Drug Class Review
on
the Triptans

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TABLE OF CONTENTS

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 (ie, 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]

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.

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.

Within the research literature, what kinds of studies provide the best evidence by which to compare different triptan drugs? It is widely agreed that well-designed, double-blind, randomized controlled trials that directly compare two or more triptans provide the best evidence, *if* they compare several effectiveness measures as well as adverse events, enabling the reader to judge the "trade-offs" between the compared drugs.[15] This review emphasizes these "head-to-head" trials.

For some outcome measures and some combinations of triptans, head-to-head trials do not exist. In these cases, trials using active or placebo controls may be helpful. Although they do not directly address how triptans compare, randomized trials comparing a triptan to a nontriptan drug or to a placebo can provide information on which triptans have been demonstrated to improve certain outcomes and which have not.

Scope and Key Questions

The 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, 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 (2002, Issue 3), Medline (1966-November, 2002), EMBASE (1980-November, 2002), 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. The criteria are available at (available at http://www.ohsu.edu/epc/ after 3/10/03). 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 sufferes, 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

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 I, 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 I, 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 I, 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 I, Table 4.

Randomized, Controlled Head-to-Head Trials

The electronic searches, in combination with submissions from manufacturers and review of reference lists, identified 891 publications, including 168 controlled trials (see Figure 1). Sixty-six trials were excluded 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), or the wrong outcomes (that is, none of the outcomes listed in Table 2.) We identified 29 head-to-head trials and 28 trials of a triptan vs. an active control (such as an ergot drug or NSAID). The remaining trials were open-label (54) or placebo-controlled randomized trials. From the placebo-controlled trials, we selected those that concerned the efficacy of triptans for subgroups of interest, migraine associated with menstruation, or long-term outcomes not addressed in head-to-head trials.

Of the 29 randomized, controlled head-to-head trials of various triptans, eight met the inclusion criteria for this key question. As summarized in Appendix II, 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, four trials[28, 34-36] were excluded because they used encapsulated sumatriptan rather than standard sumatriptan tablets. While data about the effects of encapsulation are conflicting,[37-39] 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. The results of recent studies that used encapsulation are summarized in Appendix III.

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 were baseline differences in the compared groups. These differences, while they did not in themselves confound the study results, they 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. Seven of the nine trials had a sumatriptan comparator. In these trials, sumatriptan was compared with rizatriptan (3 trials), zolmitriptan (3 trials), and naratriptan (1 trial). The 2 other trials compared rizatriptan to naratriptan and to zolmitriptan.[40, 41] None of the included studies evaluated almotriptan, eletriptan, or frovatriptan (See Appendix II).

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.[42] 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.[41] 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%).[43] 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),[44] 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[45] 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.[40] 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. [46, 47] or sumatriptan 100 mg.[48] 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%; $p<0.001$).[47]

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.

0.5-hour pain relief(% of patients)

Ref.	Internal Validity	p value	R5	R10	S25	S50	S100	Z2.5	Z5	N2.5
Bomhof [41]	Fair	NS	-	14	-	-	-	-	-	11
Pascual [40]	Fair	NS	-	14	-	-	-	14.9	-	-
Tfelt-Hansen [45]	Fair	NS	12	13	-	-	11	-	-	-

0.5-hour pain free(% of patients)

Ref.	Internal Validity	p value	R5	R10	S25	S50	S100	Z2.5	Z5	N2.5
Bomhof [41]	Fair	NS	-	1.5	-	-	-	-	-	1
Pascual [40]	Fair	NS	-	2.7	-	-	-	0.7	-	-
Tfelt-Hansen [45]	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,[41] zolmitriptan 2.5 mg,[40] and sumatriptan 100 mg;[45] 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.[46, 47]

One-hour pain relief(% of patients)

Ref.	Internal Validity	p value	R5	R10	S25	S50	S100	Z2.5	Z5	N2.5
Havanka[42]	Poor-Fair	NS	-	-	-	-	35	-	-	30
Bomhof[41]	Fair	p<0.029	-	**38**	-	-	-	-	-	**27.8**
Pascual[40]	Fair	p<0.03	-	**42.5**	-	-	-	**35.3**	-	-
Tfelt-Hansen[45]	Fair	p=0.010	30	**37**	-	-	**28**	-	-	-
Geraud[48]	Fair	NS	-	-	-	-	35	-	34	-
Gallagher[47]	Good	p=0.017	-	-	39.2	**41.7**	-	43.4	**45.5**	-
Gruffyd-Jones[46]	Good	NS	-	-	-	38	-	36.9	39.5	-

Seven 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 [45] and to zolmitriptan 5 mg,[48] 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%, $p<0.05$).[41] 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 sumatriptan 100 mg, zolmitriptan 2.5 mg, and naratriptan 2.5 mg, more patients taking rizatriptan 10 mg were pain-free 2 hours. Sumatriptan 100 mg and zolmitriptan 5 mg had similar efficacy.

Two-hour pain-free(% of patients)

Ref.	Internal Validity	p value	R5	R10	S25	S50	S100	Z2.5	Z5	A12.5	N2.5
Bomhof[41]	Fair	<0.001	-	**44.8**	-	-	-	-	-	-	**20.7**
Pascual[40]	Fair	<0.05	-	**43.2**	-	-	-	**35.6**	-	-	-
Tfelt-Hansen[45]	Fair	<0.05	25	**40**	-	-	**33**	-	-	-	-
Lines[49]	Fair	NS	22	**-**	-	28	-	-	-	-	-
Geraud[48]	Fair	NS	-	**-**	-	**-**	30	-	29	-	-
Gruffyd-Jones[46]	Good	NS	-	**-**	-	35.3	-	32.4	36	-	-

Satisfaction. Four included trials reported two-hour satisfaction outcomes. 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[40] 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[41] 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. Three 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[45] 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[45] demonstrated superiority of rizatriptan 10 mg to sumatriptan 100 mg (27% vs. 19%; p=0.017). Finally, at 2 hours, three trials[40, 41, 45] showed continued superiority of rizatriptan 10 mg over sumatriptan 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 I, 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 zolmitriptan 5 mg (Geraud) or rizatriptan 10 mg (Tfelt-Hansen).[43] There were also no differences between sumatriptran 50 mg and zolmitriptan 2.5 mg (Gruffyd-Jones, Gallagher)[46, 47] or rizatriptan 5 mg (Lines). Rizatriptan 10 mg was superior to zolmitriptan 2.5 mg (Pascual, NNT=11)[43] and naratriptan 2.5 mg (Bomhof, NNT=8.3),[41] and zolmitriptan 2.5 mg and zolmitriptan 5 mg were superior to sumatriptan 25 mg. The remaining study (Havanka) defined a sustained response as no worsening of headache, recurrence, or use of rescue medication from 4 to 24 hours;[42] 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.

Use of additional or escape medications (% patients)

Ref.	Internal Validity	Escape or additional medication	P value	R5	R10	S25	S50	S100	Z2.5	Z5	A12.5	N2.5
Bomhof[41]	Fair	Additional	NS	-	40.3	-	-	-	-	-	-	46.5
Pascual[40]	Fair	Additional	NS	-	39.4	-	-	-	43.6	-	-	-
Gruffyd-Jones[46]	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%; $p<0.05$)[45] and zolmitriptan 2.5 mg (74.8 vs. 67.5; $p=0.046$).[40] 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.[40, 41] Rizatriptan 10 mg was found to be equal to sumatriptan 100 mg[45] 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%) ($p<0.05$).[41] 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, however.

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.[47, 50] 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.

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.[51] 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.[46] 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%, $p <= 0.001$)[52] In another randomized, open-label, crossover trial,[53] 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.[54] 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.[55]

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 6. 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[56]	Almotriptan, 12.5 mg, open study	806	1 year	81%	Yes	51.3% of patients
Gerth, 2001[57]	Almotriptan, 12.5 mg, open study	582	6 months	76%	Yes	Drug-related chest pain 1.5%
Heywood, 2000[58]	Naratriptan, 2.5 mg, open study	417	1 year	70%	Yes	16% of attacks
Cady, 2001[59]	Rizatriptan wafer, various doses, open study	458	6 months	82%	Yes	
Tansey, 1993[60]	Sumatriptan, 100 mg, open study	288	1 year	84%	Yes	16%
Tepper, 1999[61]	Zolmitriptan, 2.5 and 5 mg, open study	2,499	9 months	~85%	Yes	65.7%
Cady, 2001[59]	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.[62-67] 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.[68] Productivity was also an outcome measure in a trial of stratified vs. stepped care for migraine that involved zolmitrptan.[69] Open-label, nonrandomized study data also supports the view that use of oral sumatriptan improves work attendance, productivity, and quality of life.[64, 70, 71] and reduces disability and health care utilization.[72, 73] Other improved outcomes evaluated in observational studies include health-related quality of life (rizatriptan[64] and zolmitriptan[74]).

Trials of triptans vs. active controls

Eighteen trials of triptans versus other treatments to shorten a migraine attack met the inclusion criteria. These trials are summarized in Appendix IV, Tables 1 and 2. All but 3 of the 18 trials compared sumatriptan, the first triptan, to other treatments for migraine.[65, 75-88] 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 [75] comparing sumatriptan 100 mg to cafergot (2 mg ergotamine tartrate, 200 mg caffeine) and one trial[89] 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%; $p<0.001$).

Seven trials reported pain relief at two hours. Only two of these trials noted significant findings.[75, 90] In the first of these, two-hour pain relief was experienced by 66% of patients taking sumatriptan 100 mg and 48 % of those taking cafergot ($p<0.001$). In the second trial, the percentage of patients with two-hour headache relief was 90 % with rizatriptan 10 mg and 70% with standard care ($p<0.05$). 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.

Five trials reported two-hour pain free endpoints. Data from four of these trials show that triptans (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.[84]

In two trials,[75, 78], higher proportions of patients taking sumatriptan 100 mg regarded the therapy as good-excellent when compared to an ergot alkaloid or an NSAID. However, an additional two trials[85, 87] reported 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[79, 80, 82, 85] demonstrated an earlier restoration of ability to resume activities of daily living in patients taking various preparation types of sumatriptan. One trial[83] was notable because it demonstrated improvements in HRQOL over standard treatments—an advantage that had been repeatedly demonstrated earlier for sumatriptan.

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.[78, 80, 87, 90] However, in three additional trials,[75, 77, 89] 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 more often than moderate or severe ones. Retrospective analyses of this kind provide very weak evidence that triptans may be effective in mild headache.[91, 92]

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.[93] 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.[94] 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.[95] 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.[96]

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.[97-99] 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.[100] 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.[101] The only published trial of sumatriptan nasal spray found that it is much less effective than sumatriptan given subcutaneously.[102]

Oral zolmitriptan was evaluated for cluster headache in one double-blind, randomized crossover trial.[103] 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.[104] In 1998, 16 serious cardiovascular events following use of sumatriptan sc, and 11 following oral sumitriptan 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,[45] 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, parasthesias, 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%).[45]

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?

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.[105-109] 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.

Migraine is more common among women than men and in Whites than in Blacks, and peaks in prevalence around age forty.[110] 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.[111] 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.

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.[112] 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.[113-115]

We identified one double-blind RCT of a triptan to prevent migraines associated with menses.[116] 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.[117]

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 III.[35, 118] Apart from encapsulation, the study had serious flaws and was rated poor-quality (see Appendix II). We identified two published trials of eletriptan vs. encapsulated sumatriptan 100 mg.[36, 119] The results, summarized in Appendix III, 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]

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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