	nr	nr	-	-	-	-	-	nr	-	-
Sandrini	NS	-	-	7	4	-	-	-	-	3	3	-	-
Garcia-Ramos, 2003	NS	-	-	5.2	-	4.5	-	-	-	-	-	-	-
Steiner, 2003	nr	-	-	2.3	3	-	-	-	-	-	-	1.2	-

Appendix H. Results of triptan head-to-head trials

Fatigue/Asthenia % of patients

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	NS	-	-	-	-	5	-	7	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	6	-	-	-	5	-
Tfelt-Hansen	**<0.05**	**-**	**-**	**-**	**-**	-	**2**	8	-	-	**8**	-	-
Lines	NS	-	-	-	-	-	7	-	-	5	-	-	-
Geraud	NS	-	-	-	-	-	-	-	-	-	11	-	11
Gruffyd-Jones	NS	-	-	-	-	-	-	-	-	4.5	-	5.3	6.6
Goadsby	NS	-	-	3	10	-	-	-	-	-	3	-	-
Sandrini	NS	-	-	7	11	-	-	-	-	6	8	-	-
Garcia-Ramos, 2003	NS	-	-	3.6	-	1.9	-	-	-	-	-	-	-
Steiner, 2003	nr	-	-	3.3	8.3	-	-	-	-	-	-	2.5	-

Relief of migraine-related symptoms

Nausea (%without symptoms at 2 hours)

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Havanka	stats ND	-	-	-	-	70	-	-	-	-	70	-	-
Bomhof	NS	-	-	-	-	59.4	-	68.5	-	-	-	-	-
Pascual	**0.046**	**-**	**-**	**-**	**-**	-	-	**74.8**	-	-	-	**67.5**	-
Tfelt-Hansen	**<0.05**	**-**	**-**	**-**	**-**	-	**77**	**75**	-	-	**67**	-	-
Geraud**	NS	-	-	-	-	-	-	-	-	-	35	-	33
Gallagher***	NS	-	-	-	-	-	-	-	% NR	% NR	-	% NR	% NR
Gruffyd-Jones**	NS	-	-	-	-	-	-	-	-	52	-	54	54
Goadsby**	NS	-	-	30	22	-	-	-	-	-	34	-	-
Sandrini**	<0.05	-	-	**29**	35	-	-	-	-	40	**42**	-	-
Mathew, 2003	<0.01	-	-	**74**	-	-	-	-	-	-	**67**	-	-
Garcia-Ramos, 2003	NS	-	-	73	-	68	-	-	-	-	-	-	-
Steiner, 2003	<0.05	-	-	-	**72**	-	-	-	-	-	-	**64**	-
Steiner, 2003	<0.05	-	-	**72**	-	-	-	-	-	-	-	**64**	-

Appendix H. Results of triptan head-to-head trials

Vomiting (%without symptoms at 2 hours)

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	NS	-	-	-	-	92.3	-	95.5	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	96.1	-	-	-	96.4	-
Gallagher**	NS	-	-	-	-	-	-	-	% NR	% NR	-	% NR	% NR
Goadsby	n/a	-	-	nr	nr	-	-	-	-	-	nr	-	-
Sandrini	n/a	-	-	nr	nr	-	-	-	-	nr	nr	-	-

Photophobia (%without symptoms at 2 hours)

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Havanka	stats ND	-	-	-	-	56*	-	-	-	-	61*	-	-
Bomhof	**<0.05**	**-**	**-**	**-**	**-**	**47.2**	-	**59.2**	-	-	-	-	-
Pascual	**0.029**	**-**	**-**	**-**	**-**	-	-	**64.4**	-	-	-	**56.5**	-
Tfelt-Hansen	NS	-	-	-	-	-	57	61	-	-	58	-	-
Geraud**	NS	-	-	-	-	-	-	-	-	-	33	-	37
Gallagher***	NS	-	-	-	-	-	-	-	% NR	% NR	-	% NR	% NR
Gruffyd-Jones**	NS	-	-	-	-	-	-	-	-	52	-	54	54
Goadsby*	NS	-	-	37	29	-	-	-	-	-	43	-	-
Sandrini	<0.05	-	-	40	**30**	-	-	-	-	49	**46**	-	-
Mathew, 2003	<0.01	-	-	**71**	-	-	-	-	-	-	**63**	-	-
Steiner, 2003	NS	-	-	-	71	-	-	-	-	-	-	74	-

Appendix H. Results of triptan head-to-head trials

Phonophobia (%without symptoms at 2 hours)

Ref.	p value	A12.5	A25	E40	E80	N2.5	R5	R10	S25	S50	S100	Z2.5	Z5
Bomhof	**<0.05**	**-**	**-**	**-**	**-**	**51.9**	-	**65**	-	-	-	-	-
Pascual	NS	-	-	-	-	-	-	66.3	-	-	-	63.9	-
Tfelt-Hansen	NS	-	-	-	-	-	63	66	-	-	60	-	-
Geraud**	NS	-	-	-	-	-	-	-	-	-	36	-	39
Gallagher***	NS	-	-	-	-	-	-	-	% NR	% NR	-	% NR	% NR
Gruffyd-Jones**	NS	-	-	-	-	-	-	-	-	53	-	57	54
Goadsby	n/a	-	-	nr	nr	-	-	-	-	-	nr	-	-
Sandrini	<0.05	-	-	**38**	32	-	-	-	-	45	**48**	-	-
Sandrini	<0.01	-	-	38	**32**	-	-	-	-	45	**48**	-	-
Mathew, 2003	<0.01	-	-	**74**	-	-	-	-	-	-	**67**	-	-
Steiner, 2003	0.064	-	-	-	73	-	-	-	-	-	-	68	-

*combined photophobia/phonophobia; **percent with symptoms at 2 hours; ***time endpoint unclear; ¶ presence of symptoms

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Havanka 2000	Multicenter single-dose DB RCT conducted in Europe of naratriptan vs. sumatriptan vs. placebo	Patients were treated in clinic	643	Age nr 88% women 99% white	I H S criteria 18-55 men and women.	1-year history of migraine, 1 to 6 moderate to severe attacks per month during the past 2 months
Bomhof 1999	Multicenter single-dose RCT conducted in Europe of naratriptan vs. rizatriptan	Not stated	618	39 years 84% female 82% white 17% Hispanic	I H S criteria 18-65 men and women.	6-month history of migraine; 1-8 reports per month; no evidence of CVD or of drug or alcohol abuse; pregnant or nursing.

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Havanka 2000	History suggestive of cardiovascular or cerebrovascular disease; hypertension; pregnant or lactating; history of drug or alcohol or ergotamine abuse; use of MAO inhibitors, SSRIs, lithium, or flunarizine.	Glaxo, co-investigator	Prophylactic medications stopped 1 week before the study; rescue drugs not permitted	NR	NR
Bomhof 1999	H.O cva, cardiovascular disease, significant ecg abnormality, history or drug or alcohol use, past use of study drugs	Merck, co-investigator (maker of rizatriptan)	Permitted	NR	96 (did not take study medication)

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Havanka 2000	Fair; but baseline information inadequate	Poor-fair; possibly a highly selected population	
Bomhof 1999	Fair +	Fair.	

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Pascual 2000	Multicenter single-dose stratified DB RCT conducted at 66 international sites of rizatriptan vs. zolmitriptan, 9 month study period.	Not stated	882	38.8 years 83% female 77% white 19% Hispanic	I H S criteria 18-65 men and women.	6-month history of migraine; 1-8 reports per month.
Tfelt-Hansen 1998	Multicenter single-dose DB RCT conducted in Europe of rizatriptan vs. sumatriptan	Not stated	1268	38 years 81% female race/ethnicity not stated	I H S criteria 18-65 men and women.	6-month history of migraine; 1-8 attacks per month; good general health
Lines 1997 Lines 2001	Multicenter single-dose DB RCT conducted in Sweden, Norway, the United Kingdom and Switzerland of rizatriptan vs. sumatriptan vs. placebo	Not stated	792	40 years 80% women ethnicity nr	I H S criteria 18-65 men and women.	6-month history of migraine; 1-8 attacks per month

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Pascual 2000	Cardiovascular disease, hypertension, EKG abnormality; drug or alcohol abuse; pregnant or breast-feeding	Merck, co-investigator (maker of rizatriptan)	Recent propranolol, ergot, MAO inhibitor, opiates prohibited; other prophylaxis permitted; NSAIDs and opiates permitted for rescue	NR	116 (did not take study medication)
Tfelt-Hansen 1998	CVD, hypertension, drug or alcohol abuse; pregnant or nursing.	Merck, co-investigator	Escape medication permitted; NSAIDs not permitted	NR	169 (did not take study medication)/2 lost to fu
Lines 1997 Lines 2001	NR	Merck, co-investigator	Escape medications, consisting of standard analgesics or anti-emetics, were allowed from 2 hours onwards.	NR	141 (did not take study medication)

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Pascual 2000	Fair +	Fair.	Stratified by prior use of triptans.
Tfelt-Hansen 1998	Fair - rizatriptan group were 2.2 years younger.	Fair.	
Lines 1997 Lines 2001	Fair		

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Geraud 2000	Multicenter, single-dose DB RCT conducted in Europe and Australia of zolmitriptan vs. sumatriptan vs. placebo in 8:8:1 ratio	Outpatient	1311	38 years 85% female race/ethnicity not reported	IHS criteria; 1 year history of migraine	Average of 1-6 attacks per month for the 6 months preceding the study.
Gallagher 1999, 2000	Multicenter, multiple-dose analysis of DB RCT, 6 month study; conducted in Europe of zolmitriptan vs. sumatriptan.	Not stated	1212	39 years 85% female race/ethnicity not reported	IHS criteria; 1 year history of migraine	For women, use of reliable contraception. Patients who had 2 or more migraines included in the analysis.
Gruffyd-Jones 2001	Multicenter, double-dummy RCT conducted in 21 countries of zolmitriptan vs. sumatriptan.	Not stated	1787	42 years 86% female 96% white	IHS criteria 18-65 men and women; 1 year history of migraine with age of onset < 50	Average of 1-6 attacks per month for 2 months preceding the study.

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Geraud 2000	H/o ischemic heart disease, arrhythmias, uncontrolled hypertension, use of psychoactive drugs, history of drug or alcohol abuse; certain types of migraine; any condition that could interfere with efficacy assessments, pregnant or breastfeeding.	Maker of zolmitriptan, co-investigator	Permitted	NR	253; 225 did not take medication, 28 were lost to followup
Gallagher 1999, 2000	H/o ischemic heart disease, arrhythmia, hypertension, some types of migraine; drug or alcohol abuse, abnormal lab tests	Zeneca, co-investigator	Some permitted	NR	233 who had only 1 headache
Gruffyd-Jones 2001	Pregnancy, lactating, inadequate contraception in females, ischemic heart disease, arrhythmias, cardiac accessory pathway disorders, hypertension, use of MAO inhibitors, recent history of alcohol or drug abuse, abnormal clinical lab result, STDs, hepatitis B.	Astra-Zeneca, funder	Most prohibited	NR	620, many because they did not have 6 attacks

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Geraud 2000	Fair + (more information about baseline characteristics provided; but high loss to f/u	Fair	
Gallagher 1999, 2000	Poor-Fair. Baseline results not reported for the entire sample.	Good--reports many long-term outcomes not addressed in other studies	Adverse events depend on whether it is the 1st vs subsequent attacks. consistency of effect may be important.
Gruffyd-Jones 2001	Good except for high dropout rate, but dropout wasn't different among groups.	Selected for consistent migraine over months.	

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Visser, 1996	Multicenter, single-attack, DB RCT conducted in the US and Dutch outpatient facilities Rizatriptan vs encapsulated sumatriptan	Outpatient	581	40.2 years 89.5% female Race nr	Men and women between 18 and 55 years of age with a six-month history of migraine with or without aura	8 or fewer migraine attacks per month
Goadsby, 2000 Jackson, 1998	Multicenter, single-attack, DB RCT conducted in Europe and Australia Eletriptan vs encapsulated sumatriptan	nr	849	40.4 years 82.1% female Race nr	IHS criteria; 18 years of age or older	At least one acute attack every 6 weeks

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Visser, 1996	History, clinical evidence, or an electrocardiogram that wqas suggestive of a significant cardiovascular disease; hypertension (at screening; resting SBP > 160 mm Hg or DBP > 95 mm Hg); or renal, gastrointestinal, pulmonary, hepatic, endocrine, neurological (other than migraine), or other systemic disease	Merck	Rescue medication allowed after 4 hours	nr/nr/581	132/581 (22.7%) withdrawn/6 (4%) lost to fu
Goadsby, 2000 Jackson, 1998	>6 migraine attacks per month, frequent tension-type headaches, recent history of alcohol or other substance misuse, serious allergic reactions to drugs, use of any experimental drug within the past month, pregnant or breastfeeding women, severely limited gastrointestinal absorption, any medical condition that might interfere with the interpretations of the study results, coronary artery disease, heart failure, uncontrolled hypertension, and receiving medication specifically contraindicated with sumatriptan	Pfizer, Ltd.	Rescue medication allowed after 2 hours	nr/nr/857	157/849 (18.5%) not treated; 17/692(2.4%) withdrawn; lost to fu nr

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Visser, 1996	Poor Encapsulation of sumatriptan; baseline results not reported for entire sample; problems with randomization methods suggested by higher proportion of sumatriptan patients with severe baseline pain and all sumatriptan patients came only from the Netherlands	Selected for histories absent of adverse reaction to sumatriptan	
Goadsby, 2000 Jackson, 1998	Fair-poor; encapsulation of sumatriptan; baseline results not reported for entire sample	Fair	

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Sandrini, 2002 Pryse-Phillips, 1999	Multicenter, three-attack, DB RCT conducted in Europe, Canada and South Africa Eletriptan vs encapsulated sumatriptan	nr	1008	38.2 years 88% female Race nr	IHS criteria; 18 years of age or older (age limit of 65 in Canada)	At least one acute attack every 6 weeks

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Sandrini, 2002 Pryse-Phillips, 1999	Patients who had previously taken oral eletriptan or any formulation of sumatriptan were excluded from the trial, as were patients who had taken any experimental drug within the previous month; patients with frequent nonmigrainous headache, atypical migraine that had not previously responded to therapy, migraine with prolonged aura, familial hemiplegic migraine, basilar migraine, or migrainous infarction were excluded from the trial; patients with a history of heart disease, uncontrolled hypertension, cardiac arrhythmias, abnormalities on laboratory tests or EKGs, documented allergic reactions to drugs or any other clinically significant disease	Pfizer, Ltd.	Rescue medication allowed two hours after optional second dose of study medication	1013/nr/1008	234/1008 (23%) not treated/386/774(49.9 %) withdrawn/lost to fu nr

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Sandrini, 2002	Poor. Encapsulation of sumatriptan; baseline results not reported for entire sample; 29 (3.7%) patients excluded from analysis of 2-hour data	Results generalizable to patients who have NEVER taken any formulation of sumatriptan	
Pryse-Phillips, 1999			

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Mathew 2003	Multicenter, international, single-dose RCT of eletriptan vs sumatriptan (encapsulated) using a double-dummy design.	nr	2421	41.5 years 86.6% female Race nr	IHS criteria; 18-65 men and women; 1-6 attacks/month	IHS criteria for migraine with or without aura; monthly frequency of 1-6 attacks

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Mathew 2003	Concurrent nonmigrainous headache or treatment-resistant migraine; migraine variants; coronary artery disease; heart failure; uncontrolled hypertension; abnormal ECG; clinically significant medical illness or laboratory abnormality; severe reduction in gastrointestinal absorption;	Pfizer, Ltd.	Rescue medication allowed after 2 hours	nr/nr/2421	308(12.7%) not treated; 4(0.2%) discontinued; 2072; 349(14.4%) not included in ITT population

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Mathew 2003	Fair-poor; encapsulation of sumatriptan; baseline results not reported for entire sample	Fair	

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Dowson, 2002 Cabarrocas, 1998	Multicenter, single-dose RCT conducted in Europe of almotriptan vs sumatriptan	Primary care	668	41.8 years 84.9% female Race nr	IHS criteria; 18-65 men and women; 1 year history	1-6 attacks/month; age of onset of less than 50 years and at least 24 h free from headache between attacks
Colman, 2001 Spierings, 2001	Multicenter, single-dose RCT conducted in the US of almotriptan vs sumatriptan	nr	1255	40.7 years 89% female Race nr	Men and women between 18 and 65 years; at least a 6-month migrainehistory (IHS criteria)	An average of at least 2 moderate or severe migraine headaches per month during the preceding 3 months, with an interval of at least 24 hours between consecutive attacks

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Dowson, 2002 Cabarrocas, 1998	Migraine with prolonged aura; familial hemiplegic migraine; migrainous infarction; vertebrobasilar migraine or Raynaud's phenomenon associated with migraine; any other significant medical condition; cardiovascular disease (cardiac ischaemia, atherosclerosis, cardiac arrhythmia or hypertension); alcoholism; drug abuse or mental retardation	Laboratorios Almirall SA	Escape medication as chosed by investigator (valproic acid, beta blockers, calcium antagonists) allowed if migraine pain did not disappear or become mild within 2 hours of treatment	nr/nr/668	8(1.2%) withdrawals/lost to fu nr
Colman, 2001 Spierings, 2001	Subjects could not have uncontrolled hypertension, defined as a diastolic blood pressure higher than 95 mm Hg or a systolic blood pressure higher than 160 mm Hg, or clinically significant disease affecting any system but especially the cardiovascular or gastrointestinal tract	Pharmacia	Rescue medications allowed at 2 hours	nr/nr/1255	nr/nr

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Dowson, 2002 Cabarrocas, 1998	Fair; higher proportion of patients in almotriptan groups with severe pain when compared to placebo group	Fair	
Colman, 2001 Spierings, 2001	Poor Encapsulation of sumatriptan; baseline characteristics of untreated patients not reported; significantly higher mean weight for almotriptan patients; reporting discrepancies between the two publications (Spierings and Colman)		

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Dowson 2003	Open, crossover RCT Zolmitriptan orally disintegrating tablet (ODT) 2.5 mg Sumatriptan 50 mg (conventional)	Not stated	218	Median age=45 years 86% female Ethnicity nr	Patients aged 18-65 years and with an established diagnosis of migraine, with or without aura according to IHS criteria; Migraine Disability Assessment Scale (MIDAS) score of ≥ 11 (moderate or severe disability)	At least 1 migraine per month during the previous three months

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Dowson 2003	In addition to the standard exclusion criteria applied to migraine studies, patients with previous experience of any orally disintegrating triptan drug or use of zolmitriptan or sumatriptan during the previous three months	nr	Escape medication allowed two hours after the first dose; except erot derivative or non-trial triptan	nr/nr/218 randomized	32(14.7%) not treated/18(10.7%) didn't take both study treatments/lost to fu nr

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Dowson 2003	Poor Open trial. Methods of randomization and allocation concealment nr. Comparison of groups' baseline characteristics nr. Masking of outcome assessor nr. ITT analysis was not used: 18 (10.7%) of treated population excluded from analysis (post-randomization exclusions).	Fair	

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Garcia-Ramos 2003 UK/Latin America Fair quality	Multicenter, single-attack, DB RCT conducted in the UK and Latin America Eletriptan vs encapsulated naratriptan	Not stated	548	Mean age=36.8 81% female Ethinicity nr	Male or female adults, aged 18-80 years that met IHS criteria for migraine with or without aura	A minimum of 1 acute migraine attack every 6 weeks

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Garcia-Ramos 2003 UK/Latin America Fair quality	1) Coronary artery disease, heart failure, uncontrolled hypertension or abnormal ECG; 2) frequent migraine or concommitant nonmigrainous headache (<6 per month), migraine variants (e.g. familial hemiplegic or basilar migraine), and/or migraines which, in the clinical judgement of the investigator, had consistently failed to respond to adequate medical therapy; 3) hypersensitivity or known contra-indication to treatment with elatriptan or naratriptan; 4) concommitant use of potent CYP3A4 inhibitors or use of MAO inhibitors in the 2 weeks prior to study entry; 5) any clinically significant medical illness or laboratory abnormalities; 6) severe reduction in gastrointestinal absorption; 7) misuse or abuse of alcohol or other substances, including analgesics or egotamine; 8) use of any experimental drug within the past month; 9) (if female) current pregnancy, breast-feeding, or not using a medically accepted form of contraception	Pfizer	Rescue medication allowed by 4 hours post-dose (excluding any other triptan, ergotamine, or ergotamine-like substance)	563 screened/548 randomized/483 treated an attack	65 not treated/4 withdrawn/1 (0.2%) lost to fu/459 (95%) analyzed at 1 hr; 464 (96%) analyzed at 2 hr

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Garcia-Ramos 2003 UK/Latin America Fair quality	Fair Encapsulation of naratriptan; 5% of treated patients excluded from analysis of 2-hour data	Fair	

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients	Inclusion criteria
Steiner 2003 Europe	Multicenter, single-attack, DB RCT conducted in Europe Eletriptan vs encapsulated zolmitriptan	Not stated	1587	Mean age=40.2 85% female Ethnicity nr	Male or female adults, aged 18-65 years that met IHS criteria for migraine with or without aura	Attacks at least once every 6 weeks.

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Exclusion criteria	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu
Steiner 2003 Europe	1) Migraine that had been consistently resistant to all treatments 2) basilar migraine; 3) hemiplegic migraine 4) frequent nonmigrainous headaches 5) any clinically significant medical illness or laboratory abnormalities, especially those indicative of coronary artery disease, heart failure or uncontrolled hypertension; 6) other contraindications to treatment with eletriptan or zolmitriptan including use of potent CYP3A4 inhibitors concomitantly or of MAO inhibitors within 2 weeks of entry; 7) severe reduction in gastrointestinal absorption; 8) misuse of alcohol or other substances including analgesics, ergotamine or triptans; 9) pregnancy or breast-feeding 10) Women who might become pregnant were required to use effective contraception	Pfizer	Rescue medication permitted by 2 hours post-dose, but not any triptan or ergot	1592 screened/1587 randomized/1337 treated	250 (16%) not treated/7 (0.5%) withdrawn/lost to fu nr/1337 analyzed at 1 hr (92% of treated population); 1235 analyzed at 2 hr (92% of treated population)

Evidence Table 1. Characteristics of head-to-head trials

Author Year	Internal validity	External validity	Comments
Steiner 2003 Europe	Fair Encapsulation of zolmitriptan; 8% of treated patients excluded from analysis of 2-hour data	Fair	

Evidence Table 2a. Triptans vs. active controls: assessment of internal validity

Author Year	Method of random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Geraud, 2002	Computer-generated randomization list	nr	Yes	Yes	nr	Yes
Laterre, 1991	Computer-generated randomization in blocks of 6 patients	Patients entered in ascending sequential order of patient number at each center	Yes	Yes	Unclear	Yes
Winner 1996	nr	nr	Yes	Yes	Yes	Yes, but not nurse administering injection
Dowson, 2000	nr	nr	nr	Yes	nr	Yes
Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group, 1992	Computer-generated randomization code in blocks of 6	Patients entered in acending sequential order of patient number	Yes	Yes	nr	Yes
Tfelt-Hansen, 1995	Randomization balanced in 3 blocks	nr	Yes	Yes	Yes	Yes
Diener, 1999	nr	nr	Yes	Yes	nr	Yes
Block, 1998	nr	nr	Yes	Yes	nr	2 arms were single blind and 1 was open

Evidence Table 2a. Triptans vs. active controls: assessment of internal validity

Author Year	Patient unaware of treatment?	Intention-to-treat analysis?	Maintenance of comparable groups?	Reporting of attrition, crossovers, adherence, and contamination?	Differential loss to followup or overall high loss to followup?
Geraud, 2002	Yes	Yes	Yes	Yes	1 loss to followup in each group
Laterre, 1991	Yes	Not sure	nr	Yes	nr
Winner 1996	Yes	Yes	Yes (only treatment of 1 attack)	NA	Followup was in 24 hours, no loss
Dowson, 2000	Yes	Efficacy I population (120) used for primary and secondary efficacy parameters	nr	Yes	Not sure
Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group, 1992	Yes	358 took treatment; 355 evaluable for 1st attack (3 not have diary cards available)	nr	Yes	Unclear
Tfelt-Hansen, 1995	Yes	Yes	2nd attack: 102 placebo, 120 LAS+MTC, 105 sumatriptan	Yes	No loss to followup
Diener, 1999	Yes	Yes	nr	Yes	nr
Block, 1998	1 arm was open	Unclear	Yes	Yes	Unclear

Evidence Table 2a. Triptans vs. active controls: assessment of internal validity

Author Year	Method of random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Touchon, 1996	nr	nr	Unclear (deomographics given at crossover time)	Yes	Unclear	Yes
Freitag, 2001	nr	nr	Yes	Yes	Yes	Yes
Boureau, 2000	nr	nr	Yes	Yes	Unclear	Yes
Boureau, 1995	nr	nr	Yes	Yes	No	No
Myllyla, 1998	Computer-generated randomization in blocks of 6 patients	nr	Yes	Yes	All analyses were made before the randomization code was broken	Yes
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	Not randomized, was crossover	Not applicable	Not applicable	Yes	No	No
Schoenen, 1994	Not randomized, was crossover	Was open study	Not applicable (crossover)	Yes	Open study	Open study

Evidence Table 2a. Triptans vs. active controls: assessment of internal validity

Author Year	Patient unaware of treatment?	Intention-to-treat analysis?	Maintenance of comparable groups?	Reporting of attrition, crossovers, adherence, and contamination?	Differential loss to followup or overall high loss to followup?
Touchon, 1996	Yes	Crossover analysis on 266 evaluable patients 317 randomized)	Yes	Yes	Was 24 hr followup after each attack, 8 patients withdrawn after 1st attach (no reason given)
Freitag, 2001	Yes	137 patients enrolled, 1265 had efficacy data analyzed	nr	Yes	2/137 lost to followup
Boureau, 2000	Yes	Yes (for all patients treating an attack)	nr	Yes	Unclear
Boureau, 1995	No	Not clear	Unclear	Yes	Not high loss to followup
Myllyla, 1998	Yes	Unclear	Yes	Yes	3/154 lost to followup
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	No	Evaluable population = all patients who treated at least 1 migraine with sumatriptan (582/479)	Not applicable	Yes	58/749 not return to clinic
Schoenen, 1994	Open study	No difference between ITT population and sumatriptan population	Not applicable	Yes	64/479: no 2nd visit 14/479: received sumatriptan at 1st visit

Evidence Table 2a. Triptans vs. active controls: assessment of internal validity

Author Year	Method of random assignment?	Allocation concealed?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors blinded?	Care provider blinded?
Gerth, 2001	nr	nr	Yes	All patients completing previous RCT were invited to participate in this extension	No	No
Bussone, 1999	nr	nr	nr	Yes	nr	Yes
Friedman, 2001	Computer-generated random numbers	nr	nr	Yes	nr	No
Christie, 2003	Adequate: computer-generated random numbers	nr	Yes	Yes	nr	yes
Diener, 2002	Adequate: computer-generated pseudo-random numbers	Adequate	Yes	Yes	nr	yes
Stronks, 2003	nr	nr	n/a (crossover)	Yes	yes	yes

Evidence Table 2a. Triptans vs. active controls: assessment of internal validity

Author Year	Patient unaware of treatment?	Intention-to-treat analysis?	Maintenance of comparable groups?	Reporting of attrition, crossovers, adherence, and contamination?	Differential loss to followup or overall high loss to followup?
Gerth, 2001	No	Unclear	nr	nr	nr
Bussone, 1999	Yes	Yes	nr	Yes	2/156 lost to followup
Friedman, 2001	Would not be blinded to sumatriptan treatement vs. Some kind of oral chilling	Yes (no loss to followup)	nr	No attrition	No loss to followup
Christie, 2003	Yes	Evaluable population = all patients who treated both attacks (362 of 488)	nr	nr	nr
Diener, 2002	Yes	Evaluable population=733/937(78%)	Yes	nr nr nr nr	nr
Stronks, 2003	yes	nr	nr	nr nr nr nr	nr

Evidence Table 2b. Triptans vs. active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Geraud, 2002	Multicenter, DB, RCT, parallel group, 3 attack single dose study	Not specific - France	719	41 years; 85% female >95% caucasian	Male and Female aged 18-65

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Geraud, 2002	Established diagnosis of migraine with symptoms of at least 1 year's duration and age of onset<50. 1-6 reports per month moderate to severe intensity 3 months prior to inclusion.	basilar, opthalmoplegic or hemiplegic migraine; non-migraine on more than 10 days per month over proceeding 6 months; pregnancy; lactation or inadequate contraception in females; recent history of repitive, prolonged use of analgesics ; ischaemic heart disease; vascular spasms; arhythmias uncontrolled hypertension; any gastrointestinal problems, history of drug abuse

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Geraud, 2002	AstraZeneca	Escape medication permitted Long term prophylactic migrane treatment were permitted provided they were kept consistent throughout the study	778 eligible patients from 169 centers were screened.	None.	Zolmitriptan 2.5 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	Pain Free in 2 hours	Symptom-free (or no functional disability) at 2 hours	24-hour sustained pain-free response
Geraud, 2002	acetylsalicylic acid 900 mg plus metoclopramide 10 mg	In 1st attack after 1st dose Zolmitriptan 60.4% acetysalicylic plus metoclopramide 66.5% In all 3 attacks after 1st dose Zolmitriptan 33.4% acetylsalicylic plus metoclopramide 32.9%	In all 3 attacks after 1st dose Zolmitriptan 10.7% acetylsalicylic plus metoclopramide 5.3%	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Geraud, 2002	NR	Zol- 1.8 Ace acid plus - 4.1	Zol - 18.7 Ace acid plus- 22.4	Zol - 34.0 Ace acid plus - 30.9	Zol - 45.4 Ace acid plus - 42.6	Satisfaction at last attack Poor - Zol - 16.3 Ace Acid - 25.0 Fair - Zol - 24.5 Ace Acid - 19.1 Good - Zol - 35.9 Ace Acid - 38.5 Excellent - Zol 23.3 Ace Acid - 17.4

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	**Headache recurrence within 24 hours**	**Vomiting relief within 2 hours**	**Nausea Relief within 2 hours**	**Photophobia Relief within 2 hours**	**somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain**	
Geraud, 2002	All attacks treated with a 2nd dose Zolmitriptan - 53.6% Acetylsalicylicacid plus metoclopramide - 55.4%	Zolmitriptan - 23.1% acetylsalicylic acid plus metoclopramide - 24.2%				Vertigo, somnolence, paraesthesia, Asthenia, tightness, chills, nausea, abdominal pain, dizziness, dry mouth, tremor, Diarrhea	Zolmitriptan - 1 dizziness 1- Somnolence 1 - dizziness and vasodilatation Ace acid - 2 diarrohea 1 palpitationa plus asthenia 1 - anxiety plus dry mouth 1- phlebitis

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Geraud, 2002	Zol - 3.7 Ace Acid - .6			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Adelman, 2001	**Retrospective analysis from several head-to-head RCTs.**				
Laterre, 1991	Multicenter, DB, RCT, parallel group, 3 attack single dose study(only attack 1 reported in detail)	47 clinics in Austria, Belgium, Denmark, Finland, France, Germany, Netherlands, Norway, Sweden	580	40 years; 83% female Ethnicity not reported	I H S criteria 18-65 men and women.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Adelman, 2001		
Laterre, 1991	1-6 migrane attacks of moderate or severe intensity per month for at least one year. Patients had to be able to recognize the early symptoms of their migrane attacks. Female - adequate contraceptive measures.	Pregnant, regular requirement for opiate analgesics or major tranquillizers, drug/alcohol abuse, ischaemic heart disaease, high blood pressure (supine diastolic blood pressure greater than 95 mm Hg., not receiving B-Blockers or calcium antagonists. Significant psychiatric illness or who had participated in more thab 3 clinical trials within th previous 3 years.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Adelman, 2001					
Laterre, 1991	Glaxo, PI	Rescue medication permitted	580 treated with trial medication	3 lost at first migrane attack 38 by second migrane attack 90 by third attack Lost was due to no diary card data avilalble and or they had treated with study medication in conjunction with other migrane therapy	Sumatriptan oral 100 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Adelman, 2001			**x**	**x (SF)**	**x**
Laterre, 1991	Cafergot (2 mg ergotamine tartrate plus 200 mg cafeine)	Attack 1 (ST)(145/220) - 66% Cafergot (118/246) - 48%	Attack 1 (ST) - 35% Cafergot - 13%	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Adelman, 2001						
Laterre, 1991	NR	(ST) 20(7) Cafergot 13(5)	(ST) 72(26) Cafergot 50 (18)	(ST) 52(19) Cafergot 31 (11)	(ST) 32(12) Cafergot (39(14)	52% of of the patients receiving sumatriptan described their treatment as good or excellent, whereas only 31% of patients treated Cafergot gave this response. 66% taking sumatriptan said they would take it again. Compared with 52% of patients who received Cafergot.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	**Headache recurrence within 24 hours**	**Vomiting relief within 2 hours**	**Nausea Relief within 2 hours**	**Photophobia Relief within 2 hours**	**somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain**	
Adelman, 2001							
Laterre, 1991	Attack 1 (ST) -24% Cafergot - 44%	Recurrence reported within 48 hours (ST) - 41% Cafergot - 30%	ST - Before 9% After 8% Cafergot Before 13% After 16%	ST - Before treatment 66% After 40% Cafergot - Before 64% After 55%	ST - Before 71% After 35% Cafergot - Before 75% After 53%	Sumatriptan fatigue, nausea, vomiting, dizziness, plpitations, abdominal cramps and stiffness Cafergot depression, vertigo, blurred vision, irregular heart beats, hypersensitivity, exacerbation of the migrane attack, urtcaria, dysponea, fatigue, tachycardia, vagal discomgort, dizziness and tinnitus.	6 in sumatriptan, 9 in Cafergot

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Adelman, 2001				
Laterre, 1991	NR			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Winner, 1996	Multicenter, DB, RCT , Parallel group, single dose	26 Clinics and private neurology practices	310	41 years; 88% female, ethnicity not reported	I H S criteria 18-65 men and women.
Dowson, 2000	Multicenter, DB, RCT, double dummy, crossover	23 primary care practices in the UK	204 (initially recruited)	42.8 Years 92% female, Caucasian (except 1)	Men and women 18-65

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Winner, 1996	History of Migrane for at least 1 year at a frequency of one to six moderate to severe per month	chronic tension or cluster headaches or hemiplegic, aphasic, or baslar migrane headache, duration of aura more than 60 minutes, active psychiatric disorders peripheral vascular disorders, current use of macrolide n\antibotics, significant hepatic or renal impairment, history of treatment failures to sumatriptan , drug addiction chronic use of opiod or analgesics, use of serotonin reuptake inhibitors.
Dowson, 2000	Established diagnosis of migraine with symptoms of at least 1 year's duration and age of onset<50. Patients also had a history of at least two moderateor severe attacks every 12 weekswith a gap of at least 24 hours between attacks	Pregnancy, breastfeeding or inadequate contraception, cardiovascular conditions, chronic renal/hepatic disease or hypertension Known snsitivty to either trail treatment and those who had tried either treatment in the past and found it ineffective.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Winner, 1996	Sandoz, co-investigator	Rescue medication permitted	NR	15 ineligible for efficacy analysis - 10 disallowed medications after treatment drug, 3 did not complete a 120 minute evaluation, 2 did not receive the drug according to protocol	Sumatriptan sc 6 mg
Dowson, 2000	Servier Laboratories Ltd.	Rescue medication permitted Patients were allowed to continue using tricyclic anti-depressants and certain prophylactic medications for migrane prevention as long as these had been used for at least 3 months and were kept constant throughout the study.	204 recruited, Efficacy II = 161(received 1 dose of 1 med), Efficacy I = 120 (received both study meds)	Of 204 recruited, 4 - no migrane attack 39 withdrawn due to faliure to attend second clinic visit 41 not take 2nd med so 161 analyzed for safety, 120 analyzed for primary and secondary efficacy	Sumatriptan 50 mg + placebo

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Winner, 1996	1mg subcutaneous dihydroergotamine mesylate	Sumatriptan - 85.3% Dihydroergotamine - 73.1%	NR	Only improvement over baseline reported	Of those with relief (ST)- 69.6% and 81.5% in the dihydroergotamine group had no pain at all.
Dowson, 2000	domperamol (a combination of 10 mg domperidone and 500 mg paracetamol) + placebo	Sumatriptan - 33.3% Domperamol - 36.4% At 4 hrs Dom = 49.2%, Suma = 41.9%	NR	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Winner, 1996	NR	NR	ST 78.0% Dihydro 56.6%	NR	ST 73.1% Dihydro - 85.3%	NR
Dowson, 2000	NR	NR	NR	NR	Suma= 3.3%, Dom = 36.4%	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Winner, 1996	ST n = 23 Dihydroergotamine n= 43	Of 270 who experienced relief Sumatriptan (140) 45% dihydroergotamine (130) 17.7%	Baseline complaint:: ST - n = 9 - 6% Dihydro n = 14 - 9.7% At 1 hour ST n= 6 - 4.0% Dihydro = n = 8 - 5.5%	Baseline complaints: ST - n = 114 - 76% Dihydro - n = 102 - 70.3% At 2 hours ST n= 16 Dihydro n= 40	NR	nausea, vomiting, chest pain, injection site discomfort	2 patients (dihydro group)
Dowson, 2000	NR	NR	Dom from 9.2% nausea prior to 5.0% in 2 hrs and 3.3% at 4 hrs, Suma=10% nausea prior to 5.8% in 2 hrs and 0.8% in 4 hrs	Dom from 70% nausea prior to 36.7% in 2 hrs, Suma=70% nausea prior to 39.2% in 2 hrs		dizziness and nausea	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Winner, 1996	ST - 5.9% Dihydro - 0.9%			
Dowson, 2000	None			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group	Multicenter, Double blind, double dummy, equally randominized, parallel group, single dose, 3 attacks	neurology department, private clinics and general practice surgeries 37 centers in 8 countries (Austria, Denmark, Germany, France, New Zealand, Sweden, Switzerland, UK) Medication was taken by patient at home	382 randomized to receive med, 24 of these did not treat an attack	41years, 80% female all but 5 were caucasian	I H S criteria 18-65 men and women.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group	At least a 1 year history of one to six severe or moderately severe migrane attacks per month, were able to recognize early signs of an attack and were not taking prophylactic medication.	Participation in a previous sumatriptan trial; a history of narcotic or ergotamine abuse or regular requirement for these drugs; existing alcohol or drug abuse; hypersensitivit to to treatment drugs; lactatio; pregnancy or inadequate contraceptive measures; history of ischaemic heart disease, uncontrolled hypertension, serious psychiatric illness or other systemic disease; need for continuing migrane prophylaxis or participation in more than three clinical trails within the previous 3 years.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group	Glaxo Group Researc h	Rescue medication permitted	358 took treatment (175 on suma and 183 on aspirin and meto); 355 evaluable for at least one attack	358 treated for 1st attack, 3 in S not analyzed for efficacy S: 175 1st attack, 172 evaluable A&M: 183 1st attack, 183 evaluable 2nd attack: S: 159, 153 evaluable, A&M: 175, 172 evaluable 3rd attack: S 149, 142 evaluable, A&M 161, 156 evaluable	Sumatriptan oral 100 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group	900 mg aspirin plus 10 mg oral metoclopramide	Attack 1 (ST) (74/133) - 56% Asprin + (62/138) - 45% Attack 2 (ST) - 58% A&M - 36% Attack 3 (ST) - 65% A&M - 34%	Attack 1 (ST) - 26% A&M - 14% Attack 2 (ST) - 23% A&M - 15% Attack 3 (ST) - 34% A&M - 12%	Resume normal activities within 6 hours Attack 1 (ST) 50% A&M - 30% Attack 2 (ST) - 53% A&M - 34% Attack 3 (ST) - 53% A&M - 36%	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group	NR	NR	NR	NR		(ST)66% vs Aspirin + 45% of patients considered treatment to be excellent, good or reasonable (ST) 70% vs Aspirin + 46% said they would take the medication again.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group		Recurrence reported within 48 hours Attack 1 (ST) 42% Aspirin + - 33% Attack 2 (ST) 37% Aspirin + - 27% Attack 3 (ST) 42% Asprin+ - 30%	Pretreatment vomiting: 1st attack: S = 12%, A&M= 14%, 2nd attack: S=14%, A&M=18%, 3rd attack: S=12%, A&M=19% Vomiting after 2 hrs: 1st attack: S = 15%, A&M= 10%, 2nd attack: S=9%, A&M=13%, 3rd attack: S=6%, A&M=13% (significant)	Proportion free of nausea:Attack 1 (ST) - 57% Aspirin+ - 55% Attack 2 (ST) - 63%, A&M 63% Attack 3 (ST) - 56% Asprin+ - 55%	Proportion free of phobia: Attack 1 (ST) 57% Aspirin + - 50% Attack 2 (ST) - 59% Aspirin + - 51% Attack 3 (ST) - 54% Aspirin + - 43%	nausea, vomiting, fatigue, dizziness, distribuance of taste, sweating, worsening of migrane, abdominal discomfort, throat symptoms, headache, others are listed	5 in the ST group withdrew due to adverse advents

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group	ST n= 4 - 2% Aspirin + n = 1<1%			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Tfelt-Hansen, 1995	DB, Randomised, 3 parallel group study, 2 attacks	Patients were treated at home over a period of 8 weeks with a monthly control visit, 68 centers in Belgium, France, the Netherlands, and Denmark	421	39 years; 78% female, Ethnicity not reported	I H S criteria 18-65 men and women.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Tfelt-Hansen, 1995	At least a 1 year history of 2-6 attacks per month within the last three months.	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Tfelt-Hansen, 1995	NR	Rescue medications , except for ergot alkaloids or morphinomimetic drugs, were allowed.	NR	Of 421 randomized, 32 patients did not report any attacks, 4 failed to record details, 58 patients did not have a 2nd attack, analysis of 1st attack was 385 (126 placebo, 137 LAS-MTC, 122 sumatriptan), analysis of 2nd attack was 327 (102 placebo, 120 LAS&MTC, 105 sumatriptan)	Sumatriptan 100 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Tfelt-Hansen, 1995	1. lysine acetylsaicylate (equivalent to 900 mg aspirin) and 10 mg metoclopramide 2. Placebo	1st attack ST - 53% (63/119) LAS+MTC - 57% (76/133) Placebo - 24% (30/124) 2nd Attack ST - 55% LAS+ MTC - 43% Placebo - 25%	Effect on headache (Success) : 1st Attack ST 30% (36/122) LAS+MTC 22% (29/135) Placebo 8% (10/126) 2nd Attack ST 33% (35/105) LAS+MTC 24% (28/119) Placebo 11% (11/101)	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Tfelt-Hansen, 1995	NR	NR	NR	NR	1st attack ST - 53% (63/119) LAS+MTC - 57% (76/133) Placebo - 24% (30/124) 2nd Attack ST - 55% LAS+ MTC - 43% Placebo - 25%	Good or excellent effect as rated by patients 1st Attack ST -45% (54/121) LAS +MTC - 46% (74/137) Placebo - 20% (24/123) 2nd Attack ST - 49% (49/101) LAS +MTC - 58% (70/120) Placebo - 23% (23/98)

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Tfelt-Hansen, 1995	More frequent with placebo than with active drugs, no difference between active drugs	1st Attack ST 38% (24/63) LAS - 36% (27/76) Placebo 30% (9/30) 2nd attack ST - 32% (18/65) LAS+MTC - 31% (16/51) Placebo - 12% (3/25)	Prior to treatment ST - 8% (10/121) LAS+MTC - 7% (10/136) Placebo - 9% (11/125) 1st Attack ST 9% (11/121) LAS - 5% (7/132) Placebo 12% (15/121) 2nd attack Prior to treatment ST - 10% (10/104) LAS+MTC - 9% (11/199) Placebo - 11% (11/100) ST - 8% (8/104) LAS+MTC - 4% (4/115) Placebo - 11% (11/99)	Prior to treatment ST - 69% (84/122) LAS+MTC - 77% (106/137) Placebo - 64% (81/126) 1st Attack ST 48% (58/122) LAS - 44% (60/135)) Placebo 58% (72/125) 2nd attack Prior to treatment ST - 73% (77/105) LAS+MTC - 67% (80/120) Placebo - 72% (73/102) ST - 47% LAS+MTC - 49% (58/118) Placebo - 58% (53/100)	NR	Nausea/vomiting, somnolence, fatigue, abdominal pain, Paraesthesiae, heaviness in lower limbs, back or neck pain, syncope, vertigo/dizziness	7 patients

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Tfelt-Hansen, 1995	ST 6 (4.8%) LAS - 0 Placebo - 0			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Diener, 1999	Multicenter, DB, double-dummy, RCT, 3 parallel groups, single dose, 1 attack	17 outpatient clinics of neurology departments and offices of neurologists and pain specialists in Germany	279 assigned to three treatment groups	41 years, 80% female	I H S criteria, 18-65 men and women.
Block, 1998	Long-term open label (up to 1 year), multicenter, RCT, single dose	100 multinational sites	1,831 (from 2,252 who complated acute phase of 3 multicenter phase III studies)	42 years, 86% female, 96% caucasian	I H S criteria, 18-65, men and women who had completed the double, blind, acute phase of three mulitcenter phase III studies were offered extension treatment for up to 12 months

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Diener, 1999	At least 1 year history of migrane and experiencing 2-6 migrane attacks per month during the last 12 months	Participation in a study during the 30 days immediately prior to the start of the study, including the treatment of a second migrane attack, intake of analgesics, or migrane drugs 24 h before administration of the study medication, intake of compund analegisics on more than 10 days per month, hypertension, coronary heart disease, asthma, drug or alcohol abuse alergic diatheses
Block, 1998	At least 6 month history of migrane, with a frequency of 1-8 attacks per month to enter the acute phase of the 3 studies.	Pregnant or breast-feeding, drug/alcohol abuse, significant organ system disease, history of or at risk for coronary heart disease.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Diener, 1999	Bayer Vital. GmbH & Co., Germany	Rescue medication permitted	275 valid cases for analysis of efficacy: 119 with L-ASA, 114 with sumatriptan, 42 with placebo	1 dropped out prior to start (278 took med) 3 withdrawn due to violation of exclusion criteria.	Sumaptriptan sc 6 mg
Block, 1998	Merck Research Laboratories (PI and co-investigator)	Patients in the rizatriptan groups were not to use ergot deratives, sumatriptan or isometheptene for 24 hours before or after treating with test medication.Because of possible drug interaction propranol and metoprol were prohibited in the 10 mg rizatriptan group	2252 patients who completed the acute phase were eligible for extension treatment, 1831 entered treatment, 1767 treated at least 1 headache	64 no attack 63 adverse experience Lack of effect -11% of riz 5 mg and 4% of riz 10% discontinued treatment	Rizatriptan po 5 mg group 10 mg group

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Diener, 1999	2 other arms: 1.Intraveneous L-ASA 1.8 (corrresponding to 1 g acetylsalicylic acid) and 2. Placebo (ratio between placebo & active treatment =1:6)	(ST) (104/114) - 91.2% L-ASA(88/119) - 73.9% Placebo - 23.8%	(ST) - 76.3% L-ASA - 43.7% Placebo - 14.3%	Time between administration of medication and the patient's ability to resume work or usual activities. Mean Time (ST) 8.2 hours L-ASA 12.7 hours Placebo 19.4 hours	NR
Block, 1998	Standard Care: Sumatriptan either alone or in combo with other therapies; NSAIDS; Other ususal care	Overall median percent of attacks in which patients achieved pain relief after 2 hours was 90% for rizatriptan 10 mg, 80% for rizatriptan 5 mg, and 70% for standard care.	A median of 50% of attacks treated with rizatriptan 10 mg, 35% with rizatriptan 5 mg and 29th% with standard care were pain free	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Diener, 1999	NR	See Fig 2	See Fig 2	See Fig 2		NR
Block, 1998	NR	NR	NR	NR		NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Diener, 1999	ST=1.8%, L-ASA=4.2%, Placebbo=16.7%	(ST) - 23.1% L-ASA - 18.2% Placebo - 20.0%	(ST) Not existing - n = 95 - 83.3% Resolved n = 18 - 15.8% L-ASA Not existing - n= 99 - 83.2% Resolved = 20 - 16.8% Placebo Not existing n= 36 - 85.7% Resolved n= 5 - 11.9%	(ST) Not existing - N=17 - 14.9 % Resolved -n= 86 - 75.4% L-ASA Not existing - n = 27 - 22.7 % Resolved n = 77 - 64.7% Placebo Not existing n = 7 - 16.7% Resolved n= 12 - 28.6%	(ST) Not existing - n = 20 - 17.5% Resolved n = 82 - 71.9% L-ASA Not existing - n = 17 - 14.3% Resolved n = 79 - 66.4% Placebo Not existing - n = 6 - 14.3% Resolved n = 15 - 35.7%	Fatigue, Dizziness/vertigo, Nausea, Injection site reactions, Chest symptoms, tight feeling in other parts of the body	NR
Block, 1998	Allowed, but not reported	Not spefic as to when	NR	NR	NR	Serious Adverse Experiences - Serious clinical adverse experiences were reported by 2.1% Rizatriptan 10 mg, 1.5% 5 mg, 2.7% standard care, adverse effects were nausea, dizziness, somnolence, asthenia/fatigue, headache, vomiting, chest pain, paresthesia	63 Patients discontinued due to a clincal adverse experience, 4.2% Rizatriptan 10 mg, 3.6% 5 mg and 1.5% standard care

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Diener, 1999	ST - n = 4 - 3.4% L-ASA n= 0 Placebo = n = 1 - 2.3%			
Block, 1998	Rizatriptan 5 mg<1 Rizatriptan 10 mg 1 Standard Care 2			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Touchon, 1996	At first onset, multicenter, DB, DD, crossover, single dose, 2 attacks	Outpatient, in 34 centers in France	317	42 years, 86% female,	I H S criteria, 18-65 men and women

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Touchon, 1996	At least 1 year history of 1-6 migrane attacks per month and were able to differentiate migrane attacks from other types of headaches	pregnancy, lactation, or inadequate contraception, a history suggest of ischemic heart disease, uncontrolled hypertension or othe systemic disease, drug/alcohol abuse, containdications to the use of DHE, and hypersensitivty to or intolarance of sumatriptan or DHE.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Touchon, 1996	Glaxo Wellcome Research and Development, co-investigator	Rescue medication was permitted.		28 no attack, so 289 (145 S & 145 DHE) 12 were withdrawn after 1st attack 11 failed to treat a 2nd attack, so 266 evaluale in crossover analysis (133 S & 133 DHE)	Sumatriptan sc 6 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Touchon, 1996	DHE 2 nasal spraysof 0.5 mg (1 spay in each nostril)	See Fig 1	See Fig 1	One hour postdosing, 38% of the SC sumatriptan-treated patients were able to perform their work or daily activities normally compared with 16% of patients taking DHE Nasal spray	Headache relief for 24 hrs in 54% of S vs. 39% of DHE

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Touchon, 1996	NR	See Fig 1	Meaningful relief was achieved by more patients treated with sumatriptan (76% versus 46% and as an earlier time (40 vs. 60 minutes)	See Fig 1	See Fig 1	Treatment efficacy was assessed as good or excellent by 55% of the patients treated with SC sumatriptan and by 23% of those treated with DHE. At the end of the study, 64% of patients preferred sumatriptan compared with 24% who preferred DHE.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	**Headache recurrence within 24 hours**	**Vomiting relief within 2 hours**	**Nausea Relief within 2 hours**	**Photophobia Relief within 2 hours**	**somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain**	
Touchon, 1996	Patients randominized to the DHE treatment arm had the option of taking a 2nd dose of nasal spray 30 minutes after the first if their headache was not completely relieved. To maintain blinding , patients in the sumatriptan treatment arm took a second dose of placebo nasal spray.	S = 31%, DHE = 17%	The frequency of vomiting pretreatment in both treatment groups was low (on average 12% of patients).	SC sumatriptan was significantly better DHE nasal spray at relieving nausea. At all points from 30 minutes after dosing, fewer patients taking SC sumatriptan reported nausea compared with patietns taking DHE	Results for photophobia were similar to those observed for nause, with rapid improvement in SC and significant differences compared with DHE 15 minutes postdosing.	fatigue, flushing nausea, tingling and injection site reactions	4 patients withdrew due to adverse events, 3 in S group and 1 in DHE group

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Touchon, 1996	1 person in S group withdrew because of pressure in chest			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Freitag, 2001	At first onset, mild to moderate migrane, multicenter, DB, RCT parallel - groups	United States	137	42 years, 89% female, 92% caucasian	I H S criteria

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Freitag, 2001	1 year history of 2-8 migrane attacks per month and those with aura had to have attacks typically progressing to the painful phase of migrane. English speaking	Not using acceptable method of contraception, patients whose migrane historically led to vomiting more than 20% of the time were excluded, as well as those who required bedrest for at least half their attacks. Patients who had a history of headaches being unresponsive to eith isomethepteneene combination or sumatriptan, as were those who had daily headaches. History of over use of analgesics.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Freitag, 2001	Canrick Laboratories	Preventive medications for migrane were continued if the dose had been stable prior to study enrollment. Patients were not allowed to have used a monoamine oxidase inhibitor or methysergide within 2 weeks of study enrollment.		Of 137 enrolled, 126 evaluable; 11:7 patients did not treat within the alloted time, 2 lost to follow-up, 1 patient committed protocol violation and 1 patient vomited before and after taking the study medication	Sumatriptan Succinate, 25 mg, with repeat dose at 2 hrs

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Freitag, 2001	Isometheptene Mucate, Dichloralphenazone with Acetaminophen (2 capsules, then 1 at 1 hr, 1 at 2 hrs, 1 at 3 hrs)	Patients with no or mild head pain: ST - 68.9% Isometheptene Combination - 63.1%	NR	Mild or not impairment: Sumatriptan = 68.9%, isometheptene combo = 80%	No or mild head pain: sumatriptan =81.7, isometheptene combo = 81.1%

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Freitag, 2001	No or mild impairment: sumatriptan = 86.7%, isometheptene combo = 93.7%	No or mild head pain: sumatriptan = 39.3%, isometheptene combo = 29.2%	No or mild head pain: sumatriptan = 44.3%, isometheptene combo = 44.6%	NR		7-point scale (1=completely satisfied, 6=completely dissatisfied): 3.49 for isometheptene, 3.35 for sumatriptan

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Freitag, 2001	NR	Recurrence in 10 sumatriptan patients, in 11 isometheptene combo patients	% with vomiting at 2 hrs: 0 for both groups	% without nausea at 2 hrs: sumatriptan=65.6%, isomethptene combo= 73.9%	% without photophobia at 2 hrs: sumatriptan=52.5%, isomethptene combo= 49.2%	abdominal pain, nausea, diarrhea, lightheadedness, sleepiness, dry mouth, heat flashes, head pressure, tremor, sweating, palpitations, chest pain, enlarged thyroid, sore throad, laryngitis, bruises, stiff neck, drug taste, confusion	None

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Freitag, 2001	2 sumatriptan patients			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Boureau, 2000	mulitnational, multicenter, RCT, DB, DD, crossover study, 2 attacks, single dose	Outpatient, 52 centers in Belgium, France, Portugal and Switzerland	405	41 years, 84% female, Ethncity NR	I H S Criteria 18-65 men and women

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Boureau, 2000	At least 1 year history of 1-6 migrane attacks per month over the last 12 months that were severe or moderately severe	patients were excluded if they had participated in any other clinical research study within 4 weeks; were pregnant, likely to become pregnant, or breast feeding, or not using adequate contraceptive methods, current cardiovascular disease, drug/alcohol abuse, Ergotamine abuse; any co-existing medical condition that could affect the intrepetation of the data, andy condition or medication that would contradindicate the use of sumatriptan or DHE.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Boureau, 2000	Glaxco, Wellcome	Patients randominized to active treatment with DHE had the option of taking a second dose of nasal spray 30 minutes after the first, if insufficient relief was obtained. Rescue medication was permitted at 2 hours. Patients who normally took prophylactic medication for migrane were permitted to continue therapy provided it did not contain ergotamine or DHE and the dosage remained the same throughout the study.	405 total enrolled: 207 treated 1st attack with sumatriptan, 198 with DHE; 368 in 2nd attack	crossover analysis on 327 patients who treated 2 attacks rated moderate or severe	ST Nasal Spray 20 mg (plus placebo DHE)

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Boureau, 2000	DHE Nasal Spray 1 mg (plus placebo ST)	ST- 63% DHE - 51%	At 1 hour ST - 22% DHE - 16%	At 2 hours after dosing 46% of patients were able to work and function normally after ST, compared with 38% after DHE.	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Boureau, 2000	NR	See Fig 1; at 45 minutes, sumatriptan=38 %, DHE=31%	Headache relief was reported by ST - 53% DHE 41%	ST - 60% DHE 48%	ST- 63% DHE - 51%	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	**Headache recurrence within 24 hours**	**Vomiting relief within 2 hours**	**Nausea Relief within 2 hours**	**Photophobia Relief within 2 hours**	**somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain**	
Boureau, 2000	The optional 2nd dose of study medication at 30 minutes was taken for 76% of migranes treated with Sumatriptan and 81% of those treated with DHE.	Headache recurrence was reported by 23% of patients following sumatriptan dose and 13% following DHE dose. (not specific as to when)	At 1 hour after dosing , 7% of patients in each group reported vomiting	At 1 hour 64% of patients reported relief of nausa following sumatriptan compared with 40% following DHE At 90 minutes, ST - 67%, 53% DHE	at 1 hr sumatriptan=47% , DHE=52%	disturbance of taste, nasal congestion, irritation, nasal swelling, rhinitis, nausea, vomiting, conjunctivitis, facial congestions, edema of eyelid, flatulence	2 patients withdrew due to adverse events

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Boureau, 2000	NR			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Boureau, 1995	multicenter, equally randomised, open label, early onset, crossover trial	46 neurology centers in France	246	42 years, 82% female, Ethnicity not reported	I H S Criteria 18-65 men and women

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Boureau, 1995	1-6 severe attacks per month	lactation, pregnancy or inadequate contraceptive measure, a history suggestive of ischaemic heart disease, uncontrolled hypertension or other systemic disease, a history of narcotic or ergotamine abuse, drug or alcohol abuse, hypersensitivity to or intolerance of sumatriptan.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Boureau, 1995	Laboratoires Glaxo, co-investigator	A second dose was allowed if headache recurred after initially relieved, provided that 2 h had elapsed since the first dose. Rescue medication was permitted. Prophylactic treatments for migrane were authorized provided the dosage remained unchanged during the study.	246 randomized, 8 not have attack, of 238 w/ attacks, 120 treated 735 attacks w/ sumatriptan and 118 treated 932 attacks with usual treatement	Period I 8 did not treat a migrane attack, 13 withdrawn for adverse events (10 sumatriptan, 3 usual treatment) Period II: 225 entered 8 had no attacks 8 dropped out (4 per group), Crossover analyzed on 217 patients with total of 3,181 attacks	Sumaptriptan sc 6-m.g s.c injection

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Boureau, 1995	Usual Acute Treatments: Combinations of various analgesics Ergotamine Noramidopyrin Paracetamol Non-steroidal anti-inflammatory drugs Acetylsalicylic acid DHE Other	Period I ST 80% Usual treatments 30% Period II ST 76% Usual treatments 39%	Period I ST 62% Usual Treatments 13% Period II ST 65% Usual Treatments 17%	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Boureau, 1995	Assessed at baseline and end of study Relative increase from baseline Global ST 21% UT - 7% Functional ST 21% UT 6% Psychological ST 16% UT 6% Social ST 23% UT 4% Iatrogenic distribuance - ST 16% UT - 14%	NR	Period I ST 70% Usual Treatments 21% Period II ST - 63% Usual Treatments 28%	NR	Period I ST 80% Usual treatments 30% Period II ST 76% Usual treatments 39%	ST - 85% UT - 10% No preference - 5% Patients assessed ST as being "well tolerated"in 88-89% of attacks and UT 78-82% of attacks

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Boureau, 1995	Period I ST - 33% UT - 24% Period II ST - 28% UT 20%	NR	On average less than 10% of attacks per patient; this however was significantly less 1 and 2 h after ST compared to UT.	Presence of Nausea Period I Pre-treatment ST 48% UT 45% At 2 h 14% UT 36% Period II Pre-treatment ST - 49% UT - 41% At 2 h ST - 13% UT - 30%	NR	tingling, malaise, nausea, injection site reaction, stomach pain, dizziness, sleepliness, fatigue	13 patients withdrew in period I for minor adverse effects, 8 withdrew in period II but reasons not given

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Boureau, 1995	ST 7%			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Myllyla, 1997	multicenter, randominized,early onset, DB, placebo-controlled, parallel-group study	5 neurological centers in Finland	154	42 years, 95% female, Ethnicity not reported	I H S criteria 18-65 men and women

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Myllyla, 1997	History of Migrane for at least 1 year and with more than one but less than four attacks per month characterized by severe or moderate	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Myllyla, 1997	A/S GEA Farmaceutisk Fabrick	If headache had not improved the patient was allowed an extra dose of test medicine at 1 hour. Escape medication was allowed after 2 hours.		3 were lost to followup 10 were withdrawn (1 hypertension, 1 adverse effects, 8 no attack)	Rizatriptan po 100 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Myllyla, 1997	1. Tolfenamic Acid Rapid Release 200 mg, 2. placebo	Attack 1 ST 79% (33/42) R-TA 77% (33/43) Placebo 29% (12/41) Attack 2 ST 64% (25/39) R-TA 70% (30/43) Placebo 39% (15/38)	Attack 1 ST 50% (21/42) R-TA 37% (16/43) Placebo 7% (3/41) Attack 2 ST 26% (10/39) R-TA 16% (7/43) Placebo 11% (4/38)	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Myllyla, 1997	NR	NR	NR	NR	Attack 1 ST 79% (33/42) R-TA 77% (33/43) Placebo 29% (12/41) Attack 2 ST 64% (25/39) R-TA 70% (30/43) Placebo 39% (15/38)	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Myllyla, 1997	Extra dose of test Med at 1 hour Attack 1 ST 61% ((28/46) R-TA 72% (34/47) Placebo 94% (45/48) Attack 2 ST 76% (34/45) R-TA 80% ((36/45) Placebo 83% (39/47)	Attack 1 ST 22% (10/45) R-TA 23% (11/47) Placebo 25% (12/48) Attack 2 ST 24% (11/45) R-TA 27% (12/45) Placebo 13% (6/47)	Vomting at Attack 1 ST 4% (2/45) RT 9% (4/46) Placebo 8% (4/48) 2 hours Attack 1 ST 11% (5/46) R-TA 9% (4/46) Placebo 8% (4/48) Vomiting at Attack 2 ST 2% (1/42) R-TA 2% (1/44) Placebo 4% (2/45) 2 hours Attack 2 ST - 9% (4/45) R-TA - 9% (4/44) Placebo - 15% (7/47)	Nausea at Attack 1 ST 43% (20/46) R-TA 47% (22/47) Placebo 42% (20/48) 2 hours Attack 1 ST 41% (19/46) R-TA 26% (12/47) Placebo 42% (20/48) Nausea at Attack 2 ST 56% (22/45) R-TA 62% (28/45) Placebo 47% (22/47) 2 hours Attack 2 ST - 44% (20/45) R-TA - 36% (16/45) Placebo - 45%(21/47)	Photophobia at Attack 1 ST 84% (38/45) R-TA 79% (37/47) Placebo 88% (42/48) 2 hours Attack 1 ST 41% (19/46) R-TA 38% (18/47) Placebo 67% (32/48) Photophobia at Attack 2 ST 84% (37/44) R-TA 79%(39/45) Placebo 83% (39/47) 2 hours Attack 2 ST - 44% (20/45) R-TA - 51% (23/45) Placebo - 68% (32/47)	Tachycardia, palpitation, muscle pain, Dysuria, nervous system symptoms, nausea, vomiting, gastronintestinal symptoms, Allergic	1

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Myllyla, 1997	ST - 7 R-TA -2 Placebo - 0			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	Open label , not random, 1st phase patients took their customary therapy (non-sumatriptan to treat unlimited number of migranes for 12 weeks, follwed by 24 weeks treatment with ST SC.	1993-1995 at 69 clinics in 5 countries: Australia, Canada, Germany, Italy, Sweden	Not randomized	39 years, 83% female, 98% Caucasian	I H S criteria 18-65 male and female

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	An average of 2 - 6 moderate or severe attacks per month	Those who had previously treated > 3 attacks with ST outside a clinical trial or had used ST within the past 6 months within a clinical trial. Those receiving prophylactic ergotamine containing or any prophylactic medication for migrane where the dose might changeduring the study, patients with ischamic heart disease, patients with diastolic blood pressure greater than 95 mm Hg or severe hypertension, ergotamine abuse within the past year, drug/alcohol abuse, inadequate contraception, breastfeeding or pregnant.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	Glaxo Wellcome (co-investigators)	Rescue medication was permitted (but not ergotamine).	749 were recruited and 637 received at least one dose of ST 582 had some evaluable data 482 patients completed all 36 weeks	Failure to return to clinic (n=58), lack of efficacy (n=53), sumatriptan adverse events (n=33), protocol violations (n=31), loss of interest in the study (n=21) and other reasons (n=21)	Sumatriptan 6 mg sc

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	Pain Free in 2 hours	Symptom-free (or no functional disability) at 2 hours	24-hour sustained pain-free response
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	Customary Therapy such as (47%dimenhydrinate/paracetamol/coedine; aspirin/antiinflamatories (60% such as ibuprofen; narcotics/analgesics (62%) such as coedine; and hypnotics/sedatives/anticonvulsants (11%) such as diazepam	See Fig. 1, about 75% of migraines successfully treated on sumatriptan, about 35% on customary therapy	ST - 36% Customary Therapy 1%	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	NR	See Figure 4	Median time to relief was 30 minutes on sumatriptan and 60 minutes with customary therapy	See Figure 4	See Figure 4	Scores on each of the 3 migrane spcific quality of life questionaire dimensions (role function restrictive, role function preventive and emotional function) were significantly higher after 12 weeks of ST compared with customary therapies. Of the 482 patients who responded 21.9% said they would ask their doctor for ST in the future if their doctor recommend it, 6.5% were not sure, 2.3% said only if the doctor insisted 2.3% said they would not use ST again. (See Dahlof and Bouchard articles for more detail.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	NR for time periord	NR	NR	NR	NR	No serious adverse events were reported . An adverse event was reported by 50% of patients during the 12 week customary therapy phase and 89% of patients during the 24 week ST phase. During customary therapy: tingling, pressure sensation, nausea and/or vomiting . During ST, nausea/vomiting, musculosketal symptoms, pressure sensation, injection site reaction, throat symptoms, feelings of heaviness.	Adverse events sumatriptan=33

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Heywood, 1997 Dahlof, 1997 Bouchard, 1997	ST -5.5% over 12 weeks			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Schoenen, 1994	multicenter, open label, long-term	outpatient - 92 centers in Belgium	479	40 years; 84% female, ethnicity not reported	I H S criteria Male and Female aged 18-65

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Schoenen, 1994	Diagnosis of migrane and who had experienced for at least 6 months between 1-6 attacks of moderate or severe intensity per month.	Patients who had a regular requirement for opiate analgesics or major tranquillizers, or who had a history within the last year of abuse of ergotamine or alcohol. Ischemic heart disease or a supine diastolic blood pressure greater than 95mm Hg. Major psychiatric illness.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Schoenen, 1994	Glaxo, Belgium (co-investigators)	prophylactic meds allowed, non-ergotamine-containg rescue medication	NR	64 patients did not come back for the 2nd visit. 14 patients erroneously received ST at their first visit. 4 did not come back for followup visit 4 -Lack of efficacy + adverse events 22 adverse events 3 Other	Sumatriptan 6 mg sc

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Schoenen, 1994	simple analgesics (16%), combination analegisics (29%) ergot derivatives (36% NSAIDS (7%), nacotics (2%) antiemetics (7%) others 2%.	Customary Treatment (see Table 3) 1st attack 33% 2nd attack 29% 3rd attack 30% ST (See Table 5) Attack 1 317(82) Attack 2 286(82) Attack 3 238(80)	See Table 6 ST Attack 1 78 (21) Attack 2 76(22) 55 (20)	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Schoenen, 1994	NR	NR	Customary Treatment (See Table 3) ST (See Table 5)	NR	Customary Treatment (see Table 3) 1st attack 33% 2nd attack 29% 3rd attack 30% ST (See Table 5) Attack 1 317(82) Attack 2 286(82) Attack 3 238(80)	ST Ineffective - 30(7) Poor - 24(6) Reasonable 54(13) Good 140(34) Excellent 167(40)

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	**Headache recurrence within 24 hours**	**Vomiting relief within 2 hours**	**Nausea Relief within 2 hours**	**Photophobia Relief within 2 hours**	**somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain**	
Schoenen, 1994	Number with 2nd injection ST Attack 1 115(31) Attack 2 104(31) Attack 3 92(32)	ST Attack 1 127(34) Attack 2 115(34) Attack 3 96(33)	ST- Before 19% 2hours 3% See Fig 2	ST - Before 71% 2 hours 17% See Fig. 2	ST Before 77% 2 hours 21% See Fig 2	ST Tingling, Dizziness, Warm, Nausea and/or vomiting, tight feeling, fatigue, pricking sensation, malaise, pressure sensation, drowsiness, chest pressure, heaviness, flushing, palpitations, headache, injection site reactions, dyspnea, neck pain, anxiety, sweating, swelling	22(5%)

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Schoenen, 1994	2.8% of 1136 attacks			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Gerth, 2001	Non-blinded, parallel group, extention trial (Improvement in Health-Related Quality of Life)	Outpatient, 23 sites in the United States	265 Randomly assigned 4:1to rizatriptan or standard care	41 years, 83% female 95% caucasain	Male and Female aged 18-65

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Gerth, 2001	Patients who had completed an RCT with rizatriptan at 23 US sites	Patients in the rizatriptan group were not to use sumatriptan, ergot derivatives or isometheptine for 24 hours before or after treating a migrane attack with the test drug; monomamine oxidase inhibitors and methysergide were prohibited for the duration of the study.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Gerth, 2001	Merck & Co. Inc. (PI)	NR	313 invited, 265 elected to participate	NR	Rizatriptan po 10 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	Pain Free in 2 hours	Symptom-free (or no functional disability) at 2 hours	24-hour sustained pain-free response
Gerth, 2001	Standard Migrane Therapy 66% used sumatriptan (oral or subcutaneous), also NSAIDS (70%), barbiturates (40%), paracetamol (40%) and opiods (30%) for at least 1 attack.	NR	NR		

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Gerth, 2001	24-HrMQoLQ Mean Scores Work Functioning RT 13.9 SMT - 12.5 Social Functioning RT 13.6 SMT 11.8 Energy/Vitality RT 13.7 SMT 11.6 Feelings/Concerns RT 13.3 SMT 10.6 Mental Health Component of SF-36 RT 50.3 SMT - 48.0	NR	NR	NR	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Gerth, 2001	NR	NR	NR	NR	NR	NR	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Gerth, 2001	NR			Point of paper to measure improvement in health-related quality of life, rizatriptan had better QoL than usual meds

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Bussone, 1999	multicenter, DB, RCT within patient trial, early onset, single dose	Italy?	156	33 years, 76.3% female, ethnicity not reported	I H S male and female, aged 19-70

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Bussone, 1999	Disease duration of a least 1 year and attack frequency of 2-6 per month over the past 6 months	Patients suffering from other types of headaches

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Bussone, 1999	Novartis Pharma AG (co-investigator) used to be Ciba-Geigy	The use of beta-blockers or calcium antagonists on a constant dosing regimen was allowed during the trial. Paracetamol was allowed as rescue medication	NR	12 did not experience an attack 29 were discontinued after 1 treatment for the following reasons 17 did not report a furter attack, 5 withdrew their consent, 4 adverse effects 1 no longer required treatment, 2 were lost to follow-up, 144 received at least 1 treatment, 115 completed treatment of 4 attacks	Sumatriptan oral 100 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Bussone, 1999	Diclofenac-K (50mg) , Diclofenac-K (100 mg), Placebo	100 mm visual analog scale: at baseline 50 mm for all, after DK 50 mg =26mm, DK 100 mg=22 mm, sumatriptan=29 mm, placebo=42 mm	NR	Patient reporting normal functioning increased from D-K 50 mg 13% to 49% by 2 h after dosing; for D-K 100 mg from 21% to 53%; for ST from 16% to 38%; and for placebo from 17% to 30%.	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Bussone, 1999	NR	See Figure 1	See Figure 1	See Figure 1	See Figure 1	More patients thought the tolerability was good or excellent when taking diclofenac 50 mg (79%), diclofenac-K 100 mg (76%), and plaebo (76%) than when taking ST (67%),

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	**Headache recurrence within 24 hours**	**Vomiting relief within 2 hours**	**Nausea Relief within 2 hours**	**Photophobia Relief within 2 hours**	**somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain**	
Bussone, 1999	36% of DK either dose, 41% of sumatriptan, 60% of placebo	Of the 115 patients who completed all 4 migrane attacks, 22% in the D-K 50 mg group, 24% in the D-K 100 mg group, 26% in the ST group and 19% in the placebo group reported recurrence within 48h after resolution of initial attack.	Baseline Diclofenac -K 50 mg 9 (8) Diclofennac - K 100 mg 10 (9) ST 12 (11) Placebo 5(5) 2hours DK 50 mg 4 (4) DK 100 mg 3 (3) ST 14 (13) Placebo 8 (7)	Baseline Diclofenac -K 50 MG 47 (43) Diclofenac - K 100 mg 50 (46) ST 58 (53) Placebo 52 (48) 2hours DK 50 mg 24 (22) DK 100 mg 29 (27) ST 45 (41) Placebo 47 (43)	Baseline Diclofenac -K 50 mg 55 (51) Diclofenac - K 100 mg 49 (45) ST 59 (54) Placebo 51 (47) 2hours DK 50 mg 35 (32) DK 100 mg 32 (29) ST 41 (38) Placebo 43 (39)	asthenia, Fatigue dizziness, paresthesia, somnolence, Dyspesia, nausea, abdominal pain, vomiting, Tachycardia, anxiety	4 withdrew

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Bussone, 1999	DK 50 - 100 mg none ST 4(3) Placebo 1(1)			

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Design	Setting	Number randomized	Age Gender Ethnicity	Patients
Friedman, 2001	Randominized controlled trial	A tertiary care academic medical center and a faculty practice located at a community hospital in US.	35	80% female, Average age and ethnicity NR	I H S criteria, men and women, 18-63 years.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Inclusion criteria	Exclusion criteria
Friedman, 2001	1) symptomatic migrane 2) previous migrane history and	1) chronic (constant headache) 2) headache lasting longer than 5 days 3) excessive headache (rebound headache) 4) extreme cold sensitivity 5) pregnant or nursing 6) cardiovascular disease.

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Funding sources and role of funder	Other medications	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/ analyzed	Triptan
Friedman, 2001	DextraBaldwib McGonagle Foundation Inc.		3 groups: sumatriptan, intraoral chilling, tongue chilling (control)	35 analyzed	Sumatriptan oral 50 mg

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Other Drugs	Results			
		Headache relief at 2 hours	**Pain Free in 2 hours**	**Symptom-free (or no functional disability) at 2 hours**	**24-hour sustained pain-free response**
Friedman, 2001	1. 40 minutes of bilateral MIC 2. Sham (tongue) chilling	Pain Score: Baseline: Sumatriptan=7.2, intraoral=7.3,control-7.2; after 2 hrs: sumatriptan= 4.6, intraoral=3.5,control=6.0	NR	NR	24 pain score: sumatriptan=2.9, oral=1.2,control=4.5

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results					
	24-hour quality of life	**Time to headache relief within .5 hours**	**Time to headache relief 1 hour**	**Time to headache relief 1.5 hours**	**Time to headache Relief 2 hours**	**Satisfaction / patient preference**
Friedman, 2001	NR		See Table 1	NR	See Table 1	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Results Continued					Adverse events	Withdrawals due to adverse events
	Need for additional medication from 2 or 4 to 24 hours for recurrence	Headache recurrence within 24 hours	Vomiting relief within 2 hours	Nausea Relief within 2 hours	Photophobia Relief within 2 hours	somnolence, dizziness, asthenia, nausea, vomiting, abdominal pain, chest pain	
Friedman, 2001	NR	See Fig 3	NR	Nausea Score: Baseline: Sumatriptan=3.2, intraoral=2.9,control-3.3; after 2 hrs: sumatriptan= 1.4, intraoral=1.3,control=3.1	NR	ST dizziness, paresthesia, and somnolence Side effects due to chilling included dizziness and posttreatment gingival tenderness	NR

Evidence Table 2b. Triptans vs active controls: Characteristics and outcomes

Author Year	Chest Pain or tightness	Quality rating (good/fair/poor)	External validity	Comments
Friedman, 2001	NR			

Evidence Table 3a. Triptans vs. placebo controls: assessment of internal validity

Internal Validity

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis
Eletriptan Steering Committee in Japan, 2002	Adequate	Unclear; pre-packaged drug kits supplied using randomization codes	Yes	Yes	nr	nr	nr	Yes nr nr nr	No No	Difference of 19 patients (6.8%) between evaluable population=326(81 %) and analyzed population=307(76 %)
Sakai, 2002	nr	nr	Yes	Yes	nr	nr	nr	Yes nr nr nr	No No	Difference of 29 (12.5%) between evaluable population=231/289 (79.9%) and analyzed population=202/289 (69.9%)

Evidence Table 3a. Triptans vs. placebo controls: assessment of internal validity

Author Year Country	Post-randomization exclusions	Quality Rating	External Validity: Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Eletriptan Steering Committee in Japan, 2002	yes	Fair	nr/nr/402	Severely limited gastrointestinal absorption; other exclusion criteria "identical to those used in previous clinical studies" not reported	no	no	Yes	Pfizer, Ltd. Role nr	100% Japanese
Sakai, 2002	yes	Fair	nr/nr/289	History of basilar, ophthalmoplegic or hemiplegic migraine; non-migraine headaches reported on >10 days per month during the previous 6 months; ischaemic heart disease, dysrhythmias or cardiac accessory pathway disorders (e.g., Wolff-Parkinson-White syndrome); severe liver or renal impairment; uncontrolled hypertension; pregnancy or lactation; severe allergies or hypersensitivity to drugs; participation in a clinical study during the past 3 months; or required use of ergotamine preparations	no	no	Yes	nr	100% Japanese

Evidence Table 3a. Triptans vs. placebo controls: assessment of internal validity

Internal Validity

Author Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis
Carpay	nr	nr	yes	yes	yes	yes	yes	yes	no	yes
2004								nr	no	
Europe								nr		
								nr		

Evidence Table 3a. Triptans vs. placebo controls: assessment of internal validity

Author Year Country	Post-randomization exclusions	Quality Rating	External Validity: Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Carpay 2004 Europe	49 (10.2%) withdrawn post-randomization due to not being treated	Fair	nr/nr/481 randomized	Patients with > 6 migraines monthly during either of the 2 months before screening; uncontrolled hypertension (diastolic blood pressure ≥ 95 mm Hg or systolic blood pressure ≥ 160 mm Hg); suspected or confirmed cardiovascular or cerebrovascular disease; or ophthalmic, basilar, or hemiplegic migraine; use of migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide; use of a monoamine oxidase inhibitor within 2 weeks before the study; and, in countries where the combination of a slsective serotonin reuptake inhibitor and a triptan is not allowed, need for a selective serotonin receptor inhibitor during the study	no no	no	yes	nr	yes

Evidence Table 3b.Triptans vs. placebos: Characteristics and outcomes

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Eletripan Steering Committee 2002 Japan *Fair quality*	Randomized controlled trial Multicenter Single dose	IHS criteria; 1 attack per 6-week period	Eletriptan (ele) 20, 40 and 80 mg Placebo (pla)	Rescue medication permitted nr	Primary efficacy endpoint: Proportion of patients who experienced headache response 2 hours post-dose. Patients recorded migraine severity in a diary at 0.5, 1, 2, 4, and 24 hours post-dose.
Sakai 2002 Japan *Fair quality*	Randomized controlled trial Multicenter Single dose	IHS criteria of migraine with or without aura; age of migraine onset <50 years; migraine history ≥1 year; 1-6 attacks/month in preceding 3 months	Zolmitriptan (zol) 1, 2.5, 5 mg Placebo (pla)	Type(s) of rescue medication approved 4-hours post-dose nr	Primary efficacy endpoint: proportion of patients with headache response at 2h post-dose. Patients recorded migraine intensity on diary cards at 0.5, 1, 2, and 4h post-dose.

***p<0.01 vs placebo**
‡pp<0.05 vs placebo
§p<0.001 vs placebo

Evidence Table 3b.Triptans vs. placebos: Characteristics and outcomes

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Eletripan Steering Committee 2002 Japan *Fair quality*	n=402 avg age 35.5 74.1% female 100% Japanese	Without aura=48.6% With aura=34.2% With and without aura=17.1% Baseline severity assessment: No pain=0% Mild pain=0% Moderate pain=75.7% Severe pain=22.4%	nr/nr/402	76(18.9%) withdrawals/3(0.7%) lost to fu/321 analyzed for safety; 309 for primary endpoint; 307 for other efficacy endpoints
Sakai 2002 Japan *Fair quality*	n=289 avg age 38.3 74.2% female 100% Japanese	Without aura=64% Associated symptoms: Nausea=90% Vomiting=54% Photophobia=56% Phonophobia=45% Severity: Moderate=73%	nr/nr/289	58/289(20%) did not take medication; a further 29/287(10%) were excluded from efficacy analysis due to protocol deviations/lost to fu nr/202 analyzed

***p<0.01 vs placebo**
‡pp<0.05 vs placebo
§p<0.001 vs placebo

Evidence Table 3b.Triptans vs. placebos: Characteristics and outcomes

	Results			
Author Year Country Trial Name (Quality Score)	**Relief at various times**	**Pain Free at various times (% patients)**	**Presence of migraine-associated symptoms at 2 hours**	**Other efficacy outcomes**
Eletripan Steering Committee 2002 Japan *Fair quality*	At .5 hour: nr At 1 hour: nr At 1.5 hours: nr At 2 hours: ele=64%; 67%; 76% pla= 51%	At 2 hours: ele=24%; 22%; 28% pla=13%	*Vomiting:* ele=96%; 99%; 95%; pla=96% *Nausea:* ele=70%; 74%; 41: pla= 68% *Photophobia:* ele=84%; 83%; 86%; pla=71%	*Symptom free at 2 hours:* ele=65%; 65%; 75%; pla=54% *24 hour sustained pain-free:* ele=21%; 18%; 26%; pla=9%
Sakai 2002 Japan *Fair quality*	At .5 hour: zol=8.5%; 9.8%; 13.7% pla= 12.2% At 1 hour: zol=30.4%; 28.3%; 32.7% pla=26.5% At 1.5 hours: nr At 2 hours: zol=53.3%; 55.6%; 65.4% pla=37.5%	At 2 hours: zol=17.8%; 18.5%; 23.1% pla=14.6%	*Vomiting:* zol=95.6%; 98.1%; 98%; pla=95.8% *Nausea:* ele=53.3%; 61.1%; 64.7: pla= 54.2% *Photophobia:* ele=82.2%; 83.3%; 78.4%; pla=77.1%	*Symptom free at 2 hours:* nr *24 hour sustained pain-free:* Complete response (headache response at 2h and then no recurrence or use of escape medication within 24h) zol=37.8%, 46.3%, 46.2% pla=22.9%

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Evidence Table 3b.Triptans vs. placebos: Characteristics and outcomes

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Comments
Eletripan Steering Committee 2002 Japan *Fair quality*	The incidence of adverse events was detected by indirect subject questioning, physical examination, and from laboratory safety data and entries in subject diaries.	Total: ele=16.3%; 32.5%; 45.5%; pla=15.5% Asthenia: ele=1.3%, 2.5%, 11.7%; pla=1.2% Parasthesia: ele=0, 3.8%, 1.3%; pla=0 Somnolence: ele=6.3%, 10.0%, 16.9%; pla=3.6%	
Sakai 2002 Japan *Fair quality*	The assessment of tolerability was based on the reporting of adverse events in patient diaries.	Asthenia: zol=1.9%, 1.6%, 7.0%; pla=1.7% Parathesia: zol=0, 0, 5.3%; pla=0 Somnolence: zol=0, 3.3%, 5.3%; pla=1.7%	

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Evidence Table 3b.Triptans vs. placebos: Characteristics and outcomes

Author Year Country Trial Name (Quality Score)	Study Design	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment
Carpay 2004 Europe *Fair quality*	RCT DB Parallel group Single attack	Between 18 and 65 years of age; at least 1-year history of migraine (IHS criteria) with or without aura; 1-6 attacks/month in preceding 2 months; history of moderate to severe migraines typically preceded by a mild-pain phase. Patients were eligible for the study regardless of previous experience with triptan therapy.	Sumatriptan rapid release (SRR) formulation 50 mg and 100 mg Placebo	Acute migraine medication (excluding an ergo-containing medication or a triptan) allowed from 2 through 24 hours after dosing for patients who were not pain free at 2 hours or who had a return of moderate or severe pain and did not wish to take a second dose of study medication	Primary efficacy endpoint=proportion of patients who were pain free 2 hours after dosing Severity rated using 4-point scale (0=none; 1=mild; 2=moderate; 3=severe) recorded on a diary card before dosing and 30 minutes, 45 minutes, 1 hour and 2 hours after dosing

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Evidence Table 3b.Triptans vs. placebos: Characteristics and outcomes

Author Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Carpay 2004 Europe *Fair quality*	n=481 mean age=40.6 82.9% female 99% white	Without aura only=78.7% With aura only=8.3% With and without aura=13% Using triptans at study entry=75% Used triptans in past year=4.6% Used triptans sometime in past=6.2% Never used triptans=14.1% *Severity at onset* Mild=93.5% Moderate=5.3% Severe=1.1%	nr/nr/481 randomized/432 treated a migraine attack and provided ≥ 1 postdose efficacy assessment	37(8.6%) withdrawn/9(2.1%) lost to fu/432 analyzed

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Evidence Table 3b.Triptans vs. placebos: Characteristics and outcomes

	Results			
Author Year Country Trial Name (Quality Score)	**Relief at various times**	**Pain Free at various times (% patients)**	**Presence of migraine-associated symptoms at 2 hours**	**Other efficacy outcomes**
Carpay 2004 Europe *Fair quality*	nr	SRR100 vs SRR50 vs placebo 30 minutes: 10.6* vs 3.6 vs 1.9 45 minutes: 24.6§ vs 18.2‡ vs 9.1 1-hour: 44.4§ vs 36.5* vs 18.9 2-hours: 66.2§ vs 51.1§ vs 19.6 Sustained (2-24 hours) pain-free: 32.1* vs 40.1* vs 9.8	SRR50 vs SRR100 vs placebo Nausea: 15.6* vs 22.3* vs 38.4 Photophobia: 25.4* vs 23.6* vs 48.7 Phonophobia: 23.1* vs 20.4* vs 43	SRR50vs SRR100 vs placebo Migraine-free (pain-free *AND* no associated symptoms) 30 minutes: 3.7 vs 7.1* vs 2 45 minutes: 14.7 vs 16.4* vs 7.3 1 hour: 30.1* vs 31.4* vs 17.2 2 hours: 44.9* vs 50.7* vs 17.1

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Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Comments
Carpay 2004 Europe *Fair quality*	Tolerability was assessed by calculating the incidence of specific adverse events, defined as any untoward medical occurrences, regardless of suspected cause, that were reported by a patient or noted by a clinician during the study	SRR50 vs SRR100 vs placebo (% patients) Overall drug-related adverse events: 10.2% vs 16.9* vs 5.2 Nausea and vomiting: <1 vs 5 vs 2 Chest symptoms: 2 vs 3 vs 0 Malaise and fatigue: 1 vs 3 vs <1	

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