

Drug Class Review on Triptans



Update #4: Preliminary Scan Report #2

March 2008

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

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OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update:

Update #3 Final Report was completed in November of 2005. First preliminary scan for Update #4 was performed in March of 2007.

Scope and Key Questions

Key Questions

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?
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?

Inclusion Criteria

Population

Adult patients with migraine. Definition of migraine must be explicit, to exclude other types of headache (e.g. tension headache). Any level of migraine (mild, moderate, severe) and with or without aura will be included.

Interventions (oral, nasal and injectable)

Almotriptan (Axert)
Eletriptan (Relpax)
Frovatriptan (Frova)
Naratriptan HCL (Amerge)
Rizatriptan (Maxalt)
Rizatriptan orally disintegrating tablet (Maxalt-MLT)
Sumatriptan (Imitrex)

Zolmitriptan (Zomig)

Zolmitriptan orally disintegrating tablet (Zomig-ZMT)

Effectiveness 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 (e.g., change in days of work lost), quality of life, or adverse effect (including drug interactions).
- Measures: Response, time to response, pain free, sustained response, sustained pain free, significant response, rescue (use of rescue medications), relapse (reappearance of any degree of symptoms within 48 hours) after response or becoming pain free, time to relief and relief of associated symptoms.

Safety outcomes

- Withdrawals
- Withdrawals due to adverse effects
- Withdrawals due to specific adverse effects (e.g., CNS effects, chest tightness)

Study designs

1. For effectiveness, study is a controlled clinical trial in an outpatient setting or a good-quality systematic review.
2. For safety, the study is a controlled clinical trial or observational study.

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE (January 2007 to March 2008). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 38 potentially relevant citations in this scan. Of those, there are 7 new potentially relevant controlled clinical trials (Appendix A). Taken together with the 18 new trials identified in the last preliminary update scan, there are now 25 new trials to consider in deciding whether or not to initiate a full update of this review.

From the previous preliminary update scan, the majority of the new studies were placebo-controlled and were exploring alternative usages of triptans such as for early treatment of mild pain with eletriptan, rizatriptan, or sumatriptan or for treatment of morning or probable migraine with sumatriptan. There was only one new head-to-head trial and it compared eletriptan tablets to rizatriptan wafers in patients with moderate-severe migraine pain (Lainez 2006).

The Table below provides an accounting of the treatment comparisons addressed in the 7 new trials identified in the current preliminary update scan. Two of the new head-to-head trials involved comparisons with almotriptan, which has historically been one of the two triptans with the lowest strength of evidence of direct comparisons to other triptans. The other head-to-head trial compared two different oral forms of zolmitriptan 2.5mg, which is the less common of the two usual recommended dosages of 2.5 or 5mg.

Trial	Treatments
Brandes 2007	Sumatriptan-naproxen combination product vs sumatriptan vs naproxen vs placebo
Diez 2007	Almotriptan 12.5mg vs rizatriptan 10mg
Dowson 2007	Zolmitriptan ODT 2.5mg vs zolmitriptan film-coated tablets 2.5mg
Goadsby 2007	Almotriptan 12.5 vs zolmitriptan 2.5mg
Lainez 2007	Almotriptan 12.5mg vs ergotamine 2mg/caffeine 200mg
Mathew 2007	Almotriptan 12.5 vs placebo in early migraine
Silberstein 2007	Eletriptan 20mg or 40mg vs placebo for functional/work productivity

New Drugs

Sumatriptan subcutaneous injectable STATdose 4mg: approved on 2/1/2006
 Sumatriptan-naproxen fixed-dose-combination-tablet (Trexima): approval expected in late 2008

New Indications

None

New Safety Alerts

None

APPENDIX A

Brandes, J. L., D. Kudrow, et al. (2007). "Sumatriptan-naproxen for acute treatment of migraine: a randomized trial.[see comment]." *JAMA* **297**(13): 1443-54.

CONTEXT: Multiple pathogenic mechanisms may be involved in generating the migraine symptom complex, and multimechanism-targeted therapy may confer advantages over monotherapy. **OBJECTIVE:** To evaluate the efficacy and safety of a fixed-dose tablet containing sumatriptan succinate and naproxen sodium relative to efficacy and safety of each monotherapy and placebo for the acute treatment of migraine. **DESIGN, SETTING, AND PARTICIPANTS:** Two replicate, randomized, double-blind, single-attack, parallel-group studies conducted among 1461 (study 1) and 1495 (study 2) patients at 118 US clinical centers who were diagnosed as having migraine and received study treatment for a moderate or severe migraine attack. **INTERVENTIONS:** Patients were randomized in a 1:1:1:1 ratio to receive a single tablet containing sumatriptan, 85 mg, and naproxen sodium, 500 mg; sumatriptan, 85 mg (monotherapy); naproxen sodium, 500 mg (monotherapy); or placebo, to be used after onset of a migraine with moderate to severe pain. **MAIN OUTCOME MEASURES:** Primary outcome measures included the percentages of patients with headache relief 2 hours after dosing, absence of photophobia, absence of phonophobia, and absence of nausea for the comparison between sumatriptan-naproxen sodium and placebo, and the percentages of patients with sustained pain-free response for the comparison between sumatriptan-naproxen sodium and each monotherapy. **RESULTS:** Sumatriptan-naproxen sodium was more effective than placebo for headache relief at 2 hours after dosing (study 1, 65% vs 28%; $P < .001$ and study 2, 57% vs 29%; $P < .001$), absence of photophobia at 2 hours (58% vs 26%; $P < .001$ and 50% vs 32%; $P < .001$), and absence of phonophobia at 2 hours (61% vs 38%; $P < .001$ and 56% vs 34%; $P < .001$). The absence of nausea 2 hours after dosing was higher with sumatriptan-naproxen sodium than placebo in study 1 (71% vs 65%; $P = .007$), but in study 2 rates of absence of nausea did not differ between sumatriptan-naproxen sodium and placebo (65% vs 64%; $P = .71$). For 2- to 24-hour sustained pain-free response, sumatriptan-naproxen sodium was superior at $P < .01$ (25% and 23% in studies 1 and 2, respectively) to sumatriptan monotherapy (16% and 14% in studies 1 and 2), naproxen sodium monotherapy (10% and 10% in studies 1 and 2), and placebo (8% and 7% in studies 1 and 2). The incidence of adverse events was similar between sumatriptan-naproxen sodium and sumatriptan monotherapy. **CONCLUSION:** Sumatriptan, 85 mg, plus naproxen sodium, 500 mg, as a single tablet for acute treatment of migraine resulted in more favorable clinical benefits compared with either monotherapy, with an acceptable and well-tolerated adverse effect profile. **TRIAL REGISTRATION:** clinicaltrials.gov Identifiers: NCT00434083 (study 1); NCT00433732 (study 2).

Diez, F. I., A. Straube, et al. (2007). "Patient preference in migraine therapy. A randomized, open-label, crossover clinical trial of acute treatment of migraine with oral almotriptan and rizatriptan." *Journal of Neurology* **254**(2): 242-9.

OBJECTIVE: To assess patient preference for almotriptan 12.5 mg vs rizatriptan 10 mg for the acute treatment of migraine. **METHODS:** Randomized, multicenter, open-label, crossover trial in which triptan-naïve patients treated two moderate/severe migraine attacks, the first with one triptan and the second with the other: 183 patients took rizatriptan followed by almotriptan and 189 treated in the reverse order. Patient preference was assessed with a self-administered questionnaire. **RESULTS:** Of those recording a preference (209), 54.5% preferred almotriptan, but statistical significance was not achieved. The main reason for preference for one or the other triptan was efficacy: 43% of patients preferring almotriptan gave faster headache relief as the reason and 34% cited faster return to normal activities. The corresponding values for rizatriptan were 47% and 38%. A significantly greater proportion of those preferring almotriptan cited fewer adverse events (AEs) as the reason. Almotriptan and rizatriptan were of comparable efficacy and

both treatments were well tolerated; 9% of patients experienced AEs probably or possibly related to study medication after almotriptan vs 14% after rizatriptan. Almotriptan was associated with a significantly lower incidence of triptan-associated AEs in triptan-naïve patients (8.5% vs 18% with rizatriptan). **CONCLUSION:** Physicians should use information from meta-analyses and preference studies like this one to aid in the selection of a triptan with a high likelihood of providing rapid, sustained relief from pain coupled with an absence of AEs. About 55% of patients recording a preference in this trial preferred almotriptan, perhaps because of its combination of good efficacy and lower incidence of triptan-associated AEs.

Dowson, A., M. Bundy, et al. (2007). "Patient preference for triptan formulations: a prospective study with zolmitriptan." *Headache* **47**(8): 1144-51.

OBJECTIVES: To investigate patterns of patient preference for 3 formulations of zolmitriptan, in a primary care study utilizing a naturalistic longitudinal design. **BACKGROUND:** Although differences in efficacy between individual triptans tend to be small, migraine patients show clear preferences for individual triptans and formulations. The groups of patients suitable for the different triptan formulations, and the reasons underlying individual preferences, are not clearly understood. **METHODS:** Migraine patients entered a prospective, randomized, open, crossover, longitudinal design study, with patients receiving zolmitriptan formulations according to UK prescribing recommendations. Patients naïve to zolmitriptan received zolmitriptan 2.5-mg film-coated tablets or 2.5-mg Orally Disintegrating Tablets (ODT) for 1 month, before being crossed over to receive the alternative formulation for Month 2. All patients then received zolmitriptan nasal spray 5 mg for Month 3. Patients could then choose the formulation(s) of their choice for a further 7 months. Patients recorded their preferences for individual formulations, the reasons for their preferences, and also the headache-related disability (measured by the Migraine Disability Assessment [MIDAS] score) at clinic visits. Primary endpoints were the individual preferences and changes in MIDAS scores. Adverse events were also recorded. **RESULTS:** Forty-eight patients took part in the study. At baseline, most patients expressed a preference for conventional tablets. After 4 months, 46.9% of patients preferred zolmitriptan ODT, 43.8% zolmitriptan nasal spray, and 6.3% the conventional tablet. The most common reasons given for preferring conventional tablets were personal reasons: for zolmitriptan ODT, convenience and, to a lesser extent, speed of onset; for zolmitriptan nasal spray, speed of onset, and overall efficacy. MIDAS scores decreased significantly following treatment with zolmitriptan. Zolmitriptan was well tolerated. **CONCLUSIONS:** Patient experience of newer zolmitriptan formulations influenced a change in preference away from conventional tablets. Speed and efficacy were the key drivers of preference for zolmitriptan nasal spray, while convenience mostly drove preference for the ODT formulation. Open, longitudinal, naturalistic studies may, allowing for biases, sometimes be an appropriate way of conducting migraine studies in primary care.

Goadsby, P. J., H. Massiou, et al. (2007). "Almotriptan and zolmitriptan in the acute treatment of migraine." *Acta Neurologica Scandinavica* **115**(1): 34-40.

OBJECTIVE: To compare almotriptan and zolmitriptan in the treatment of acute migraine. **METHODS:** This multicentre, double-blind trial randomized adult migraineurs to almotriptan 12.5 mg (n = 532) or zolmitriptan 2.5 mg (n = 530) for the treatment of a single migraine attack. The primary end point was sustained pain free plus no adverse events (SNAE); other end points included pain relief and pain free at several time points, sustained pain free, headache recurrence, use of rescue medication, functional impairment, time lost because of migraine, treatment acceptability, and overall treatment satisfaction. **RESULTS:** No significant difference was seen in SNAE (almotriptan 29.2% vs zolmitriptan 31.8%) or the other efficacy end points measured. The incidence of triptan-associated AEs and triptan-associated central nervous system AEs was significantly lower for patients receiving almotriptan compared to zolmitriptan. **CONCLUSIONS:** Almotriptan and zolmitriptan were associated with similar efficacy and overall tolerability in the

treatment of acute migraine. Almotriptan was associated with a significantly lower rate of triptan-associated AEs.

Lainez, M. J. A., J. Galvan, et al. (2007). "Crossover, double-blind clinical trial comparing almotriptan and ergotamine plus caffeine for acute migraine therapy." *European Journal of Neurology* **14**(3): 269-75. In this randomized, double-blind, crossover clinical trial, adult patients treated two migraine attacks: one with almotriptan 12.5 mg and the other with ergotamine 2 mg plus caffeine 200 mg. Treatment with almotriptan was associated with a significantly greater proportion of patients achieving 2-h pain free (20.9% vs. 13.7%; $P < 0.05$) and 2-h pain relief (57.7% vs. 44.5%; $P < 0.01$) compared with ergotamine plus caffeine therapy; significant differences were not seen at 1 h. Rates for sustained pain free and sustained pain free plus no adverse events (AEs) also were significantly greater after almotriptan treatment than after the use of ergotamine plus caffeine ($P < 0.05$). Almotriptan was associated with a significantly lower rate of photophobia at 90 min ($P < 0.05$), phonophobia at 60, 90, and 120 min ($P < 0.05$ to <0.01), and nausea and vomiting at 90 and 120 min ($P < 0.01$) compared with ergotamine plus caffeine. A significantly greater proportion of patients were more satisfied with almotriptan than with ergotamine plus caffeine ($P < 0.05$). Sixteen patients reported adverse events during almotriptan treatment and 27 patients reported AEs during the ergotamine plus caffeine therapy. Most AEs were mild-to-moderate and did not result in treatment-related discontinuations. In conclusion, almotriptan was associated with significantly greater efficacy for treating migraine compared with ergotamine plus caffeine, was generally well tolerated and was associated with greater rate of treatment satisfaction.

Mathew, N. T., G. Finlayson, et al. (2007). "Early intervention with almotriptan: results of the AEGIS trial (AXERT Early Migraine Intervention Study)." *Headache* **47**(2): 189-98.

OBJECTIVE: To evaluate prospectively the efficacy and safety of almotriptan 12.5 mg as compared to placebo when administered within 1 hour of headache pain onset for the acute treatment of 3 migraine headaches. **BACKGROUND:** Although clinical trials have reported improved outcomes when triptans were used early or to treat mild pain, acceptance of this treatment strategy has been hampered by both efficacy and tolerability issues. **METHODS:** In this multicenter, double-blind, placebo-controlled, parallel-group trial, patients with IHS-migraine were randomized in a 1:1 ratio to treat 3 consecutive migraine attacks with either almotriptan 12.5 mg or placebo. Patients were instructed to take their study medication at the first sign of headache pain of any intensity, within 1 hour of onset, and to record their symptoms at multiple time points during their headaches using a personal digital assistant. Clinical trial efficacy results for the first study headache and safety data for the entire study are presented. **RESULTS:** A total of 378 patients were randomized, 189 to each group; 162 almotriptan-treated patients, and 155 placebo-treated patients were evaluable for efficacy. Almotriptan treatment, compared to placebo, resulted in a significantly greater proportion of patients achieving 2-hour pain free (37.0% vs 23.9%, $P = .010$), 2-hour pain relief (72.3% vs 48.4%, $P < .001$) and sustained pain free (24.7% vs 16.1%, $P = .040$). Significant differences in pain free ($P = .026$) and pain relief ($P = .019$) between almotriptan and placebo also were observed at 1 hour. At 2 to 4 hours and 4 to 24 hours after treatment, the mean intensity of phonophobia and photophobia were significantly lower in the patients treated with almotriptan compared to the placebo-treated patients. A greater proportion of patients treating with almotriptan versus placebo reported normal functionality within 2 hours postdose (54.4% vs 38.1%, $P = .007$) and 4 hours postdose (74.5% vs 54.3%, $P < .001$). The percentage of patients experiencing 1 or more treatment-emergent adverse events (AE) was 9.8% for almotriptan and 6.4% for placebo. The only treatment-emergent AEs that occurred with a frequency of at least 1% (equivalent to 2 or more patients) in the almotriptan and placebo groups, respectively, were somnolence (1.1% and 2.3%), nausea (1.1% and 1.7%), vomiting (1.1% and 0.6%), and fatigue (1.1% and 0%). **CONCLUSION:** Treatment with almotriptan within 1 hour of migraine onset resulted in significantly better clinical outcomes than placebo and tolerability

similar to placebo. Acute medications, such as almotriptan, that are both effective and well tolerated may encourage patients to access acute treatment earlier.

Silberstein, S. D., R. K. Cady, et al. (2007). "Efficacy of eletriptan in migraine-related functional impairment: functional and work productivity outcomes." *Headache* 47(5): 673-82.

OBJECTIVE: To provide a multidimensional assessment of the extent of functional impairment during an acute migraine attack, and of the improvement in functioning in response to treatment, using 4 concurrently administered scales: the 7-item work productivity questionnaire (PQ-7), the functional assessment in migraine (FAIM) activities and participation (FAIM-A&P) subscale, the FAIM-impact of migraine on mental functioning (FAIM-IMMF) subscale, and the traditional 4-point global functional impairment scale (FIS). **METHODS:** Outpatients with an International Classification of Headache Disorders diagnosis of migraine were randomized to double-blind treatment of a single attack with either oral eletriptan 20 mg (n = 192) once-daily, eletriptan 40 mg (N = 213) once-daily, or placebo (n = 208). Patients were encouraged to take study medication as soon as they were sure they were experiencing a typical migraine headache, after the aura phase (if present) had ended. Patients with moderate-to-severe functional impairment were identified on each of the 4 disability scales, and 2-hour functional response was compared between treatments. **RESULTS:** At baseline, the PQ-7 and FAIM-IMMF items that assessed ability to perform tasks requiring concentration, sustained work or attention, and ability to think quickly or spontaneously, were especially sensitive to the effects of mild headache pain, with 27% to 48% of patients (n = 92-112) reporting moderate-to-severe impairment. Only 11.3% of patients (n = 112) reported this level of impairment due to mild pain on the FIS. Functional response at 2 hours was significantly higher on eletriptan 40 mg versus placebo on the FAIM-A&P (63% vs 36%; n = 218; P < .0001); on the PQ-7 (56% vs 34%; n = 116; P = .0052); and on the FAIM-IMMF (50% vs 34%; n = 215; P = .017). These rates were all lower than the functional response rates on the FIS for eletriptan 40 mg (75%) and eletriptan 20 mg (70%) versus placebo (45%; P < .001). **Conclusions.**-In this exploratory analysis, use of multidimensional scales was found to provide a sensitive measure of headache-related functional impairment, especially for detecting clinically meaningful cognitive effects, and for detecting drug versus placebo differences.