# Drug Class Review on Triptans

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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) |
| Alniditan | not available** | |
| Avitriptan | not available** | |
| Donitriptan | not available | |
| Eletriptan | Oral | 20, 40, 80 † |
| Frovatriptan (Frova) | Oral | **2.5** |
| Naratriptan (Amerge) | Oral | **2.5** (1, 5) |
| Rizatriptan (Maxalt) | oral, sublingual wafer | **10** (5) |
| Sumatriptan (Imitrex) | oral, S.C., intranasal | Oral: 25, 50, 100 sc: **6** |
| Zolmitriptan (Zomig) | Oral | **2.5** (1, 5) |

* **Usual recommended dose** is bold. For sumatriptan, maker now states that 100 mg is the recommended oral dose.
** Development ceased.
† Approved by the FDA in December, 2002. Eletriptan is being marketed in 20 mg, 40 mg, and 80 mg tablets, but Pfizer cautions that 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 also 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] as well as several 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 2 hours, is measured on a 4-point scale (severe, moderate, mild, none.) Typically, patients must wait until they have a moderate to severe headache before taking the study medication. Two hours after taking the medication, the patient rates the severity of headache again. A "response" is defined as a reduction in headache from "moderate" or "severe" to "mild" or "none."

Overdependence on the two-hour pain relief measure has been criticized. As mentioned earlier, the main criticism is that a 2-hour response may not be as important to patients as some other measures, such as pain-free response or time to response. Another criticism is that the change from "moderate/severe" 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 or 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* relief pain or other symptoms? |
| Functional status/disability | Migraine Disability Assessment Scale (MIDAS) and various others |

*"Meaningful migraine relief" is a global measure that combines function and pain response

Finally, if a patient responds well to a triptan, consistently, and without experiencing disabling side effects, she may prefer it to triptans that have a higher overall 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, reader to 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 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 key questions for this review were:

1. 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?

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?

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?

These questions, and the eligibility criteria for this systematic review, were developed and refined with input from a subcommittee comprised of local experts (pharmacists, primary care clinicians, and individuals who have migraine headaches.)

## Methods

### Eligibility criteria

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

1. Adult patients with migraine. 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 Library (*2nd Quarter 2003*), Medline (1966- *August Week 2 2003*), EMBASE (1980-*3rd Quarter 2003*), 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.) 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] Finally, we searched Premedline on 1/29/03, specifically looking for trials of frovatriptan and eletriptan. All citations were imported into an electronic database (EndNotes™ 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 followup, 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 A). 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. Some trial characteristics that greatly reduce applicability to practice were incorporated into our exclusion criteria: for example, we excluded trials that recruited patients who did not have migraine headaches, evaluated triptans that are not marketed in the U.S., or used encapsulated a drug that is normally delivered as a tablet.

Other 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 an evidence table 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 2 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 by-study results when appropriate.

# Results

## Overview

Searches identified 1,132 citations: 46 from Cochrane Central Register of Controlled Trials (2nd Quarter 2003), 333 from Medline (1966 to August Week 2 2003), 645 from EMBASE (1980 to 3rd Quarter 2003), 49 from manufacturer dossiers and 59 from hand searching and reference lists. We excluded 225 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. Reasons for exclusion of these and 862 other publications are detailed in Figure 1.

## 1. What is 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. A major flaw of this study is that 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. This flaw invalidates the study's results for eletriptan. The main results of the study are summarized in Appendix B, Table 1.

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 B, Table 2), 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 B, Table 3). 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 B, Table 4.

## Randomized, controlled head-to-head trials

Of the 31 randomized, controlled head-to-head trials of various triptans, eight met the inclusion criteria for this key question. As summarized in Appendix C, most of the excluded head-to-head trials were reported only in abstract form[22-32] or were of poor internal validity.[33] In addition, six trials[28, 34-38] used encapsulated sumatriptan rather than standard sumatriptan tablets; we analyzed these separately. Four of these trials compared eletriptan to sumatriptan, one compared rizatriptan to sumatriptan, and one compared almotriptan to sumatriptan. While data about the effects of encapsulation are conflicting,[39-41] uncertainty about its effect implies that, other things being equal, studies that used encapsulation provide lower-quality evidence than head-to-head trials that used a double-dummy design. We plan to present our statistical analysis of the effects of encapsulation in a future update. The results of recent studies that used encapsulation are summarized in Appendix D.

Table 4 summarizes the design characteristics of the eight 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.

Table 5 summarizes the results of the eight included trials by outcome measure. Portions of Table 5 are repeated in the following sections, which describe the results for each reported endpoint. Six of the eight trials had a sumatriptan comparator. In these trials, sumatriptan was compared with rizatriptan (2 trials), zolmitriptan (3 trials), and naratriptan (1 trial). The 2 other trials compared rizatriptan to naratriptan and to zolmitriptan.[42, 43] None of the included studies evaluated almotriptan, eletriptan, or frovatriptan (See Appendix C).

Pain relief by two hours. All eight included trials reported two-hour headache response rates, which was usually the primary study endpoint.

*Naratriptan vs. sumatriptan.* One of the two included trials was a randomized, double-blind dose-ranging study that compared naratriptan 1, 2.5, 5, 7.5, and 10 mg 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 4 hours. From 85 to 98 patients were in each group. Results indicated similar response rates at two hours for all studied dosages of naratriptan and sumatriptan (52%, 54%, 68%, and 69% 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 vs. 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 1 hour (38.7% vs. 27.8%) and at 2 hours (68.7% vs. 48.7%). Also at 2 hours, rizatriptan was more likely to result in a pain-free response (44.8% and 20.7%) and in normal function (39.3% vs. 22.6%). More patients had a sustained pain-free response for 24 hours with rizatriptan (29% vs. 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 2 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 vs. 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 vs. zolmitriptan.* A trial of zolmitriptan 2.5 vs. rizatriptan 10 mg.[42] found no difference in 2-hour pain relief. No trials comparing zolmitriptan 5 mg vs. rizatriptan 10 mg were identified.

*Sumatriptan vs. 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 2 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% vs. 59.6%; $p<0.001$).[49]

Pain outcomes by one-half hour and by one hour. Three included head-to-head trials reported headache relief and pain-free responses at 0.5-hour. These trials found no differences

between rizatriptan 10 mg and naratriptan 2.5, sumatriptan 50 mg or 100 mg, and zolmitriptan 2.5 mg.

**Table 6a. 0.5-hour pain relief(% of patients)**

| Ref. | Internal Validity | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | N2.5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof [43] | Fair | NS | - | 14 | - | - | - | - | - | 11 |
| Pascual [42] | Fair | NS | - | 14 | - | - | - | 14.9 | - | - |
| Tfelt-Hansen [47] | Fair | NS | 12 | 13 | - | - | 11 | - | - | - |

**Table 6b. 0.5-hour pain free(% of patients)**

| Ref. | Internal Validity | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | N2.5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof [43] | Fair | NS | - | 1.5 | - | - | - | - | - | 1 |
| Pascual [42] | Fair | NS | - | 2.7 | - | - | - | 0.7 | - | - |
| Tfelt-Hansen [47] | Fair | NS | 1 | 2 | - | - | 1 | - | - | - |

More information is available for headache relief and headache-free outcomes in the first hour post-dose. Seven included head-to-head trials studied headache relief at one hour. The results of these trials are shown in the table below. (In the table, as in Table 5, statistically significant comparisons are indicated by bold type.) In a series of four fair-quality trials, 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.)

In other studies, 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]

**Table 7. One-hour pain relief(% of patients)**

| Ref. | Internal Validity | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | N2.5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Havanka[44] | Poor-Fair | NS | - | - | - | - | 35 | - | - | 30 |
| Bomhof[43] | Fair | p<0.029 | - | **38** | - | - | - | - | - | **27.8** |
| Pascual[42] | Fair | p<0.03 | - | **42.5** | - | - | - | **35.3** | - | - |
| Tfelt-Hansen[47] | Fair | p=0.010 | 30 | **37** | - | - | **28** | - | - | - |
| Geraud[50] | Fair | NS | - | - | - | - | 35 | - | 34 | - |
| Gallagher[49] | Good | p=0.017 | - | - | 39.2 | **41.7** | - | 43.4 | **45.5** | - |
| Gruffyd-Jones[48] | Good | NS | - | - | - | 38 | - | 36.9 | 39.5 | - |

Five of the trials reported the proportion of patients who were pain-free by one hour. For this endpoint, sumatriptan 100 mg was similar to rizatriptan 10 mg [47] and to zolmitriptan 5 mg,[50] sumatriptan 50 mg was similar to almotriptan 12.5 and zolmitriptan 5 mg, and rizatriptan 10 mg was similar to zolmitriptan 2.5 mg. In one trial, a higher proportion of patients who took rizatriptan 10 mg versus naratriptan 2.5 mg were pain-free at one hour (9.5% vs. 3.3%, $p<0.05$).[43] In a published crossover study, rizatriptan 10 mg was superior to sumatriptan 50 mg (11.1% vs. 7.6% for pain-free at one-hour, $p<0.05$). However, another crossover trial (Study #

052) similar in design to this one and conducted by the same investigators, has not been published, raising a question of publication bias.

Pain-free at 2 hours. Compared with naratriptan 2.5 mg, sumatriptan 100 mg, and zolmitriptan 2.5 mg, more patients taking rizatriptan 10 mg were pain-free 2 hours. Sumatriptan 100 mg and zolmitriptan 5 mg had similar efficacy.

**Table 8. Two-hour pain-free(% of patients)**

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof[43] | Fair | <0.001 | - | - | **20.7** | - | **44.8** | - | - | - | - | - |
| Pascual[42] | Fair | <0.05 | - | - | - | - | **43.2** | - | - | - | **35.6** | - |
| Tfelt-Hansen[47] | Fair | <0.05 | - | - | - | 25 | **40** | - | - | **33** | - | - |
| Lines[51] | Fair | NS | - | - | - | 22 | - | - | 28 | - | - | - |
| Geraud[50] | Fair | NS | - | - | - | - | - | - | - | 30 | - | 29 |
| Gruffyd-Jones[48] | Good | NS | - | - | - | - | - | - | 35.3 | - | 32.4 | 36 |

Satisfaction. Four included 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[42] 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 (62.7% vs. 54.6%; p=0.045). One trial[43] reported a higher mean satisfaction score for patients taking rizatriptan 10 mg than those taking naratriptan 2.5 mg (3.55 vs. 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. The two-hour satisfaction of patients taking sumatriptan 50 mg didn't differ from those taking zolmitriptan 2.5 mg, either.

Return to normal function. Four trials reported results of patients' records of their functional disability at 1, 1.5, and 2 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). All three trials compared rizatriptan 10 mg to other triptans. At 1 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% vs. 9%; p=0.031). At 1.5 hours, one trial[47] demonstrated superiority of rizatriptan 10 mg to sumatriptan 100 mg (27% vs. 19%; p=0.017). Finally, at 2 hours, four trials[33, 42, 43, 47] showed continued superiority of rizatriptan 10

mg over sumatriptan 50 mg (47% vs 42%; p=0.033) and 100 mg (42% vs. 33%; p=0.015), naratriptan 2.5 mg (39.3% vs. 22.6%; p<0.001) and zolmitriptan 2.5 mg(45.4% vs. 37%; p=0.025).

Endpoints at 24-hours. The trials used inconsistent methods to measure outcomes at 24 hours (see Table 5). 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 2 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,[52] Colman),[53] zolmitriptan 5 mg [50] or rizatriptan 10 mg.[47] There were also no differences between sumatriptran 50 mg and zolmitriptan 2.5 mg [48, 49] or rizatriptan 5 mg.[51] 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. 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.

Three trials reported use of additional medication or escape medication from 2 to 24 hours; none found significant differences. The results are shown in the table below.

**Table 9. Use of additional or escape medications (% patients)**

| Ref. | Internal Validity | Escape or additional medication | P value | A12.5 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof[43] | Fair | Additional | NS | - | 46.5 | - | 40.3 | - | - | - | - | - |
| Pascual[42] | Fair | Additional | NS | - | - | - | 39.4 | - | - | - | 43.6 | - |
| Gruffyd-Jones[48] | Good | Escape | NS | - | - | - | - | - | 23 | - | 23.6 | 22.2 |

Relief of migraine-related symptoms. Seven 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% vs. 67%; p<0.05)[47] and zolmitriptan 2.5 mg (74.8 vs. 67.5; p=0.046).[42] 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% vs. 47.2; p<0.05) and zolmitriptan 2.5 mg (64.4% vs. 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.

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] Results from the remaining trials were insignificant.

Only three 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, 54] 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 and 1043 completed the study. To measure consistency, the authors calculated the proportion of patients who responded at 2 hours in 80% to 100% of attacks (Table). The results indicate that the 2-hour response is not a reliable indicator of consistency across multiple attacks.

**Table 10. 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.[55] 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 2-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 vs. 35.7%, p <= 0.001)[56] In another randomized, open-label, crossover trial,[57] 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.[58] 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.[59]

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 6) 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 11. 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[52] | Almotriptan, 12.5 mg, open study | 806 | 1 year | 81% | Yes | 51.3% of patients |
| Gerth, 2001[60] Mathew, 2002[61] | Almotriptan, 12.5 mg, open study | 582 | 6 months | 76% | Yes | Drug-related chest pain 1.5% |
| Pascual, 2001[62] | Almotriptan, 12.5 mg, open study | 762 | 1 year | 84.2% | Yes | 51.3% |
| Heywood, 2000[63] | Naratriptan, 2.5 mg, open study | 417 | 1 year | 70% | Yes | 16% of attacks |
| Cady, 2001[64] | Rizatriptan wafer, various doses, open study | 458 | 6 months | 82% | Yes | |
| Tansey, 1993[65] | Sumatriptan, 100 mg, open study | 288 | 1 year | 84% | Yes | 16% |
| Tepper, 1999[66] | Zolmitriptan, 2.5 and 5 mg, open study | 2,499 | 9 months | ~85% | Yes | 65.7% |
| Cady, 1998[67] | 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.[68-73] 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 trials demonstrated reductions in self-reported work and productivity loss among patients taking oral rizatriptan.[74] Productivity was also an outcome measure in a trial of stratified vs. stepped care for migraine that involved zolmitrptan.[75] Open-label, nonrandomized study data also supports the view that use of oral sumatriptan improves work attendance, productivity, and quality of life.[70, 76, 77] and reduces disability and health care utilization.[78, 79] Other improved outcomes evaluated in observational studies include health-related quality of life (rizatriptan[70] and zolmitriptan[80]).

## Trials of triptans vs. active controls

Twenty trials of triptans versus other treatments to shorten a migraine attack met the inclusion criteria.[60, 68, 71, 72, 81-97] These trials are summarized in Appendix E, Tables 1 and 2. All but 5[60, 94-97] 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[81] comparing sumatriptan 100 mg to cafergot (2 mg ergotamine tartrate, 200 mg caffeine) and one trial[96] comparing zolmitriptan 2.5 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%; $p<0.001$).

Eight trials reported pain relief at two hours. Three of these trials noted significant findings.[81, 94, 95] 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 five trials found no significant differences between either sumatriptan (50 mg and 100 mg) or zolmitriptan 2.5mg vs metoclopramide combinations, domperamil or tolfenamic acide.

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). The remaining trial found no significant difference between sumatriptan 100 mg and tolfenamic acid in two-hour pain free effectiveness.[89]

In two trials,[81, 84] 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.[94]

However, an additional two trials[90, 92] 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[85, 86, 90, 98] demonstrated an earlier restoration of ability to resume activities of daily living in patients taking various preparation types of sumatriptan. One trial[88] 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[94] reported that more patients taking rizatriptan 10 mg were functioning normally at 2 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.[84, 86, 92, 99] However, in three additional trials,[81, 83, 96] small between-groups differences in withdrawals due to adverse events favored the triptans.

## 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 requires 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.[100, 101]

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.[102] In a small 1996 pilot study, 3 of 16 patients who gave themselves zomitriptan during the aura did not develop a migraine headache, versus 0 of 16 for placebo.[103] In a small randomized trial, 50% of patients who took a rizatriptan sublingual wafer at the onset of headache experienced complete relief by 1 hour—but so did 50% of patients who took a placebo.[104] 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.[105]

## Cluster headache

Cluster headaches cause unilateral excruciating pain associated with autonomic disturbances. Episodes usually last from 15 minutes to 2 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.[106-108] 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.[109] 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.[110] The only published trial of sumatriptan nasal spray found that it is much less effective than sumatriptan given subcutaneously.[111]

Oral zolmitriptan was evaluated for cluster headache in one double-blind, randomized crossover trial.[112] 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.

### 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.[113] 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 Table 5. Generally, descriptions of the methods used to assess intensity, duration, seriousness and relationship to study medication were unclear or not provided. In general, 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% vs. 1%; p<0.05), but was not different for sumatriptan 100 mg and rizatriptan 10 mg (6% vs. 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% vs. 2%; p<0.05), but was not different for sumatriptan 100 mg and rizatriptan 10 mg (8% vs. 8%).[47]

### 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.[114] 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.[115]

Two placebo controlled trials published in 2002[116, 117] (Appendix F Tables 1 and 2) 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 2 hours, 24-hour recurrence, escape medication use, relief of associated symptoms at 2 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.[118-122] 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.[123] 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.[124-126]

We identified one double-blind RCT of a triptan to prevent migraines associated with menses.[127] In this trial, across 4 menstrual periods, more patients treated with naratriptan, 1 mg, were headache-free 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.[128]

## 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. Of the 8 head-to-head trials that met our inclusion criteria, only 4 compared the currently recommended dosages of both drugs: sumatriptan 100 mg has been compared with naratriptan 2.5 mg, rizatriptan 10 mg, and zolmitriptan 5 mg; and naratriptan 2.5 mg has also been compared with rizatriptan 10 mg. The main findings of these 4 studies were:

- A fair-to-poor-quality trial found naratriptan 2.5 mg and sumatriptan 100 mg to be similar in several efficacy measures except for 4-hour pain relief, for which sumatriptan 100 mg was superior (NNT=6). Adverse events were similar.
- A fair-quality trial found rizatriptan 10 mg to be more efficacious than sumatriptan 100 mg in some efficacy measures (1-hour pain relief (NNT=11), 2-hour pain-free (NNT=14), return to normal function by 1 hour and 2 hours (NNT=9), and nausea-free at 2 hours (NNT=12.5). For other efficacy measures and for adverse events, the two drugs were similar.
- A fair-quality trial found no differences between zolmitriptan 5 mg and sumatriptan 100 mg on any efficacy or tolerability measure.

- A fair-quality trial found rizatriptan 10 mg to be more efficacious than sumatriptan 100 mg in some efficacy measures (1-hour pain relief (NNT=9), 1-hour pain free (NNT=16), 2-hour pain relief (NNT=5), 2-hour pain-free (NNT=4), and relief of photophobia (NNT=8). For other efficacy measures and for adverse events, the two drugs were similar.

The remainder of the included studies, including the only two good-quality ones, used sumatriptan 50 mg, formerly the standard dosage in the U.S., or zolmitriptan 2.5 mg, as a comparator. No triptan had an advantage in 24-hour quality of life or satisfaction after 24 hours, and, except for zolmitriptan 5 mg vs. sumatriptan 50 mg, the consistency of response, patient satisfaction with treatment over time, and patient preference over time have not been evaluated in head-to-head double-blind trials of triptans.

None of the included head-to-head trials evaluated almotriptan, eletriptan, or frovatriptan. The results of a published trial of almotriptan 12.5 mg vs. encapsulated sumatriptan are summarized in Appendix D.[35, 53] Apart from encapsulation, the study had serious flaws and was rated poor-quality (see Appendix C). We identified three published trials of eletriptan vs. encapsulated sumatriptan 100 mg.[28, 36, 38] The results, summarized in Appendix D, suggest that eletriptan 80 mg and, to a lesser extent, eletriptan 40 mg, have advantages over sumatriptan 100 mg. Because of the use of encapsulated sumatriptan, there is more uncertainty about these findings than studies of comparable quality that used standard sumatriptan. To shed light on this issue, Ferrari and colleagues compared the efficacy of sumatriptan 100 mg in these eletriptan trials to its efficacy in other head-to-head trials.[11] They found (page 647): "The efficacy rates [for sumatriptan 100 mg] are remarkably consistent across companies except for substantially lower pain-free and sustained pain-free rates in the Pfizer-conducted eletriptan-sumatriptan comparator studies. In these studies sumatriptan 100 mg performed less well than in studies conducted by other companies." A third trial of compared eletriptan to sumatriptan in sumatriptan-naive patients, but has been published only in abstract form.[29]

Three additional trials (n=2,139) of eletriptan, sumatriptan and placebo (Pfizer protocols 160-305, 160-307 and 160-318) were cited in a 2001 meta-analysis.[18] An abstract of a trial (n=514) of the effect of eletriptan, sumatriptan and placebo on time loss and overall impact in migraineurs was made available by Pfizer, Inc. dossier. These sources provided insufficient detail to fully rate results and quality. It is unclear as to whether sumatriptan was encapsulated or if the rates of pain relief, pain-free response and other efficacy endpoints for eletriptan and sumatriptan are comparable to those from the trials reported in full detail, discussed above.

Observational data support a high level of consistency of effectiveness over time for patients who respond to sumatriptan, rizatriptan, naratriptan, and zolmitriptan. However, there are no reliable data directly comparing long-term consistency in patients randomized to different triptans.

There is no evidence that any triptan is less effective in one or another group, but evidence is limited to retrospective analyses of placebo-controlled trials, most of which included relatively few or no elderly or Black subjects.

While adverse event rates vary among the triptans, there is limited information about the comparative duration and severity of adverse events or about their impact on quality life. Methods for assessing adverse events are not comparable across studies, and most studies do not take into account the severity of the event.

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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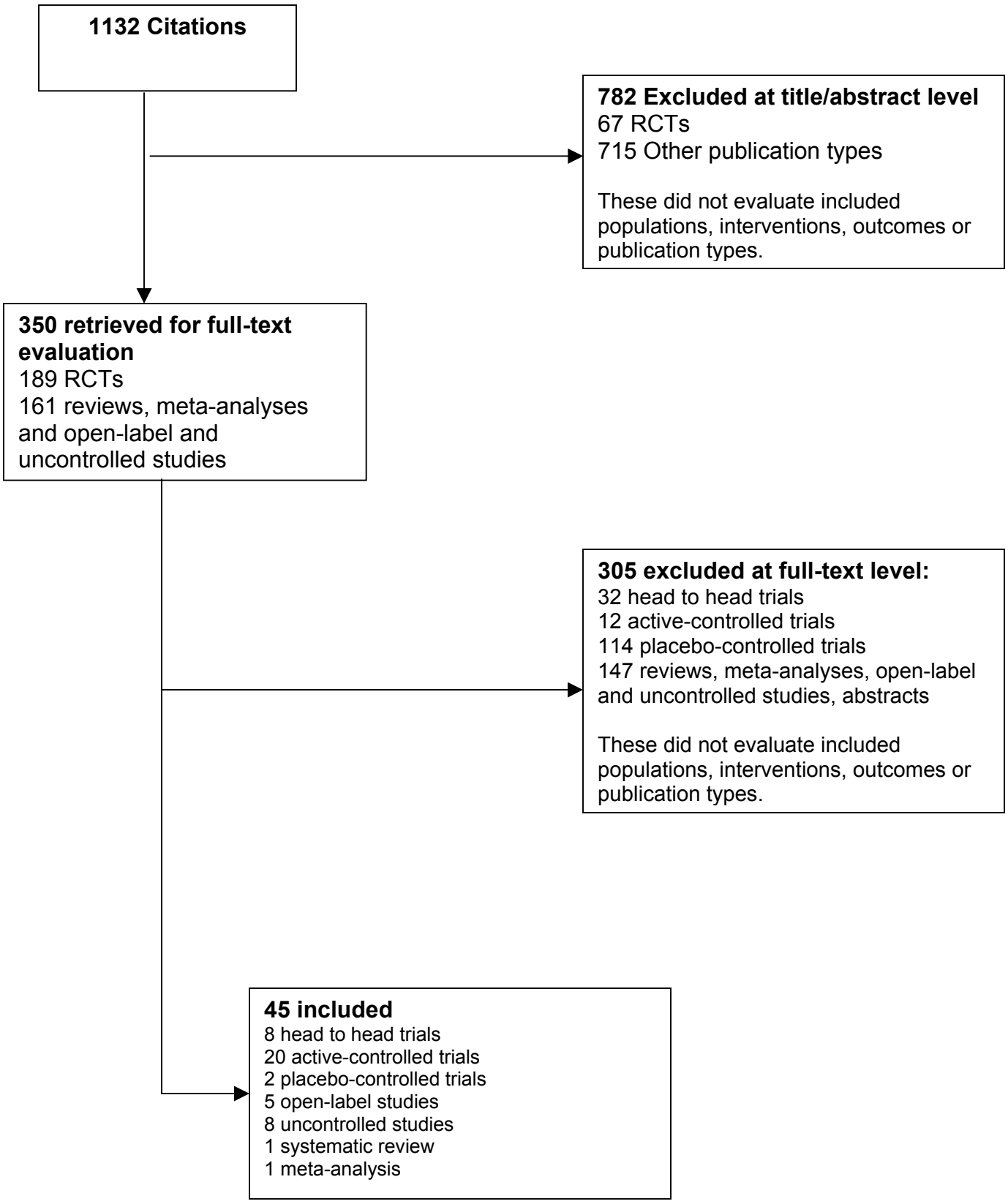
**Figure 1: Triptans Drug Class Review Flow Diagram**



## Table 4. Head-to-head trials of oral triptans

| Author, Year | Design | Setting | Number randomized | Age Gender Ethnicity | Patients | Inclusion criteria | Exclusion 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<br>88% women<br>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 | 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. |
| Bomhof 1999 | Multicenter single-dose RCT conducted in Europe of naratriptan vs. rizatriptan | Not stated | 618 | 39 years<br>84% female<br>82% white<br>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. | H.O cva, cardiovascular disease, significant ecg abnormality, history or drug or alcohol use, past use of study drugs |
| 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<br>83% female<br>77% white<br>19% Hispanic | I H S criteria 18-65 men and women. | 6-month history of migraine; 1-8 reports per month. | Cardiovascular disease, hypertension, EKG abnormality; drug or alcohol abuse; pregnant or breast-feeding |
| Tfelt-Hansen 1998 | Multicenter single-dose DB RCT conducted in Europe of rizatriptan vs. sumatriptan | Not stated | 1268 | 38 years<br>81% female<br>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 | CVD, hypertension, drug or alcohol abuse; pregnant or nursing. |
| Lines 1997<br>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<br>80% women<br>ethnicity nr | I H S criteria 18-65 men and women. | 6-month history of migraine; 1-8 attacks per month | nr |

## Table 4. Head-to-head trials of oral triptans (continued)

| Author, Year | Design | Setting | Number randomized | Age Gender Ethnicity | Patients | Inclusion criteria | Exclusion 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<br>85% female<br>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. | 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. |
| 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<br>85% female<br>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. | H/o ischemic heart disease, arrhythmia, hypertension, some types of migraine; drug or alcohol abuse, abnormal lab tests |
| Gruffyd-Jones 2001 | Multicenter, double-dummy RCT conducted in 21 countries of zolmitriptan vs. sumatriptan. | Not stated | 1787 | 42 years<br>86% female<br>96% white | HIS criteria<br>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. | 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. |

## Table 4. Head-to-head trials of oral triptans (continued)

| Author, Year | Funding sources and role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to fu | Internal validity | External validity | Comments |
|---|---|---|---|---|---|---|---|
| Havanka 2000 | Glaxo, co-investigator | Prophylactic medications stopped 1 week before the study; rescue drugs not permitted | NR | NR | Fair; but baseline information inadequate | Poor-fair; possibly a highly selected population | |
| Bomhof 1999 | Merck, co-investigator (maker of rizatriptan) | Permitted | NR | 96 (did not take study medication) | Fair + | Fair. | |
| Pascual 2000 | 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) | Fair + | Fair. | Stratified by prior use of triptans. |
| Tfelt-Hansen 1998 | Merck, co-investigator | Escape medication permitted; NSAIDs not permitted | NR | 169 (did not take study medication)/2 lost to fu | Fair - rizatriptan group were 2.2 years younger. | Fair. | |
| Lines 1997 Lines 2001 | 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) | Fair | | |

## Table 4. Head-to-head trials of oral triptans (continued)

| Author, Year | Funding sources and role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to fu | Internal validity | External validity | Comments |
|---|---|---|---|---|---|---|---|
| Geraud 2000 | Maker of zolmitriptan, co-investigator | Permitted | NR | 253; 225 did not take medication, 28 were lost to followup | Fair + (more information about baseline characteristics provided; but high loss to f/u | Fair | |
| Gallagher 1999, 2000 | Zeneca, co-investigator | Some permitted | NR | 233 who had only 1 headache | 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 | Astra-Zeneca, funder | Most prohibited | NR | 620, many because they did not have 6 attacks | Good except for high dropout rate, but dropout wasn't different among groups. | Selected for consistent migraine over months. | |

## Table 5. Results of triptan head-to-head trials

**0.5-Hour Pain Relief** % of patients

| Ref. | Internal Validity | p value | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | NS | 11 | - | 14 | - | - | - | - | - |
| Pascual | Fair | NS | - | - | 14 | - | - | - | 14.9 | - |
| Tfelt-Hansen | Fair | NS | - | 12 | 13 | - | - | 11 | - | - |

**0.5-Hour Pain Free** % of patients

| Ref. | Internal Validity | p value | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | NS | 1 | - | 1.5 | - | - | - | - | - |
| Pascual | Fair | NS | - | - | 2.7 | - | - | - | 0.7 | - |
| Tfelt-Hansen | Fair | NS | - | 1 | 2 | - | - | 1 | - | - |

**1 Hour Pain Relief** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Havanka | Poor-Fair | NS | - | - | 30 | - | - | - | - | 35 | - | - |
| Bomhof | Fair | p<0.029 | - | - | **27.8** | - | **38** | - | - | - | - | - |
| Pascual | Fair | p<0.05 | - | - | - | - | **42.5** | - | - | - | **35.3** | - |
| Tfelt-Hansen | Fair | p<0.05 | - | - | - | 30 | **37** | - | - | **28** | - | - |
| Geraud | Fair | NS | - | - | - | - | - | - | - | 35 | - | 34 |
| Gallagher | Good | p=0.014 | - | - | - | - | - | 39.2 | **41.7** | - | 43.4 | **45.5** |
| Gruffyd-Jones | Good | NS | - | - | - | - | - | - | 38 | - | 36.9 | 39.5 |

**1 Hour Pain Free** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | <0.05 | - | - | **3.3** | - | **9.5** | - | - | - | - | - |
| Pascual | Fair | NS | - | - | - | - | 12.7 | - | - | - | 10.4 | - |
| Tfelt-Hansen | Fair | NS | - | - | - | 7 | 10 | - | - | 8 | - | - |
| Geraud | Fair | NS | - | - | - | - | - | - | - | 11 | - | 8 |
| Gruffyd-Jones | Good | NS | - | - | - | - | - | - | 11.4 | - | 9.1 | 12 |

## Table 5. Results of triptan head-to-head trials

**2 Hour Pain Relief** % of patients

| Trial | Internal | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Havanka (4-hr) | Fair-Poor | NS | - | - | 52 | - | - | - | - | 60 | - | - |
| Bomhof | Fair | <0.001 | - | - | **48.4** | - | **68.7** | - | **-** | - | - | - |
| Pascual | Fair | NS | - | - | - | - | 70.5 | - | **-** | - | 66.8 | - |
| Tfelt-Hansen | Fair | NS | - | - | - | 60 | 67 | - | **-** | 62 | - | - |
| Lines | Fair | NS | - | - | - | 63 | **-** | - | 67 | - | - | - |
| Geraud | Fair | NS | - | - | - | - | - | - | - | 61 | - | 59 |
| Gallagher | Good | <0.001 | - | - | - | - | - | **66.2** | 67.9 | - | **72.2** | **72.2** |
| Gruffyd-Jones | Good | NS | - | - | - | - | - | - | 66.6 | - | 62.9 | 65.7 |

**2 Hour Pain Free** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | <0.001 | - | - | **20.7** | - | **44.8** | - | - | - | - | - |
| Pascual | Fair | <0.05 | - | - | - | - | **43.2** | - | - | - | **35.6** | - |
| Tfelt-Hansen | Fair | <0.05 | - | - | - | 25 | **40** | - | - | **33** | - | - |
| Lines | Fair | NS | - | - | - | 22 | **-** | - | 28 | - | - | - |
| Geraud | Fair | NS | - | - | - | - | **-** | - | **-** | 30 | - | 29 |
| Gruffyd-Jones | Good | NS | - | - | - | - | **-** | - | 35.3 | - | 32.4 | 36 |

**24-Hour Sustained Relief** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Havanka | Poor-Fair | nr | - | - | 48 | - | - | - | - | 44 | - | - | |
| Bomhof | Fair | nr | - | - | 21 | - | 33 | - | - | - | - | - | |
| Pascual | Fair | nr | - | - | - | - | 28 | - | - | - | 29 | - | |
| Gallagher | Good | <0.001 | - | - | - | - | **-** | **33.1** | **-** | - | **40.7** | **42.5** | |
| Gruffyd-Jones | Good | nr | - | - | - | - | **-** | - | 30.6 | - | 30.3 | 29.9 | Sustained Recurrence rate |

## Table 5. Results of triptan head-to-head trials

**Satisfaction**

| Ref. | Internal Validity | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | N2.5 | | Recurrence rate Sustained |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pascual | Fair | 0.045 | - | **62.70%** | - | - | - | **54.60%** | - | - | 2 hr data | Recurrence rate |
| Havanka | Poor-Fair | NS | - | - | - | - | 51% | - | - | 49% | time NR | Recurrence rate |
| Bomhof | Fair | <0.001 | | **3.55** | - | - | - | - | - | **4.2** | 2hr mean | |
| Gruffyd-Jones | Good | NS | - | **-** | - | 65.90% | - | 65.80% | 69.70% | **-** | time NR | |

**Return to Normal Function** % of patients

| Ref. | Internal Validity | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | N2.5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pascual | Fair | 0.025 | - | **45.4** | - | - | - | **37** | - | - | 2 hr |
| Tfelt-Hansen | Fair | 0.031 | - | **14** | - | - | **9** | - | - | - | 1 hr |
| Tfelt-Hansen | Fair | 0.017 | - | **27** | - | - | **19** | - | - | - | 1.5 hr |
| Tfelt-Hansen | Fair | 0.015 | - | **42** | - | - | **33** | - | - | - | 2 hr |
| Bomhof | Fair | <0.001 | - | **39.3** | - | - | - | - | - | **22.6** | 2 hr |

**Treatment emergent adverse events**

**Cardiovascular system**

***Chest pain/tightness*** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | NS | - | - | 2 | - | 3 | - | - | - | - | - |
| Pascual | Fair | NS | - | - | - | - | 2 | - | - | - | 4 | - |
| Tfelt-Hansen | Fair | <0.05 | - | - | - | **1** | 3 | - | - | **6** | - | - |
| Lines | Fair | NS | - | - | - | 2 | - | - | 5 | - | - | - |
| Geraud | Fair | NS | - | - | - | - | - | - | - | 2 | - | 1 |
| Gallagher | Good | NS | - | - | - | - | - | 0.9 | 2.7 | - | 2.1 | 6.5 |
| Gruffyd-Jones | Good | NS | - | - | - | - | - | - | 3.1 | - | 3.4 | 5 |

## Table 5. Results of triptan head-to-head trials

**Central Nervous System**

***Dizziness*** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | NS | - | - | 5 | - | 8 | - | - | - | - | - |
| Pascual | Fair | NS | - | - | - | - | 5 | - | - | - | 6 | - |
| Tfelt-Hansen | Fair | NS | - | - | - | 6 | 8 | - | - | 9 | - | - |
| Lines | Fair | NS | - | - | - | 5 | - | - | 5 | - | - | - |
| Geraud | Fair | NS | - | - | - | - | - | - | - | 9 | - | 9 |
| Gallagher | Good | NS | - | - | - | - | - | 4.5 | 5 | - | 6.1 | 8 |
| Gruffyd-Jones | Good | NS | - | - | - | - | - | - | 5 | - | 3.4 | 5.7 |

***Paresthesia*** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Geraud | Fair | NS | - | - | - | - | - | - | - | 7 | - | 6 |
| Gallagher | Good | NS | - | - | - | - | - | 3.6 | 4.4 | - | 4.9 | 8 |
| Gruffyd-Jones | Good | NS | - | - | - | - | - | - | 5.4 | - | 5.3 | 5.2 |

***Somnolence*** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | NS | - | - | <1 | - | 5 | - | - | - | - | - |
| Pascual | Fair | NS | - | - | - | - | 6 | - | - | - | 4 | - |
| Tfelt-Hansen | Fair | NS | - | - | - | 7 | 9 | - | - | 7 | - | - |
| Lines | Fair | NS | - | - | - | 4 | - | - | 5 | - | - | - |
| Geraud | Fair | NS | - | - | - | - | - | - | - | 6 | - | 8 |
| Gallagher | Good | NS | - | - | - | - | - | 3.6 | 3.8 | - | 4.3 | 7.7 |
| Gruffyd-Jones | Good | NS | - | - | - | - | - | - | 4.5 | - | 3.1 | 5 |

## Table 5. Results of triptan head-to-head trials

***Fatigue/Asthenia*** % of patients

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | NS | - | - | 5 | - | 7 | - | - | - | - | - |
| Pascual | Fair | NS | - | - | - | - | 6 | - | - | - | 5 | - |
| Tfelt-Hansen | Fair | **<0.05** | **-** | **-** | - | **2** | 8 | - | - | **8** | - | - |
| Lines | Fair | NS | - | - | - | 7 | - | - | 5 | - | - | - |
| Geraud | Fair | NS | - | - | - | - | - | - | - | 11 | - | 11 |
| Gruffyd-Jones | Good | NS | - | - | - | - | - | - | 4.5 | - | 5.3 | 6.6 |

**Relief of migraine-related symptoms**

***Nausea (%without symptoms at 2 hours)***

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Havanka | Poor-Fair | stats ND | - | - | 70 | - | - | - | - | 70 | - | - |
| Bomhof | Fair | NS | - | - | 59.4 | - | 68.5 | - | - | - | - | - |
| Pascual | Fair | **0.046** | **-** | **-** | - | - | **74.8** | - | - | - | **67.5** | - |
| Tfelt-Hansen | Fair | **<0.05** | **-** | **-** | - | **77** | **75** | - | - | **67** | - | - |
| Geraud** | Fair | NS | - | - | - | - | - | - | - | 35 | - | 33 |
| Gallagher*** | Good | NS | - | - | - | - | - | % NR | % NR | - | % NR | % NR |
| Gruffyd-Jones** | Good | NS | - | - | - | - | - | - | 52 | - | 54 | 54 |

***Vomiting (%without symptoms at 2 hours)***

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | NS | - | - | 92.3 | - | 95.5 | - | - | - | - | - |
| Pascual | Fair | NS | - | - | - | - | 96.1 | - | - | - | 96.4 | - |
| Gallagher** | Good | NS | - | - | - | - | - | % NR | % NR | - | % NR | % NR |

## Table 5. Results of triptan head-to-head trials

***Photophobia (%without symptoms at 2 hours)***

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Havanka | Poor-Fair | stats ND | - | - | 56* | - | - | - | - | 61* | - | - |
| Bomhof | Fair | **<0.05** | **-** | **-** | **47.2** | - | **59.2** | - | - | - | - | - |
| Pascual | Fair | **0.029** | **-** | **-** | - | - | **64.4** | - | - | - | **56.5** | - |
| Tfelt-Hansen | Fair | NS | - | - | - | 57 | 61 | - | - | 58 | - | - |
| Geraud** | Fair | NS | - | - | - | - | - | - | - | 33 | - | 37 |
| Gallagher*** | Good | NS | - | - | - | - | - | % NR | % NR | - | % NR | % NR |
| Gruffyd-Jones** | Good | NS | - | - | - | - | - | - | 52 | - | 54 | 54 |

***Phonophobia (%without symptoms at 2 hours)***

| Ref. | Internal Validity | p value | A12.5 | A25 | N2.5 | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Bomhof | Fair | **<0.05** | **-** | **-** | **51.9** | - | **65** | - | - | - | - | - |
| Pascual | Fair | NS | - | - | - | - | 66.3 | - | - | - | 63.9 | - |
| Tfelt-Hansen | Fair | NS | - | - | - | 63 | 66 | - | - | 60 | - | - |
| Geraud** | Fair | NS | - | - | - | - | - | - | - | 36 | - | 39 |
| Gallagher*** | Good | NS | - | - | - | - | - | % NR | % NR | - | % NR | % NR |
| Gruffyd-Jones** | Good | NS | - | - | - | - | - | - | 53 | - | 57 | 54 |

*combined photophobia/phonophobia
**percent with symptoms at 2 hours
***time endpoint unclear

# Appendix A: Methods for Drug Class Reviews for Oregon Health Plan Practitioner-Managed Prescription Drug Plan

## Oregon Evidence-based Practice Center

**December 14, 2001**
**Updated February 4, 2003**

### Overview

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, in developing drug class reviews for the Oregon Health Plan Practitioner-Managed Prescription Drug Plan.

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. To ensure scientific rigor and relevance of the work, the Oregon EPC develops key questions and criteria for admissible evidence, and uses these to create a literature search strategy that best captures the appropriate evidence. To consider papers identified by the searches, the teams use the criteria for admissible evidence (explicit inclusion and exclusion criteria) to select papers that provide information to help answer the key questions. They abstract key data from these selected papers. The teams use established criteria to assess the internal validity of the evidence in each paper, as well as the total internal validity, external validity, and coherence of the evidence for each key question.

#### Key Questions and Inclusion/Exclusion Criteria

Key questions are essential in focusing the literature review on a manageable and clinically relevant topic. All key questions are reviewed and approved by the topic team in the process of assessing and refining the topic before the detailed literature review. The EPC teams work with the subcommittee members of the Oregon Health Resources Commission assigned to a particular drug class to finalize the key questions for that drug class.

We clearly document the criteria by which the team chooses to admit evidence on a given key question. Such criteria might include, for example, study design (e.g., randomized

controlled trials, cohort studies), setting, sample size, population studied, language(s) of publication, and year(s) of publication.

No generic criteria for admissible evidence have been established. Rather, the criteria are determined on a topic-by-topic and key question-by-key question basis, depending on the questions involved and the amount and quality of evidence available. All inclusion/exclusion criteria are reviewed and approved by the entire topic team.

#### Databases to Be Searched and Documenting Search Terms

At a minimum, all topics include a review of the English-language literature in MEDLINE and EMBASE bibliographic databases and the Cochrane Controlled Trials Register. Other databases (e.g., nursing or psychology databases) are searched as deemed necessary by the topic team. Evidence reviews document the databases used.

Search terms used for each key question, along with the yield associated with each term, are documented in a table or set of tables; these appear in the final evidence review.

#### Database of Abstracts

The EPC, for each review, establishes a database of all abstracts (i.e., both those included and those eventually excluded from the final set of full-text articles reviewed). Information captured in the database includes the key question(s) associated with each included abstract and reason for exclusion if the abstract does not meet inclusion criteria.

#### Abstraction Forms

Although the EPC has no standard or generic abstraction form, the following broad categories are always abstracted from included articles: study design, study participant description, quality information, and outcomes. Each team uses these (and, if indicated, other) general categories to develop an abstraction form specific to the topic at hand.

#### Double Abstraction of Included Articles

The EPC teams abstract only those articles that, after review of the entire article, meet criteria for both quality and focus on the key question at hand. Key articles are always read and checked by more than one team member. All reviewers are trained in the topic, the analytic framework and key questions, and the use of the abstraction instrument. Initial reliability checks are done for quality control.

## Quality Criteria

**Assessment of Internal Validity**
To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the US Preventive Services Task Force and the NHS Centre for Reviews and Dissemination.

***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 followup or overall high loss to followup? (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 followup? (Give numbers at each stage of attrition.)

***For Reports of 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 followup or overall high loss to followup? (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 followup 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?

**Economic Studies**

Assessment of Internal Validity

*Framing*

1. Was a well-defined question posed in answerable form?

2. Was a comprehensive description of the competing alternatives given?

3. Are the interventions and populations compared appropriate?

4. Is the study conducted from the societal perspective?

5. Is the time horizon clinically appropriate and relevant to the study question?

*Effects*

1. Are all important drivers of effectiveness included?

2. Are key harms included?

3. Is the best available evidence used to estimate effectiveness?

4. Are long-term outcomes used?

5. Do effect measures capture preferences or utilities?

*Costs*

1. Are costs and outcomes measured accurately?
2. Are costs and outcomes valued credibly?
3. Are costs and outcomes adjusted for differential timing?
4. Are all appropriate downstream medical costs included?
5. Are charges converted to costs appropriately?
6. Are the best available data used to estimate costs? (like first question)
7. Are all important and relevant costs and outcomes for each alternative identified?

*Results*

1. Are incremental cost-effectiveness ratios presented?
2. Are appropriate sensitivity analyses performed?
3. How far do study results include all issues of concern to users?

Assessment of External Validity

1. Are the results generalizable to the setting of interest in the review?

**Systematic Reviews:**

1. Is the systematic review recent and relevant?
2. Is the review comprehensive in considering sources and in searching databases to find all relevant research?
3. Are inclusion/exclusion criteria reported relating to the primary studies that address the review question? If so, are they explicit and relevant?
4. Are the primary studies summarized appropriately?
5. Is sufficient detail of the primary studies presented?
6. Is there standard appraisal of the primary studies?
7. Is the validity of primary studies adequately assessed?

8. Are there valid conclusions in the systematic review?

## Appendix B. Table 1. Oldman, 2002 meta-analysis

| Outcome | Summary of results |
|---|---|
| ***Headache relief at 2 hours*** | E80 and R10 significantly superior to R5, S50 and N2.5.<br>No differences between E40, Z5, S100, Z2.5. |
| ***Headache relief at 1 hour*** | E80 and R10 significantly superior to S50.<br>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<br>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.<br>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 B. Table 2. 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 B. Table 3. Summary table of Ferrari, 2001 meta-analysis

| | Efficacy |
|---|---|
| ***Response at 2 hours*** | E80, R10 and Z2.5 significantly superior<br>E20, F2.5 and N2.5 significantly inferior<br>Not significantly different from R5, S50, Z5 or any other triptan dosages |
| ***Pain free at 2 hours*** | A12.5, E80 and R10 significantly superior<br>E20, N2.5 and S25 significantly inferior<br>No significant differences between other triptan dosages |
| ***Recurrence of headache 2-24 hours*** | Recurrence rates lower for E40 and E80<br>Recurrence rates higher for R5 and R10<br>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<br>Significantly lower rates for E20, N2.5 and S25<br>No significant differences reported for other triptan dosages |
| ***Consistency rates*** | R10 and A12.5 superior<br>S25, N2.5E20 inferior<br>No significant differences reported for other triptan dosages |
| ***Tolerability*** | S25, N2.5, A12.5 superior<br>E80 inferior<br>No significant differences reported for other triptan dosages |

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

## Appendix B. Table 4. Summary table of Ferrari, 2002 meta-analysis (head-to-head trials)

| | Efficacy | Adverse events |
|---|---|---|
| ***Sumatriptan 100 mg*** | Equivalent to A12.5 and Z5.<br>Superior to N2.5.<br>Inferior to E40 and E80 and R10. | Equivalent to E40, R10 and Z5.<br>Caused fewer adverse events than E80.<br>Caused more adverse events than A12.5 and N2.5. |
| ***Sumatriptan 50 mg*** | Comparison to A12.5 and N2.5 nr.<br>Equivalent to R5, R10, Z2.5 and Z5 on all standard parameters.<br>Inferior to E40 and E80 on standard parameters and R10 on time to response. | Comparison to A12.5 and N2.5 nr.<br>Equivalent to R10, Z2.5 and Z5.<br>Caused less adverse events than E40, E80, and R5. |
| ***Sumatriptan 25 mg*** | Comparison to A12.5 and N2.5 nr.<br>Equivalent to E40.<br>Inferior to E80, R5, R10, Z2.5 and Z5. | Comparison to A12.5 and N2.5 nr.<br>Caused less adverse events than R5 on all parameters and less than R10 and Z2.5 in *overall* and *chest* AE incidences.<br>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 C. Excluded direct comparator trials

| Trial | Reason for exclusion |
|---|---|
| (Bates and Winter 1998) | Abstract only (naratriptan) |
| (Cabarrocas 1998), (Dowson, 2002) | Encapsulation **(Note 1)** |
| (Colman 2001) | Same as (Spierings 2001)/encapsulation and poor quality. (almotriptan) **(Note 1)** |
| (Dahlof 1998) | Wrong preparation (subcutaneous naratriptan vs. subcutaneous sumatriptan) |
| (Diener 1999) | Abstract of an included study (Pascual 2000) |
| (Diener 2001) | Wrong drug (alniditan) |
| (Goadsby 2000) | Encapsulated sumatriptan vs, eletriptan |
| (Gobel 2000) | Poor quality (discrepancy in group #'s) (naratriptan) **(Note 2)** |
| (Goldstein 1998) | Poor quality (rizatriptan) **(Note 3)** |
| (Gruffydd-Jones 1997) | Compared 2 forms of sumatriptans |
| (Jackson 1998) | Abstract only (eletriptan) |
| (Jhee 1999) | Wrong drug (avitriptan) |
| (Loder 2001) | Wrong drug (rizatriptan orally dissolving tablet) |
| (Longmore 1997) | Wrong outcomes (not in vivo) |
| (Pascual 2001) | Wrong preparation of rizatriptan (wafer) |
| (Pryse-Phillips and Committee 1999) | Abstract only (eletriptan) |
| (Sandrini 2002) | Encapsulated sumatriptan (eletriptan) |
| (Schoenen 1999) | Abstract only (naratriptan vs. zolmitriptan) |
| (Spierings 2001) | Encapsulated sumatriptan and poor quality (almotriptan) **(Note 1)** |
| (Visser 1996) | Encapsulated sumatriptan (vs. rizatriptan) |
| (Visser and Jiang 1998) | Abstract only (rizatriptan) |

# 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(Colman 2001) and in December, 2000(Spierings 2001). 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 (Gobel 2000). 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.(Gobel 2000) 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.(Salonen 2000) 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.(Schoenen 1999).

Another was completed but was also reported in abstract form only(Bates and Winter 1998). It compared sumatriptan 100 mg to 4 doses of naratriptan (0.1 mg, 0.25 mg, 1 mg, and 2.5 mg).(Bates and Winter 1998) 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.(Goldstein 1998) 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..(Visser and Jiang 1998)

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.(Ferrari 2002) 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(Geraud 2002) that did not include efficacy results.

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## Appendix D. Results of encapsulated sumatriptan head-to-head trials

### Headache response

***2 Hour Pain Relief*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | <0.01 | - | - | - | - | **55** | - | - | - | | - | 65 | **77** |
| Sandrini | <0.05 | - | - | - | 50 | **53** | - | - | - | | - | **64** | **67** |
| Spierings | NS | - | - | - | 57.3 | - | - | - | 58 | | - | - | - |
| Dowson | NS | - | - | - | - | 63.7 | - | - | 56.8 | 56.5 | - | - | - |
| Mathew, 2003 | <0.0001 | - | - | - | - | 59 | - | - | - | - | - | 67 | - |

***2 Hour Pain Free*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | <0.05 | - | - | - | - | **23** | - | - | - | | - | 29 | **37** |
| Sandrini | <0.05 | - | - | - | 19 | **18** | - | - | - | | - | **31** | **37** |
| Sandrini | <0.0005 | - | - | - | 19 | **18** | - | - | - | | - | 31 | **37** |
| Spierings | NS | - | - | - | 24.6 | - | - | - | 17.9 | | - | - | - |
| Dowson | NS | - | - | - | - | 33.7 | - | - | 27.9 | 34.5 | - | - | - |
| Mathew, 2003 | <0.0001 | - | - | - | - | 27 | - | - | - | - | - | 36 | - |

### Speed of headache response

***0.5-Hour Pain Relief*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | NS | - | - | - | - | 10 | - | - | - | - | 5 | 12 |
| Sandrini | n/a | - | - | - | nr | nr | - | - | - | - | nr | nr |
| Spierings | NS | - | - | - | 12.4 | - | - | - | 12.9 | - | - | - |

***0.5-Hour Pain Free*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | n/a | - | - | - | - | nr | - | - | - | - | nr | nr |
| Sandrini | n/a | - | - | - | nr | nr | - | - | - | - | nr | nr |
| Spierings | NS | - | - | - | 0.9 | - | - | - | 1.2 | - | - | - |

***1 Hour Pain Relief*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | <0.01 | - | - | - | - | **20** | - | - | - | - | - | **38** | **41** |
| Sandrini | <0.05 | - | - | - | 24 | 27 | - | - | - | - | - | 30 | 37 |
| Spierings | NS | - | - | - | 35.5 | - | - | - | 34.2 | - | - | - | - |
| Dowson | NS | - | - | - | - | 37.8 | - | - | 35.5 | 30.9 | - | - | - |
| Mathew, 2003 | <0.01 | - | - | - | - | 27 | - | - | - | - | - | 34 | - |

***1 Hour Pain Free*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | NS | - | - | - | - | 6 | - | - | - | - | - | 8 | 17 |
| Sandrini | <0.05 | - | - | - | **5** | 7 | - | - | - | - | - | 6 | **13** |
| Spierings | NS | - | - | - | 7.1 | - | - | - | 5.4 | - | - | - | - |
| Dowson | NS | - | - | - | - | 7.8 | - | - | 4.9 | 10.9 | - | - | - |
| Mathew, 2003 | NS | | | | | 5 | | | | | | 7 | |

## Appendix D. Results of encapsulated sumatriptan head-to-head trials

### Sustained headache response

***24-Hour Sustained Relief*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | NS | - | - | - | - | 33 | - | - | - | - | - | 34 | 32 |
| Sandrini | 0.005 | - | - | - | 34 | **38** | - | - | - | - | - | 50 | **54** |
| Spierings | NS | - | - | - | - | 24 | - | - | 27.4 | - | - | - | - |
| Dowson | NS | - | - | - | - | 24.6 | - | - | 18 | 15.4 | - | - | - |
| Mathew, 2003 | <0.0003 | - | - | - | - | 43 | - | - | - | - | - | 34 | - |

### Response of other migraine symptoms

***Nausea*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | NS | - | - | - | - | 34 | - | - | - | - | - | 30 | 22 |
| Sandrini | <0.05 | - | - | - | 40 | **42** | - | - | - | - | - | **29** | 35 |
| Spierings* | NS | - | - | - | 47 | - | - | - | 46.1 | - | - | - | - |
| Dowson | NS | - | - | - | - | 31 | - | - | 32 | 29 | - | - | - |
| Mathew, 2003 | <0.01 | - | - | - | - | 67 | - | - | - | - | - | 74 | - |

***Vomiting*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | n/a | - | - | - | - | nr | - | - | - | - | - | nr | nr |
| Sandrini | n/a | - | - | - | nr | nr | - | - | - | - | - | nr | nr |
| Spierings* | NS | - | - | - | 7.2 | - | - | - | 8.9 | - | - | - | - |
| Dowson | NS | - | - | - | - | 7.7 | - | - | 3.2 | 6.8 | - | - | - |

***Photophobia*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby** | NS | - | - | - | - | 43 | - | - | - | - | - | 37 | 29 |
| Sandrini | <0.05 | - | - | - | 49 | **46** | - | - | - | - | - | 40 | **30** |
| Spierings* | NS | - | - | - | 62.3 | - | - | - | 68.4 | - | - | - | - |
| Dowson | NS | - | - | - | - | 24.7 | - | - | 26.6 | 27.7 | - | - | - |
| Mathew, 2003 | <0.01 | - | - | - | - | 63 | - | - | - | - | - | 71 | - |

***Phonophobia*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | n/a | - | - | - | - | nr | - | - | - | - | - | nr | nr |
| Sandrini | <0.05 | - | - | - | 45 | **48** | - | - | - | - | - | **38** | 32 |
| Sandrini | <0.01 | - | - | - | 45 | **48** | - | - | - | - | - | 38 | **32** |
| Spierings* | NS | - | - | - | 55.8 | - | - | - | 60.2 | - | - | - | - |
| Dowson | NS | - | - | - | - | 17.5 | - | - | 20.1 | 23 | - | - | - |
| Mathew, 2003 | <0.01 | - | - | - | - | 67 | - | - | - | - | - | 74 | - |

### Functional status

***Return to Normal Function*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | nr | - | - | - | - | 42 | - | - | - | - | 32 | 23 |
| Sandrini | <0.005 | - | - | - | 46 | **46** | - | - | - | - | **63** | 55 |
| Spierings | n/a | - | - | - | - | nr | - | - | nr | - | - | - |
| Mathew, 2003 | <0.01 | | | | | 61 | | | | | 68 | |

## Appendix D. Results of encapsulated sumatriptan head-to-head trials

### Satisfaction

***Acceptibility*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | <0.0005 | - | - | - | - | **64** | - | - | - | - | 74 | **84** |
| Sandrini | <0.05 | - | - | - | **67** | 67 | - | - | - | - | **80** | **78** |
| Spierings | n/a | - | - | - | - | nr | - | - | nr | - | - | - |
| Mathew, 2003 | <0.01 | | | | | 56 | | | | | 64 | |

### Cardiovascular adverse effects

***Chest pain/tightness*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | NS | - | - | - | - | 7 | - | - | - | - | - | 7 | 7 |
| Sandrini | NS | - | - | - | 2 | 1 | - | - | - | - | - | 1 | 5 |
| Spierings | 0.004 | - | - | - | **2.2** | - | - | - | **0.3** | **-** | - | - | - |
| Dowson | NS | - | - | - | **-** | 1 | - | - | 0 | 1.6 | - | - | - |
| Mathew, 2003 | NS | - | - | - | **-** | 2 | - | - | **-** | **-** | - | 1.6 | - |

### Central nervous system adverse effects

***Dizziness*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | NS | - | - | - | - | 4 | - | - | - | - | - | 4 | 4 |
| Sandrini | NS | - | - | - | 7 | 5 | - | - | - | - | - | 7 | 12 |
| Spierings | NS | - | - | - | 1.7 | - | - | - | 2 | - | - | - | - |
| Dowson | NS | - | - | - | - | 2.1 | - | - | - | 2.1 | - | - | - |

***Parasthesia*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | NS | - | - | - | - | 5 | - | - | - | - | - | 2 | 8 |
| Sandrini | n/a | - | - | - | nr | nr | - | - | - | - | - | nr | nr |
| Spierings | NS | - | - | - | 0.9 | - | - | - | 1.2 | - | - | - | - |
| Dowson | NS | - | - | - | - | 3.1 | - | - | 0.05 | 1 | - | - | - |
| Mathew, 2003 | NS | - | - | - | - | 2.4 | - | - | - | - | - | 1.1 | - |

***Somnolence*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | n/a | - | - | - | - | nr | - | - | - | - | - | nr | nr |
| Sandrini | NS | - | - | - | 3 | 3 | - | - | - | - | - | 7 | 4 |
| Spierings | NS | - | - | - | 1.9 | - | - | - | 1.4 | - | - | - | - |
| Dowson | NS | - | - | - | - | 2.1 | - | - | 0.5 | 1.6 | - | - | - |

***Fatigue/Asthenia*** % of patients

| Ref. | p value | R5 | R10 | S25 | S50 | S100 | Z2.5 | Z5 | A12.5 | A25 | N2.5 | E40 | E80 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Goadsby | NS | - | - | - | - | 3 | - | - | - | - | - | 3 | 10 |
| Sandrini | NS | - | - | - | 6 | 8 | - | - | - | - | - | 7 | 11 |
| Spierings | n/a | - | - | - | nr | - | - | - | nr | - | - | - | - |
| Dowson | **0.0058** | - | - | - | - | 5.7 | - | - | **0.5** | 1 | - | - | - |

*Presence of symptoms

**photophobia/phonophobia combined

## Appendix E. Table 1. 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 |

nr= not reported

## Appendix E. Table 1. Triptans vs. active controls: assessment of internal validity (continued)

| 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 |

nr= not reported

## Appendix E. Table 1. Triptans vs. active controls: assessment of internal validity (continued)

| 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<br>Dahlof, 1997<br>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 |

nr= not reported

## Appendix E. Table 1. Triptans vs. active controls: assessment of internal validity (continued)

| 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, 1997 | Yes | Unclear | Yes | Yes | 3/154 lost to followup |
| Heywood, 1997<br>Dahlof, 1997<br>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<br>14/479: received sumatriptan at 1st visit |

nr= not reported

## Appendix E. Table 1. Triptans vs. active controls: assessment of internal validity (continued)

| 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 |

nr= not reported

## Appendix E. Table 1. Triptans vs. active controls: assessment of internal validity (continued)

| 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<br>nr<br>nr<br>nr | nr |

nr= not reported

## Appendix E. Table 2 Triptans vs. active controls: characteristics and outcomes

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Geraud, 2002 | Multicenter, DB, RCT, parallel group, 3 attack single dose study<br><br>Not specific - France | n = 719<br>avg. age 41 years<br>aged 18-65<br>85% female<br>>95% Caucasian | 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 more than 10 days per month over proceeding 6 months; pregnancy; lactation or inadequate contraception in females; recent history of repetitive, prolonged use of analgesics;ischaemic heart disease; vascular spasms; arrhythmias uncontrolled hypertension; any gastrointestinal problems, history of drug abuse |
| Laterre, 1991 | Multicenter, DB, RCT, parallel group, 3 attack single dose study (only attack 1 reported in detail)<br><br>47 clinics in Austria, Belgium, Denmark, Finland, France, Germany, Netherlands, Norway, Sweden | n = 580<br>avg. age 40 years<br>aged 18-65 meeting IHS criteria<br>83% female<br>Ethnicity not reported | 1-6 migraine 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 migraine attacks. Female - adequate contraceptive measures. | Pregnant, regular requirement for opiate analgesics or major tranquillizers, drug/alcohol abuse, ischaemic heart disease, 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 than 3 clinical trials within the previous 3 years. |
| Winner, 1996 | Multicenter, DB, RCT , Parallel group, single dose<br><br>26 Clinics and private neurology practices | n = 310<br>avg. age 41 years<br>men and women 18-65<br>meeting IHS criteria<br>88% female<br>ethnicity not reported | History of Migraine 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 migraine headache, duration of aura more than 60 minutes, active psychiatric disorders peripheral vascular disorders, current use of macrolide n\antibiotics, significant hepatic or renal impairment, history of treatment failures to sumatriptan , drug addiction chronic use of opioid or analgesics, use of serotonin reuptake inhibitors. |

## Appendix E. Table 2 Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| Geraud, 2002 | AstraZeneca | Escape medication permitted<br>Long term prophylactic migraine treatment were permitted provided they were kept consistent throughout the study | 778 eligible patients from 169 centers were screened. | None. | Zolmitriptan 2.5 mg | acetylsalicylic acid 900 mg plus metoclopramide 10 mg |
| Laterre, 1991 | Glaxo, PI | Rescue medication permitted | 580 treated with trial medication | 3 lost at first migraine attack<br>38 by second migraine attack<br>90 by third attack<br>Lost was due to no diary card data available and or they had treated with study medication in conjunction with other migraine therapy | Sumatriptan oral 100 mg | Cafergot (2 mg ergotamine tartrate plus 200 mg caffeine) |
| 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 | 1mg subcutaneous dihydroergotamine mesylate |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Geraud, 2002 | In all 3 attacks after 1st dose<br>Zolmitriptan 10.7%<br>acetylsalicylic plus metoclopramide 5.3% | nr | nr | nr | nr | nr | nr | In 1st attack after 1st dose:<br>Zolmitriptan 60.4%<br>acetysalicylic plus metoclopramide 66.5%<br>In all 3 attacks after 1st dose:<br>Zolmitriptan 33.4%<br>acetylsalicylic plus metoclopramide 32.9% |
| Laterre, 1991 | Attack 1<br>ST - 35% (p<0.001)<br>Cafergot - 13% | nr | nr | nr | nr | nr | nr | Attack 1<br>ST(145/220) - 66% (p<0.001)<br>Cafergot (118/246) - 48% |
| Winner, 1996 | 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. | nr | nr | ST 78.0%<br>Dihydro 56.6% | nr | Sumatriptan - 85.3%<br>Dihydroergotamine - 73.1% |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Geraud, 2002 | Satisfaction at last attack<br>Poor - Zol - 16.3 Ace Acid - 25.0<br>Fair - Zol - 24.5 Ace Acid - 19.1<br>Good - Zol - 35.9 Ace Acid - 38.5<br>Excellent - Zol 23.3 Ace Acid - 17.4 | All attacks treated with a 2nd dose<br>Zolmitriptan - 53.6%<br>Acetylsalicylicacid plus metoclopramide - 55.4% | Zolmitriptan - 23.1%<br>acetylsalicylic acid plus metoclopramide - 24.2% | Zolmitriptan: 5.4-6.8%<br>acetylsalicylic acid plus metoclopramide: 3.8-5.5% |
| Laterre, 1991 | 52% of the patients receiving sumatriptan described treatment as good or excellent; only 31% of patients treated Cafergot gave this response.<br>66% taking sumatriptan said they would take it again. Compared with 52% of patients who received Cafergot. | Attack 1<br>ST -24%<br>Cafergot - 44% | Recurrence reported within 48 hours ST - 41%<br>Cafergot - 30% | ST - Before 9%<br>After 8%<br>Cafergot Before 13% After 16% |
| Winner, 1996 | nr | ST n = 23<br>Dihydroergotamine n= 43 | Of 270 who experienced relief<br>Sumatriptan (140) 45%<br>dihydroergotamine (130) 17.7% | Baseline complaint::<br>ST - n = 9 - 6%<br>Dihydro n = 14 - 9.7%<br>At 1 hour<br>ST n= 6 - 4.0%<br>Dihydro = n = 8 - 5.5% |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Geraud, 2002 | Zolmitriptan: 26.5-34.2%<br>acetylsalicylic acid plus metoclopramide: 25.5-30.2% | Zolmitriptan: 36.8-43.8%<br>acetylsalicylic acid plus metoclopramide: 36.8-42.3% | Vertigo, somnolence, paraesthesia, Asthenia, tightness, chills, nausea, abdominal pain, dizziness, dry mouth, tremor, diarrhea | Zolmitriptan - 1 dizziness<br>1- Somnolence<br>1 - dizziness & vasodilatation<br>Ace acid - 2 diarrhea<br>1 palpitation plus asthenia<br>1 - anxiety plus dry mouth<br>1- phlebitis | Zol - 3.7<br>Ace Acid - .6 |
| Laterre, 1991 | ST - Before treatment 66%<br>After 40%<br>Cafergot - Before 64%<br>After 55% | ST - Before 71% After 35%<br>Cafergot - Before 75% After 53% | ***Sumatriptan:*** fatigue, nausea, vomiting, dizziness, palpitations, abdominal cramps and stiffness<br>***Cafergot:*** depression, vertigo, blurred vision, irregular heart beats, hypersensitivity, exacerbation of the migraine attack, urtcaria, dysponea, fatigue, tachycardia, vagal discomfort, dizziness and tinnitus. | 6 in sumatriptan, 9 in Cafergot | nr |
| Winner, 1996 | Baseline complaints:<br>ST - n = 114 - 76%<br>Dihydro - n = 102 - 70.3%<br>At 2 hours ST n= 16<br>Dihydro n= 40 | nr | Nausea, vomiting, chest pain, injection site discomfort | 2 patients (dihydro group) | ST - 5.9%<br>Dihydro - 0.9% |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Dowson, 2000 | Multicenter, DB, RCT, double dummy, crossover<br><br>23 primary care practices in the UK | n = 204 (initially recruited)<br>avg. age 42.8 years<br>aged 18-65<br>92% female<br>Caucasian (except 1) | Established diagnosis of migraine with symptoms of at least 1 year's duration and age of onset<50.<br>Patients also had a history of at least two moderate or severe attacks every 12 weeks with a gap of at least 24 hours between attacks | Pregnancy, breastfeeding or inadequate contraception, cardiovascular conditions, chronic renal/hepatic disease or hypertension<br>Known sensitivity to either trail treatment and those who had tried either treatment in the past and found it ineffective. |
| Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group | Multicenter, Double blind, double dummy, equally randomized, parallel group, single dose, 3 attacks<br><br>Neurology department, private clinics, general practice surgeries at 37 centers in 8 countries (Austria, Denmark, Germany, France, New Zealand, Sweden, Switzerland, UK)<br>Medication was taken by patient at home | 382 randomized to receive med, 24 of these did not treat an attack<br>avg. age 41years<br>aged 18-65 meeting IHS criteria<br>80% female<br>all but 5 were Caucasian | At least a 1 year history of one to six severe or moderately severe migraine 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; hypersensitivity to treatment drugs; lactation; pregnancy or inadequate contraceptive measures; history of ischaemic heart disease, uncontrolled hypertension, serious psychiatric illness or other systemic disease; need for continuing migraine prophylaxis or participation in more than three clinical trails within the previous 3 years. |
| Tfelt-Hansen, 1995 | DB, Randomized, 3 parallel group study, 2 attacks<br><br>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 | n = 421<br>avg. age 39 years<br>aged 18-65 meeting IHS criteria<br>78% female<br>Ethnicity not reported | At least a 1 year history of 2-6 attacks per month within the last three months. | nr |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| Dowson, 2000 | Servier Laboratories Ltd. | Rescue medication permitted<br>Patients allowed to continue using tricyclic anti-depressants and certain prophylactic medications for migraine 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 migraine attack<br>39 withdrawn due to failure to attend second clinic visit<br>41 not take 2nd med so 161 analyzed for safety, 120 analyzed for primary and secondary efficacy | Sumatriptan 50 mg + placebo | domperamol (a combination of 10 mg domperidone and 500 mg paracetamol) + placebo |
| Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group | Glaxo Group Research 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<br>S: 175 1st attack, 172 evaluable<br>A&M: 183 1st attack, 183 evaluable<br>2nd attack: S: 159, 153 evaluable, A&M: 175, 172 evaluable<br>3rd attack: S 149, 142 evaluable, A&M 161, 156 evaluable | Sumatriptan oral 100 mg | 900 mg aspirin plus 10 mg oral metoclopramide |
| 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,<br>4 failed to record details,<br>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 | 1. lysine acetylsaicylate (equivalent to 900 mg aspirin) and 10 mg metoclopramide<br><br>2. Placebo |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Dowson, 2000 | nr | nr | nr | nr | nr | nr | nr | Sumatriptan - 33.3%<br>Domperamol - 36.4% |
| Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group | Attack 1:<br>ST - 26%; A&M - 14%<br>Attack 2:<br>ST - 23%; A&M - 15%<br>Attack 3:<br>ST - 34%; A&M - 12% | Resume normal activities within 6 hours<br>Attack 1:<br>ST 50%; A&M - 30%<br>Attack 2:<br>ST - 53%; A&M - 34%<br>Attack 3:<br>ST - 53%; A&M - 36% | nr | nr | nr | nr | nr | Attack 1:<br>ST (74/133) - 56%; Aspirin + (62/138) - 45%<br>Attack 2:<br>ST - 58%; A&M - 36%<br>Attack 3:<br>ST - 65%; A&M - 34% |
| Tfelt-Hansen, 1995 | 1st Attack:<br>ST 30% (36/122); LAS+MTC 22% (29/135); Placebo 8% (10/126)<br>2nd Attack:<br>ST 33% (35/105); LAS+MTC 24% (28/119); Placebo 11% (11/101) | nr | nr | nr | nr | nr | nr | 1st attack:<br>ST - 53% (63/119); LAS+MTC - 57% (76/133); Placebo - 24% (30/124)<br>2nd Attack:<br>ST - 55%; LAS+ MTC - 43%; Placebo - 25% |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Dowson, 2000 | nr | nr | nr | Dom from 9.2% nausea prior to 5.0% in 2 hrs and 3.3% at 4 hrs, ST=10% nausea prior to 5.8% in 2 hrs and 0.8% in 4 hrs |
| Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group | ST66% vs Aspirin + 45% of patients considered treatment to be excellent, good or reasonable<br>ST 70% vs Aspirin + 46% said they would take the medication again. | | Recurrence reported within 48 hours<br>Attack 1:<br>ST 42%; Aspirin + - 33%<br>Attack 2:<br>ST 37%; Aspirin + - 27%<br>Attack 3:<br>ST 42%; Aspirin+ - 30% | Pretreatment vomiting:<br>1st attack: S = 12%, A&M= 14%<br>2nd attack: S=14%, A&M=18%<br>3rd attack: S=12%, A&M=19%<br>Vomiting after 2 hrs:<br>1st attack: S = 15%, A&M= 10%<br>2nd attack: S=9%, A&M=13%<br>3rd attack: S=6%, A&M=13% (significant) |
| Tfelt-Hansen, 1995 | Good or excellent effect as rated by patients<br>1st Attack:<br>ST -45% (54/121); LAS +MTC - 46% (74/137); Placebo - 20% (24/123)<br>2nd Attack:<br>ST - 49% (49/101); LAS +MTC - 58% (70/120); Placebo - 23% (23/98) | More frequent with placebo than with active drugs, no difference between active drugs | 1st Attack:<br>ST 38% (24/63); LAS - 36% (27/76); Placebo 30% (9/30)<br>2nd attack:<br>ST - 32% (18/65); LAS+MTC - 31% (16/51); Placebo - 12% (3/25) | 1st Attack<br>Prior to treatment:<br>ST - 8% (10/121); LAS+MTC - 7% (10/136); Placebo - 9% (11/125)<br>2 h after treatment<br>ST 9% (11/121); LAS - 5% (7/132); Placebo 12% (15/121)<br>2nd attack:<br>Prior to treatment:<br>ST - 10% (10/104); LAS+MTC - 9% (11/199); Placebo - 11% (11/100)<br>2 h after treatment<br>ST - 8% (8/104); LAS+MTC - 4% (4/115); Placebo - 11% (11/99) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Dowson, 2000 | Dom from 70% nausea prior to 36.7% in 2 hrs, ST=70% nausea prior to 39.2% in 2 hrs | | Dizziness and nausea | nr | None |
| Anonymous, 1992 (Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group | Proportion free of nausea:<br>Attack 1:<br>ST - 57%; Aspirin+ - 55%<br>Attack 2:<br>ST - 63%; A&M 63%<br>Attack 3:<br>ST - 56%; Aspirin+ - 55% | Proportion free of phobia:<br>Attack 1:<br>ST 57%; Aspirin + - 50%<br>Attack 2:<br>ST - 59%; Aspirin + - 51%<br>Attack 3:<br>ST - 54%; Aspirin + - 43% | Nausea, vomiting, fatigue, dizziness, distribuance of taste, sweating, worsening of migraine, abdominal discomfort, throat symptoms, headache, others are listed | 5 in the ST group withdrew due to adverse advents | ST n= 4 - 2%<br>Aspirin + n = 1<1% |
| Tfelt-Hansen, 1995 | 1st Attack<br>Prior to treatment:<br>ST - 69% (84/122); LAS+MTC - 77% (106/137); Placebo - 64% (81/126)<br>2 h after treatment<br>ST 48% (58/122); LAS - 44% (60/135)); Placebo 58% (72/125)<br>2nd attack:<br>Prior to treatment:<br>ST - 73% (77/105); LAS+MTC - 67% (80/120); Placebo - 72% (73/102)<br>2 h after treatment<br>ST - 47% (49); 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 | ST 6 (4.8%)<br>LAS - 0<br>Placebo - 0 |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Diener, 1999 | Multicenter, DB, double-dummy, RCT, 3 parallel groups, single dose, 1 attack<br><br>17 outpatient clinics of neurology departments and offices of neurologists and pain specialists in Germany | 279 assigned to three treatment groups<br>avg. age 41 years<br>aged 18-65 meeting IHS criteria<br>80% female | At least 1 year history of migraine and experiencing 2-6 migraine 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 migraine attack, intake of analgesics, or migraine drugs 24 h before administration of the study medication, intake of compound analgesics on more than 10 days per month, hypertension, coronary heart disease, asthma, drug or alcohol abuse allergic diatheses |
| Block, 1998 | Long-term open label (up to 1 year), multicenter, RCT, single dose<br><br>100 multinational sites | 1,831 (from 2,252 who completed acute phase of 3 multicenter phase III studies)<br>avg. age 42 years<br>aged 18-65 meeting IHS criteria<br>86% female<br>96% Caucasian | At least 6 month history of migraine, 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. |
| Touchon, 1996 | At first onset, multicenter, DB, DD, crossover, single dose, 2 attacks<br><br>Outpatient, in 34 centers in France | n = 317<br>avg. age 42 years<br>aged 18-65 meeting IHS criteria<br>86% female | At least 1 year history of 1-6 migraine attacks per month and were able to differentiate migraine attacks from other types of headaches | pregnancy, lactation, or inadequate contraception, a history suggest of ischemic heart disease, uncontrolled hypertension or other systemic disease, drug/alcohol abuse, contraindications to the use of DHE, and hypersensitivity to or intolerance of sumatriptan or DHE. |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| 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)<br>3 withdrawn due to violation of exclusion criteria. | Sumaptriptan sc 6 mg | 2 other arms: 1.Intraveneous L-ASA 1.8 (corresponding to 1 g acetylsalicylic acid) and 2. Placebo (ratio between placebo & active treatment =1:6) |
| Block, 1998 | Merck Research Laboratories (PI and co-investigator) | Patients in the rizatriptan groups were not to use ergot derivatives, 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 | 64 no attack<br>63 adverse experience<br>Lack of effect -11% of riz 5 mg and 4% of riz 10% discontinued treatment | Rizatriptan po 5 mg group 10 mg group | Standard Care: Sumatriptan either alone or in combo with other therapies; NSAIDS; Other usual care |
| Touchon, 1996 | Glaxo Wellcome Research and Development, co-investigator | Rescue medication was permitted. | | 28 no attack, so 289 (145 S & 145 DHE)<br>12 were withdrawn after 1st attack<br>11 failed to treat a 2nd attack, so 266 evaluale in crossover analysis (133 S & 133 DHE) | Sumatriptan sc 6 mg | DHE 2 nasal sprays of 0.5 mg (1 spay in each nostril) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Diener, 1999 | ST - 76.3%<br>L-ASA - 43.7%<br>Placebo - 14.3% | Time between administration of medication and the patient's ability to resume work or usual activities.<br>Mean Time<br>ST 8.2 hours<br>L-ASA 12.7 hours<br>Placebo 19.4 hours | nr | nr | nr | nr | nr | ST (104/114) - 91.2%<br>L-ASA(88/119) - 73.9%<br>Placebo - 23.8% |
| Block, 1998 | Rizatriptan 10 mg=*50% vs. Rizatriptan 5 mg=*35% and Standard care= *29% (p<0.05)<br><br>**median percent of patients' attacks showing pain-free status* | nr | nr | nr | nr | nr | nr | Rizatriptan 10 mg=*90% vs. Rizatriptan 5 mg=*80% and Standard care= *70% (p<0.05)<br><br>**median percent of patients' attacks showing relief status* |
| Touchon, 1996 | No Data (p<0.001) | 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 | nr | nr | Sumatriptan 63% (p<0.001)<br>DHE 22% | nr | No Data (p<0.001) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Diener, 1999 | nr | ST=1.8%, L-ASA=4.2%, Placebo=16.7% | ST - 23.1%<br>L-ASA - 18.2%<br>Placebo - 20.0% | ST Not existing - n = 95 - 83.3%<br>Resolved n = 18 - 15.8%<br>L-ASA Not existing - n= 99 - 83.2%<br>Resolved = 20 - 16.8%<br>Placebo Not existing n= 36 - 85.7%<br>Resolved n= 5 - 11.9% |
| Block, 1998 | nr | Allowed, but not reported | Not specific as to when | nr |
| Touchon, 1996 | 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. | Patients randomized 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). |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Diener, 1999 | ST Not existing - N=17 - 14.9 %<br>Resolved -n= 86 - 75.4%<br>L-ASA Not existing - n = 27 - 22.7 %<br>Resolved n = 77 - 64.7%<br>Placebo Not existing n = 7 - 16.7%<br>Resolved n= 12 - 28.6% | ST Not existing - n = 20 - 17.5%<br>Resolved n = 82 - 71.9%<br>L-ASA Not existing - n = 17 - 14.3%<br>Resolved n = 79 - 66.4%<br>Placebo Not existing - n = 6 - 14.3%<br>Resolved n = 15 - 35.7% | Fatigue, Dizziness/vertigo, Nausea, Injection site reactions, Chest symptoms, tight feeling in other parts of the body | nr | ST - n = 4 - 3.4%<br>L-ASA n= 0<br>Placebo = n = 1 - 2.3% |
| Block, 1998 | 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 clinical adverse experience, 4.2% Rizatriptan 10 mg, 3.6% 5 mg and 1.5% standard care | Rizatriptan 5 mg<1<br>Rizatriptan 10 mg 1<br>Standard Care 2 |
| Touchon, 1996 | 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 patients taking DHE | Results for photophobia were similar to those observed for nausea, 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 | 1 person in S group withdrew because of pressure in chest |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Freitag, 2001 | At first onset, mild to moderate migraine, multicenter, DB, RCT parallel -groups<br><br>United States | n = 137<br>avg. age 42 years<br>IHS criteria<br>89% female<br>92% Caucasian | 1 year history of 2-8 migraine attacks per month and those with aura had to have attacks typically progressing to the painful phase of migraine. 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 either isometheptene combination or sumatriptan, as were those who had daily headaches. History of over use of analgesics. |
| Boureau, 2000 | mulitnational, multicenter, RCT, DB, DD, crossover study, 2 attacks, single dose<br><br>Outpatient, 52 centers in Belgium, France, Portugal and Switzerland | n = 405<br>avg. age 41 years<br>aged 18-65 meeting IHS criteria<br>84% female<br>Ethnicity nr | At least 1 year history of 1-6 migraine 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 interpretation of the data, any condition or medication that would contraindicate the use of sumatriptan or DHE. |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| Freitag, 2001 | Canrick Laboratories | Preventive medications for migraine 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 allotted 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 | Isometheptene Mucate, Dichloralphenazone with Acetaminophen ( 2 capsules, then 1 at 1 hr, 1 at 2 hrs, 1 at 3 hrs) |
| Boureau, 2000 | Glaxco, Wellcome | Patients randomized to DHE had option of taking second dose of nasal spray 30 minutes after first, if insufficient relief was obtained. Rescue medication permitted at 2 hours. Patients who normally took prophylactic medication for migraine permitted to continue therapy provided it did not contain ergotamine or DHE and dosage remained the same throughout 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) | DHE Nasal Spray 1 mg (plus placebo ST) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Freitag, 2001 | nr | Mild or not impairment: Sumatriptan = 68.9%, isometheptene combo = 80% | No or mild head pain: sumatriptan =81.7, isometheptene combo = 81.1% | 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 = 44.6%, isometheptene combo = 44.3% | nr | Patients with no or mild head pain: ST - 68.9% Isometheptene Combination - 63.1% |
| Boureau, 2000 | nr | At 2 hours after dosing 46% of patients were able to work and function normally after ST, compared with 38% after DHE. | nr | nr | nr | Headache relief was reported by ST - 53% DHE 41% | ST - 60% DHE 48% | ST- 63% (p<0.003) DHE - 51% |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Freitag, 2001 | 7-point scale (1=completely satisfied, 6=completely dissatisfied): 3.49 for isometheptene, 3.35 for sumatriptan | nr | Recurrence in 10 sumatriptan patients, in 11 isometheptene combo patients | % with vomiting at 2 hrs: 0 for both groups |
| Boureau, 2000 | nr | The optional 2nd dose of study medication at 30 minutes was taken for 76% of migraines 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 |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Freitag, 2001 | % 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 throat, laryngitis, bruises, stiff neck, drug taste, confusion | None | 2 sumatriptan patients |
| Boureau, 2000 | At 1 hour 64% of patients reported relief of nausea following sumatriptan compared with 40% following DHE<br>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 | nr |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Boureau, 1995 | multicenter, equally randomized, open label, early onset, crossover trial<br><br>46 neurology centers in France | n = 246<br>avg. age 42 years<br>aged 18-65 meeting IHS criteria<br>82% female<br>Ethnicity not reported | 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. |
| Myllyla, 1998 | multicenter, randomized, early onset, DB, placebo-controlled, parallel-group study<br><br>5 neurological centers in Finland | n = 154<br>avg. age 42 years<br>aged 18-65 meeting IHS criteria<br>95% female<br>Ethnicity not reported | History of Migraine for at least 1 year and with more than one but less than four attacks per month characterized by severe or moderate | nr |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| 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 migraine 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 treatment | Period I<br>8 did not treat a migraine attack,<br>13 withdrawn for adverse events (10 sumatriptan, 3 usual treatment)<br>Period II: 225 entered<br>8 had no attacks<br>8 dropped out (4 per group),<br>Crossover analyzed on 217 patients with total of 3,181 attacks | Sumaptriptan sc 6-m.g s.c injection | Usual Acute Treatments:<br>Combinations of various analgesics<br>Ergotamine<br>Noramidopyrin<br>Paracetamol<br>Non-steroidal anti-inflammatory drugs<br>Acetylsalicylic acid<br>DHE<br>Other |
| 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. | 154 | 3 were lost to followup<br>10 were withdrawn (1 hypertension, 1 adverse effects, 8 no attack) | Sumatriptan po 100 mg | 1. Tolfenamic Acid Rapid Release 200 mg, 2. placebo |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Boureau, 1995 | Period I<br>ST 62%<br>Usual Treatments 13%<br>Period II<br>ST 65%<br>Usual Treatments 17% | nr | nr | Assessed at baseline and end of study<br>Relative increase from baseline<br>Global:<br>ST 21% ; UT - 7%<br>Functional:<br>ST 21%; UT 6%<br>Psychological:<br>ST 16%; UT 6%<br>Social:<br>ST 23%; UT 4%<br>Iatrogenic distribuance -<br>ST 16%; UT - 14% | nr | Period I<br>ST 70%<br>Usual Treatments 21%<br>Period II<br>ST - 63%<br>Usual Treatments 28% | nr | Period I<br>ST 80%<br>Usual treatments 30%<br>Period II<br>ST 76%<br>Usual treatments 39% |
| Myllyla, 1997 | Attack 1<br>ST 50% (21/42)<br>R-TA 37% (16/43)<br>Placebo 7% (3/41)<br>Attack 2<br>ST 26% (10/39)<br>R-TA 16% (7/43)<br>Placebo 11% (4/38) | nr | nr | nr | nr | nr | nr | Attack 1<br>ST 79% (33/42)<br>R-TA 77% (33/43)<br>Placebo 29% (12/41)<br>Attack 2<br>ST 64% (25/39)<br>R-TA 70% (30/43)<br>Placebo 39% (15/38) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Boureau, 1995 | ST - 85%<br>UT - 10%<br>No preference - 5%<br>Patients assessed ST as being "well tolerated" in 88-89% of attacks and UT 78-82% of attacks | Period I<br>ST - 33%<br>UT - 24%<br>Period II<br>ST - 28%<br>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. |
| Myllyla, 1997 | nr | Extra dose of test Med at 1 hour<br>Attack 1<br>ST 61% ((28/46)<br>R-TA 72% (34/47)<br>Placebo 94% (45/48)<br>Attack 2<br>ST 76% (34/45)<br>R-TA 80% ((36/45)<br>Placebo 83% (39/47) | Attack 1<br>ST 22% (10/45)<br>R-TA 23% (11/47)<br>Placebo 25% (12/48)<br>Attack 2<br>ST 24% (11/45)<br>R-TA 27% (12/45)<br>Placebo 13% (6/47) | Attack 1:<br>ST 4% (2/45); RT 9% (4/46)<br>Placebo 8% (4/48)<br>2 hours:<br>ST 11% (5/46); R-TA 9% (4/46)<br>Placebo 8% (4/48)<br>Attack 2:<br>ST 2% (1/42); R-TA 2% (1/44)<br>Placebo 4% (2/45)<br>2 hours:<br>ST - 9% (4/45); R-TA - 9% (4/44)<br>Placebo - 15% (7/47) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Boureau, 1995 | Presence of Nausea<br>Period I:<br>Pre-treatment:<br>ST 48%; UT 45%<br>At 2 h:<br>14%; UT 36%<br>Period II:<br>Pre-treatment:<br>ST - 49%; UT - 41%<br>At 2 h:<br>ST - 13%; UT - 30% | nr | Tingling, malaise, nausea, injection site reaction, stomach pain, dizziness, sleepiness, fatigue | 13 patients withdrew in period I for minor adverse effects, 8 withdrew in period II but reasons not given | ST 7% |
| Myllyla, 1997 | Attack 1<br>ST 43% (20/46); R-TA 47% (22/47)<br>Placebo 42% (20/48)<br>2 hours<br>ST 41% (19/46); R-TA 26% (12/47)<br>Placebo 42% (20/48)<br>Attack 2<br>ST 56% (22/45); R-TA 62% (28/45)<br>Placebo 47% (22/47)<br>2 hours<br>ST - 44% (20/45); R-TA - 36% (16/45)<br>Placebo - 45%(21/47) | Attack 1<br>ST 84% (38/45); R-TA 79% (37/47)<br>Placebo 88% (42/48)<br>2 hours<br>ST 41% (19/46); R-TA 38% (18/47)<br>Placebo 67% (32/48)<br>Attack 2<br>ST 84% (37/44); R-TA 79%(39/45)<br>Placebo 83% (39/47)<br>2 hours<br>ST - 44% (20/45); R-TA - 51% (23/45)<br>Placebo - 68% (32/47) | Tachycardia, palpitation, muscle pain, Dysuria, nervous system symptoms, nausea, vomiting, gastrointestinal symptoms, Allergic | 1 | ST - 7<br>R-TA -2<br>Placebo - 0 |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Heywood, 1997<br>Dahlof, 1997<br>Bouchard, 1997 | Open label , not random, 1st phase patients took their customary therapy (non-sumatriptan to treat unlimited number of migraines for 12 weeks, followed by 24 weeks treatment with ST SC. | Not randomized<br>avg. age 39 years<br>aged 18-65 meeting IHS criteria<br>83% female<br>98% Caucasian | 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 migraine where the dose might change during 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. |
| Schoenen, 1994 | Multicenter, open label, long-term | n = 479<br>avg. age 40 years<br>aged 18-65 meeting IHS criteria<br>84% female<br>Ethnicity not reported | Diagnosis of migraine 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. |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| Heywood, 1997<br>Dahlof, 1997<br>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<br>582 had some evaluable data<br>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 | Customary Therapy: (47%)dimenhydrinate /paracetamol/ coedine; (60%) aspirin/antiinflamatories such as ibuprofen; (62%) narcotics/ analgesics such as codeine; (11%) hypnotics/sedatives/anticonvulsants such as diazepam |
| 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.<br>14 patients erroneously received ST at their first visit.<br>4 did not come back for followup visit<br>4 -Lack of efficacy + adverse events<br>22 adverse events<br>3 Other | Sumatriptan 6 mg sc | simple analgesics (16%), combination analgesics (29%) ergot derivatives (36% NSAIDS (7%), narcotics (2%) antiemetics (7%) others 2%. |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Heywood, 1997<br>Dahlof, 1997<br>Bouchard, 1997 | ST - 36%<br>Customary Therapy 1% | nr | nr | nr | nr | nr | nr | nr |
| Schoenen, 1994 | ST 60% | nr | nr | nr | nr | ST 71%<br>Customary Treatment 16% | nr | ST - 82%<br>Customary Treatment - 35% |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Heywood, 1997<br>Dahlof, 1997<br>Bouchard, 1997 | Scores on each of the 3 migraine specific quality of life questionnaire 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. | nr for time period | nr | nr |
| Schoenen, 1994 | ST<br>Ineffective - 30(7)<br>Poor - 24(6)<br>Reasonable 54(13)<br>Good 140(34)<br>Excellent 167(40) | Number with 2nd injection<br>ST<br>Attack 1<br>115(31)<br>Attack 2<br>104(31)<br>Attack 3<br>92(32) | ST<br>Attack 1<br>127(34)<br>Attack 2<br>115(34)<br>Attack 3<br>96(33) | ST- Before 19%<br>2hours 3% |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Heywood, 1997<br>Dahlof, 1997<br>Bouchard, 1997 | 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.<br>During customary therapy: tingling, pressure sensation, nausea and/or vomiting . During ST, nausea/vomiting, musculoskeletal symptoms, pressure sensation, injection site reaction, throat symptoms, feelings of heaviness. | Adverse events sumatriptan=33 | ST -5.5% over 12 weeks |
| Schoenen, 1994 | ST - Before 71%<br>2 hours 17% | ST Before 77%<br>2 hours 21% | ST<br>Tingling, dizziness, warm, Nausea/ 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%) | 2.8% of 1136 attacks |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Gerth, 2001 | Non-blinded, parallel group, extension trial (Improvement in Health-Related Quality of Life)<br><br>Outpatient, 23 sites in the United States | n = 265<br>Randomly assigned 4:1to rizatriptan or standard care<br>avg. age 41 years<br>aged 18-65<br>83% female<br>95% Caucasian | 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 migraine attack with the test drug; monomamine oxidase inhibitors and methysergide were prohibited for the duration of the study. |
| Bussone, 1999 | multicenter, DB, RCT within patient trial, early onset, single dose<br><br>Italy | n = 156<br>avg. age 33 years<br>aged 19-70 meeting IHS criteria<br>76.3% female<br>ethnicity not reported | 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 |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| Gerth, 2001 | Merck & Co. Inc. (PI) | nr | 313 invited, 265 elected to participate | nr | Rizatriptan po 10 mg | Standard Migraine Therapy 66% used sumatriptan (oral or subcutaneous), also NSAIDS (70%), barbiturates (40%), paracetamol (40%) and opioids (30%) for at least 1 attack. |
| 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 further 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 | Diclofenac-K (50mg) , Diclofenac-K (100 mg), Placebo |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Gerth, 2001 | nr | nr | nr | 24-HrMQoLQ Mean Scores<br>Work Functioning<br>RT 13.9; SMT -12.5<br>Social Functioning<br>RT 13.6; SMT 11.8<br>Energy/Vitality<br>RT 13.7; SMT 11.6<br>Feelings/Concerns<br>RT 13.3; SMT 10.6<br>Mental Health Component of SF-36<br>RT 50.3; SMT -48.0 | nr | nr | nr | nr |
| Bussone, 1999 | 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 | nr | nr | nr | nr | nr |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Gerth, 2001 | nr | nr | nr | nr |
| Bussone, 1999 | More patients thought the tolerability was good or excellent when taking diclofenac 50 mg (79%), diclofenac-K 100 mg (76%), and placebo (76%) than when taking ST (67%), | 36% of DK either dose, 41% of sumatriptan, 60% of placebo | Of the 115 patients who completed all 4 migraine 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<br>Diclofenac -K 50 mg 9 (8)<br>Diclofennac - K 100 mg 10 (9)<br>ST 12 (11)<br>Placebo 5(5)<br>2hours<br>DK 50 mg 4 (4)<br>DK 100 mg 3 (3)<br>ST 14 (13)<br>Placebo 8 (7) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Gerth, 2001 | nr | nr | nr | nr | nr |
| Bussone, 1999 | Baseline<br>Diclofenac -K 50 MG 47 (43)<br>Diclofenac - K 100 mg 50 (46)<br>ST 58 (53)<br>Placebo 52 (48)<br>2hours<br>DK 50 mg 24 (22)<br>DK 100 mg 29 (27)<br>ST 45 (41)<br>Placebo 47 (43) | Baseline<br>Diclofenac -K 50 mg 55 (51)<br>Diclofenac - K 100 mg 49 (45)<br>ST 59 (54)<br>Placebo 51 (47)<br>2hours<br>DK 50 mg 35 (32)<br>DK 100 mg 32 (29)<br>ST 41 (38)<br>Placebo 43 (39) | asthenia, Fatigue dizziness, paresthesia, somnolence, Dyspesia, nausea, abdominal pain, vomiting, Tachycardia, anxiety | 4 withdrew | DK 50 - 100 mg none<br>ST 4(3)<br>Placebo 1(1) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Friedman, 2001 | Randomized controlled trial<br><br>A tertiary care academic medical center and a faculty practice located at a community hospital in US. | n = 35<br>Average age and ethnicity nr<br>aged 18-63 meeting IHS criteria<br>80% female | 1) symptomatic migraine<br>2) previous migraine history | 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. |
| Christie, 2003 | Randomized controlled trial<br>Multicenter<br>International<br><br>Single dose, crossover | n=488<br>avg. age 37.2<br>83.4% female<br>76.3% white | IHS criteria for migraine with or without aura; 6-month history of migraine; 1-8 attacks per month | Clinical evidence of cerebrovascular or cardiovascular disease, including significant ECG abnormality; drug or alcohol abuse within last year |
| Diener, 2002 | Randomized controlled trial<br>Multicenter<br>International<br><br>Single dose | n=937<br>avg age 40.3<br>87.3% female<br>race nr | IHS criteria for migraine with or without aura; 1-year history of migraine; at least 1 every 6 weeks but not more than 6 per month | Frequent nonmigrainous headaches (more than 6 per month on average); atypical migraine that had consistently failed to respond to medical therpy; migraine with prolonged aura; familial hemiplegic migraine; basilar migraine; migrainous infarction; know coronary artery disease; clinically significant arrhythmias; heart failure; uncontolled hypertension (presence of any hypertension in patients enrolled in Germany); peripheral vascular disease or Raynaud's syndrome; clinically significant active systemic, renal, hepatic, gastrointestinal, neurological, endocrine, metabolic or psychiatric disease; severe limitation of gastrointestinal absorption; serious documented drug allergy; alcohol or substance misuse; regular excessive use of analgesics or ergotamine (intake on more than 2 days in 7); female patients who were pregnant, breast-feeding or at risk of pregnancy because of ineffective contraceptive precautions were not considered for entry |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| Friedman, 2001 | DextraBaldwib McGonagle Foundation Inc. | nr | 3 groups: sumatriptan, intraoral chilling, tongue chilling (control) | 35 analyzed | Sumatriptan oral 50 mg | 1. 40 minutes of bilateral MIC<br>2. Sham (tongue) chilling |
| Christie, 2003 | Merck | NDAIDs, opiates, antiemetics | nr/nr/488 | 126(25.8%) withdrawals/lost to fu nr/362 analyzed | Rizatriptan (riza) po 10 mg | Ergotamine 2 mg/caffeine 200 mg (Ergo/Caf) |
| Diener, 2002 | Funder nr 5th author affiliated with Pfizer Central Research | nr | 948 screened/eligible nr/937 randomized | withdrawals and lost to followup nr 733 took trial medication and were analyzed | Eletriptan (ele) po 40 mg and 80 mg | Ergotamine 2 mg/caffeine 200 mg (Ergo/Caf) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Friedman, 2001 | nr | nr | 24 pain score: sumatriptan=2.9, oral=1.2,control=4.5 | nr | nr | nr | nr | nr |
| Christie, 2003 | Riza=49.1%<br>Ergo/Caf=24.3%<br>p≤0.001 | Riza=57%<br>Ergo/Caf=27.8%<br>p≤0.001 | *Sustained relief*<br>Riza=47.6%<br>Ergo/Caf=34.0%<br>p≤0.001<br><br>*Sustained pain free*<br>Riza=35.6%<br>Ergo/Caf=20%<br>p≤0.001 | nr | Riza=22%<br>Ergo/Caf=15.3%<br>p=0.024 | Riza=45.3%<br>Ergo/Caf=25.8%<br>p≤0.001 | Riza=64.1%<br>Ergo/Caf=37.8%<br>p≤0.001 | Riza=75.9%<br>Ergo/Caf=47.3%<br>p≤0.001 |
| Diener, 2002 | Eletriptan 40 mg=58/206(28%) (p≤0.001)<br>Eletriptan 80 mg=79/209(38%) (p≤0.001)<br>Ergotamine/caffeine=20/197(10%) | *Relief of functional impairment*<br>Eletriptan 40 mg=52%<br>Eletriptan 80 mg=62%<br>Ergotamine/caffeine=31% | Eletriptan 40 mg=20%<br>Eletriptan 80 mg=31%<br>Ergotamine/caffeine=9% | nr | nr | Eletriptan 40 mg=60/205 (29%) (p≤0.001)<br>Eletriptan 80 mg=80/206 (39%) (p≤0.001)<br>Ergotamine/caffeine=26/196(13%) | nr | Eletriptan 40 mg=111/206(54%)<br>Eletriptan 80 mg=142/209(68%)<br>Ergotamine/caffeine=65/197(33%) |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Friedman, 2001 | nr | nr | nr | nr |
| Christie, 2003 | Satisfaction (completely, very or somewhat) at 2 hours<br>Riza=69.8%<br>Ergo/Caf=38.6%<br>p≤0.001 | Riza=27.7%<br>Ergo/Caf=45.5%<br>p≤0.001 | Riza=31.4%<br>Ergo/Caf=15.3% | nr |
| Diener, 2002 | nr | nr | Eletriptan 40 mg=21%<br>Eletriptan 80 mg=22%<br>Ergotamine/caffeine=12% | nr |

## Appendix E. Table 2. Triptans vs. active controls: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Friedman, 2001 | 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<br>dizziness, paresthesia, and somnolence<br>Side effects due to chilling included dizziness and posttreatment gingival tenderness | nr | nr |
| Christie, 2003 | nr | nr | Dizziness: riza=27(6.7%); ergo/caf=21(5.3%)<br>Somnolence: riza=22(5.5%); ergo/caf=9(2.3%)<br>Nausea: riza=17(4.2%); ergo/caf=34(8.5%)<br>Chest pain: riza=3(0.7%); ergo/caf=3(0.8%)<br>Overall incidence: riza=34.5%; ergo/caf=34.5% | Riza=3 patients<br>Ergo/Caf=0 | Riza=3(0.7%)<br>Ergo/caf=3(0.8%) |
| Diener, 2002 | % patients reported in graphical format<br>Eletriptan 40 and 80 mg < Ergotamine/Caffeine (p≤0.001) | % patients reported in graphical format<br>Eletriptan 40 and 80 mg < Ergotamine/Caffeine (p≤0.001) for both photophobia and phonophobia | *Dizziness*<br>*Eletriptan 40 mg=10/210(5%)*<br>*Eletriptan 80 mg=12/214(6%)*<br>*Ergotamine/caffeine=7/203(3%)*<br>*Parasthesia: nr*<br>*Somnolence*<br>*Eletriptan 40 mg=5/210(2%)*<br>*Eletriptan 80 mg=12/214(6%)*<br>*Ergotamine/caffeine=1/203(<1%)*<br>*Fatigue/asthenia*<br>*Eletriptan 40 mg=9/210(4%)*<br>*Eletriptan 80 mg=21/214(10%)*<br>*Ergotamine/caffeine=7/203(3%)* | Eletriptan 40 mg=2/210(0.9%)<br>Eletriptan 80 mg=2/214(0.9%)<br>Ergotamine/caffeine=2/203(0.9%) | Eletriptan 40 mg=6/210(3%)<br>Eletriptan 80 mg=12/214(6%)<br>Ergotamine/caffeine=5/203(2%) |

## Appendix F Table 1. Triptans vs. placebo 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? |
|---|---|---|---|---|---|---|
| Eletriptan Steering Committee in Japan, 2002 | Adequate | Unclear; pre-packaged drug kits supplied using randomization codes | Yes | Yes | nr | nr |
| Sakai, 2002 | nr | nr | Yes | Yes | nr | nr |

## Appendix F Table 1. Triptans vs. placebo controls: assessment of internal validity (continued)

| 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? |
|---|---|---|---|---|---|
| Eletriptan Steering Committee in Japan, 2002 | nr | Difference of 19 patients (6.8%) between evaluable population=326(81%) and analyzed population=307(76%) | nr | Yes<br>nr<br>nr<br>nr | No<br>No |
| Sakai, 2002 | nr | Difference of 29 (12.5%) between evaluable population=231/289(79.9%) and analyzed population=202/289(69.9%) | nr | Yes<br>nr<br>nr<br>nr | No<br>No |

## Appendix F. Table 2. Triptans vs. placebo: characteristics and outcomes

| Author, Year | Design Setting | Population | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|
| Eletripan Steering Committee in Japan, 2002 | Randomized controlled trial<br>Multicenter<br>Japan<br><br>Single dose | n=402<br>avg age 35.5<br>74.1% female<br>100% Japanese | IHS criteria; 1 attack per 6-week period | Severely limited gastrointestinal absorption; other exclusion criteria "identical to those used in previous clinical studies" not reported |
| Sakai, 2002 | Randomized controlled trial<br>Multicenter<br>Japan<br><br>Single dose | n=289<br>avg age 38.3<br>74.2% female<br>100% Japanese | 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 | 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 |

nr = not reported

## Appendix F. Table 2. Triptans vs. placebo: characteristics and outcomes (continued)

| Author, Year | Funding sources/ role of funder | Other medications | Number screened/ eligible/ enrolled | Number withdrawn/ lost to followup/ analyzed | Triptan | Other Drugs |
|---|---|---|---|---|---|---|
| Eletripan Steering Committee in Japan, 2002 | Pfizer, Ltd. Role nr | Rescue medication permitted nr | 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 | Eletriptan (ele) 20, 40 and 80 mg | Placebo (pla) |
| Sakai, 2002 | nr | Type(s) of rescue medication approved 4-hours post-dose nr | 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 | Zolmitriptan (zol) 1, 2.5, 5 mg | Placebo (pla) |

nr = not reported

## Appendix F. Table 2. Triptans vs. placebo: characteristics and outcomes (continued)

| Author, Year | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Pain Free in 2 hours** | **Symptom-free (or no functional disability) at 2 hours** | **24-hour sustained pain-free response** | **24-hour quality of life** | **Headache relief within .5 hours** | **Headache relief 1 hour** | **Headache relief 1.5 hours** | **Headache relief 2 hours** |
| Eletripan Steering Committee in Japan, 2002 | ele=24%; 22%; 28%<br>pla=13% | *Functional response rates*<br>ele=65%; 65%; 75%<br>pla=54% | ele=21%; 18%; 26%<br>pla=9% | nr | nr | nr | nr | ele=64%; 67%; 76%<br>pla=51% |
| Sakai, 2002 | zol=17.8%, 18.5%, 23.1%<br>pla=14.6% | nr | *Complete response (headache response at 2h and then no recurrence or use of escape mecication within 24h)*<br>zol=37.8%, 46.3%, 46.2%<br>pla=22.9% | nr | zol=8.5%, 9.8%, 13.7%<br>pla=12.2% | zol=30.4%, 28.3%, 32.7%<br>pla=26.5% | nr | zol=53.3%, 55.6%, 65.4%<br>pla=37.5% |

nr = not reported

## Appendix F. Table 2. Triptans vs. placebo: characteristics and outcomes (continued)

| Author, Year | Satisfaction / patient preference | Need for additional medication from 2 or 4 to 24 hours for recurrence | Headache recurrence within 24 hours | Vomiting relief within 2 hours |
|---|---|---|---|---|
| Eletripan Steering Committee in Japan, 2002 | *Global impressions of headache improvement 24 hours after dosing:*<br>ele=73%; 82%; 82%<br>pla=67% | ele=21%; 23%; 23%<br>pla=42% | ele=10%; 17%; 14%<br>pla=24% | ele=4%; 1%; 5%<br>pla=4% |
| Sakai, 2002 | nr | *Use of escape medication at 4h post-dose*<br>zol=12.8%, 5.6%, 17.3%<br>pla=26.5% | zol=25.0%, 15.7%, 28.1%<br>pla=29.5% | zol=4.4%, 1.9%, 2.0%<br>pla=4.2% |

nr = not reported

## Appendix F. Table 2. Triptans vs. placebo: characteristics and outcomes (continued)

| Author, Year | Nausea Relief within 2 hours | Photophobia Relief within 2 hours | Adverse events | Withdrawals due to adverse events | Chest Pain or tightness |
|---|---|---|---|---|---|
| Eletripan Steering Committee in Japan, 2002 | ele=30%; 26%; 59%<br>pla=32% | ele=16%; 17%; 14%<br>pla=29% | Total: ele=16.3%; 32.5%; 45.5%; pla=15.5%<br>Asthenia: ele=1.3%, 2.5%, 11.7%; pla=1.2%<br>Parasthesia: ele=0, 3.8%, 1.3%; pla=0<br>Somnolence: ele=6.3%, 10.0%, 16.9%; pla=3.6% | None | Vasodilation: ele=1.3%, 0, 3.9%; pla=1.2% |
| Sakai, 2002 | zol=46.7%, 38.9%, 35.3%<br>pla=45.8% | zol=17.8%, 16.7%, 21.6%<br>pla=22.9% | Asthenia: zol=1.9%, 1.6%, 7.0%; pla=1.7%<br>Parathesia: zol=0, 0, 5.3%; pla=0<br>Somnolence: zol=0, 3.3%, 5.3%; pla=1.7% | nr | nr |

nr = not reported