Oregon State University College of Pharmacy
Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35, Salem, Oregon 97301-1079
Phone 503-945-5220 | **Fax** 503-947-1119

Month/Year of Review: March 2012
PDL Class: Triptans

Date of Last Review: March 2010 (literature through 2008)
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Current Preferred Agents:		Current Non-Preferred Agents:	
Sumatriptan (Imitrex ®) Injection	Sumatriptan Succinate Oral	Eletriptan (Relpax®)	Zolmitriptan (Zomig®)
Sumatriptan (Imitrex®) Nasal	Zolmitriptan (Zomig®) Nasal	Frovatriptan (Frova®) oral	Sumatriptan/naproxen (Treximet®)
Naratriptan Oral		Naratriptan	
		Rizatriptan (Maxalt®) oral	Almotriptan (Axert®) oral

Previous Recommendations:

1. In comparing the effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms in adult patients with moderate to severe migraine the oral triptans were similarly efficacious.
2. Good strength evidence for reformulated sumatriptan/naproxen versus reformulated sumatriptan 85 mg found the combination superior in pain-free at 2 hours and 24 hours and in normal renal function, overall productivity, and patient satisfaction. There is no evidence comparing the combination product to an available dose of sumatriptan. There is no evidence comparing the combination product to individual component therapy.
3. There are no fully published head-to-head trials of frovatriptan.
4. Injectable sumatriptan is effective, but there are no acceptable head-to-head studies comparing injectable to the oral form.
5. Nasal sumatriptan and zolmitriptan are effective, but there is insufficient data to determine a clinically significant difference for the comparison of zolmitriptan nasal spray vs. the oral form of the drug. There were no head to head trials comparing sumatriptan nasal spray to the oral form of the drug.
6. Most of the studies were rated fair quality or below because of variability in endpoints and lack of standard measures for pain relief or time to pain relief.
7. Based on poor strength evidence there is no evidence that any one triptan has a particular advantage or disadvantage over others in any subgroups based on age, gender, race, use of prophylactic treatment, or association with menstruation.

PA Criteria/QL: A Prior Authorization is in place to promote preferred PDL options, quantity limits to decrease potential for medication overuse, and therapeutic duplication denials.

Methods:
A MEDLINE OVID search was conducted using all included drugs in adults with any level of migraine and limits for humans, English language, and controlled clinical trials or meta-analysis from 2009 to current. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Trials:

A total of 51 citations resulted and after review for inclusions, nine potentially relevant clinical trials were identified, including 2 head to head trials that were not post-hoc sub analysis. The abstracts of these are included in appendix 1.

Study	Comparison	Population	Primary Outcome	Results	
Steeburger, et al.[1] RCT, PC, DB	Rizatriptan 10-mg ODT vs. placebo	Non-responders to sumatriptan	Two hour pain relief	<u>Response rate – two hour pain relief:</u> Riza 51% Placebo 20% RR 2.55; P<0.001	
Bartolini et al.[2] RCT, DB	Frovatriptan 2.5mg vs. almotriptan 12.5mg	History of migraine with or without aura, with at least one attack in the preceding 6 mo	Patient satisfaction	<u>Preference Score:</u> F: 3.1 ± 1.3 A: 3.4 ± 1.3 P = NS	<u>Response rate – two hour pain relief:</u> F: 143 (54%) A: 144 (56%) RR 0.96; p=NS
Allias, et al.[3] RCT, DB, PC	Almotriptan vs. placebo	Women with menstrually related migraine	Two hour pain relief	<u>Pain free at two hours:</u> A: 59 (48.4%) Pl: 32 (26.2%) RR 1.81 95% CI (1.28 -2.57); P=0.008	
Tullo, et al.[4] RCT, DB	Frovatriptan 2.5mg vs. zolmitriptan 2.5mg	Male or female subjects, 18–65 y/o, current history of migraine with or without aura	Patient satisfaction	<u>Preference Score:</u> F: 2.9 ± 1.3 Z: 3.0 ± 1.3 P = NS	<u>Response rate – two hour pain relief:</u> F: 141 (57%) A: 142 (58%) RR 0.98; p=NS
Allias, et al.[5] Post-hoc subanalysis	Forvatriptan 2.5mg vs. zolmitriptan 2.5mg	Analysis of women with menstrually related migraine selected from Tullo RCT	Number of pain-relief episodes at 2 and 24 hr.	<u>Risk of Recurrence</u> F: 11 (15%) Z: 14 (22%) P<0.05	<u>Response rate – two hour pain relief:</u> F: 31 (52%) Z: 26 (53%) RR 0.98 95% CI (0.6 to 1.5) P = NS
Spierings, et al[6] Long term, open label	Frovatriptan 2.5mg vs. placebo	Male or female, 18–65 y/o, migraine with or without aura	Tolerability and safety of frovatriptan	173 (36%) of the 486 subjects in the study did not take a second dose at 2 hours for nonresponse.	
Matthew, et al.[7] Analysis of 2 RCT, DB, PC studies	Sumatriptan/naproxen vs. placebo	Those who had discontinued a short-acting triptan in the past year because of poor response or intolerance	Number of patients with 2- through 24-hour sustained pain-free response	<u>2-hour pain free response</u> *Study 1* S/N: 54 (40%) P: 23 (17%) RR 2.35 95% CI (1.5 - 3.7) P<0.001	 *Study 2* S/N: 58 (44%) P: 19 (14%) RR 3.14 95% CI (1.9 -5) P<0.001
Cady, et al.[8] RCT, PC, DB	Rizatriptan 10mg ODT vs. placebo	≥ 18 y/o, at least a 1-year history of migraine with or without aura	Pain freedom at 2 hours	<u>Response rate – two hour pain relief:</u> R: 66% P: 28% RR 2.4 95%CI (1.68 to 3.49); P<0.001	
Ng-Mak, et al.[9] Post-hoc subanalysis, open-label	Rizatriptan 10mg vs. almotriptan 12.5mg	≥ 18 y/o, recent history of ≥1 migraines/month, rizatriptan naïve.	the times to onset of Pain relief (PR) and pain freedom (PF)	<u>Onset of PR in 2 hr</u> R: 88.6% A: 73.4% RR 1.2; P=0.007	<u>Onset of PF in 2 hr</u> R: 55.7% A: 45.6% P=NS

RCT = randomized controlled trial, PC = placebo controlled, DB = double blind

New drugs:
There were no new molecular entities FDA approved. A new formulation of sumatriptan was FDA-approved in July, 2009 for the acute treatment of migraine attacks with or without an aura.[10] Sumavel DosePro (sumatriptan) is a needle-free subcutaneous delivery system that delivers 6 mg of sumatriptan subcutaneously with a high-pressure burst of nitrogen gas instead of a needle. The needle-free system works as fast and as well as the needle injections but it can actually cause more redness, swelling, bleeding, and bruising than a needle injection. Approval was based on the demonstration of bioequivalence with traditional injected subcutaneous sumatriptan. An open-label study found the rates of attacks associated with pain relief were 30.7%, 66.4%, 80.1%, 81.6%, and 77.6% at 0.25, 0.5, 1, 2, and 24 hours after dosing, respectively.[11] Also patient satisfaction improved from baseline to the end of treatment for efficacy and functionality, but declined for ease of use (79.6±16.0 versus 69.7±25.6, p=0.0007).[11]

New FDA Indications:
Almotriptan: Acute treatment of migraine in adolescents, aged 12 to 17 years - 5/2009

New FDA safety alerts:
The only new safety information identified included changes to the Warnings and Precautions section of the product labels for almotriptan and frovatriptan. In March of 2009, information concerning the risk of serotonin syndrome with concomitant use of SSRIs/SNRIs was added for both almotriptan and frovatriptan. Additionally for almotriptan, in April of 2009, advice was added that, due to its chemical structure containing a sulfonyl group, caution should be used in prescribing almotriptan to patients with known hypersensitivity to sulfonamides.

New Systematic Reviews:
Four recent systematic reviews from the Cochrane Collaboration were published evaluating the efficacy of sumatriptan as oral, subcutaneous, intransal, and rectal routes of administration in acute migraine attacks in adults (Appendix 2).[12-15] These reviews concluded that oral, subcutaneous, and intransal sumatriptan is effective as an abortive treatment for migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability, but are associated with increased adverse events. There was limited data for sumatriptan administered rectally (3 studies; 866 participants) that demonstrated 25 mg administered rectally an effective treatment for acute migraine attacks in reducing pain and functional disability.[12] But there was insufficient data to make conclusions on the relief of headache-associated symptoms or incidence of adverse events for rectal administration of sumatriptan.

Twelve studies (4755 participants) compared intranasal sumatriptan with placebo or an active comparator.[13] Most of the data were for the 10 mg and 20 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes. Pain was reduced from moderate or severe to no pain by two hours in approximately 2 in 10 people (24%) taking sumatriptan 10 mg, compared with about 1 in 10 (10%) taking placebo.[13] Pain was reduced from moderate or severe to no worse than mild pain by two hours in 5 in 10 people (50%) taking sumatriptan 10 mg, compared with approximately 3 in 10 (32%) taking placebo. Direct comparison of sumatriptan with active treatments was limited to two studies, one comparing sumatriptan 20 mg and dihydroergotamine (DHE) 1 mg, and one comparing sumatriptan 20 mg with rizatriptan 10 mg. The proportion of participants who were pain-free at two hours was 37% (76/208) with sumatriptan 20 mg and 40% (79/200) with rizatriptan. In the one active comparator study with rizatriptan, the overall incidence of serious adverse events was 0.48% (1/208) for sumatriptan 20mg, compared with 0% for rizatriptan 10mg. The overall incidence of adverse event withdrawal compared to placebo was 0.19% for all doses of sumatriptan and there were no withdrawals due to adverse events when compared to rizatriptan.[13]

Thirty-five studies (9365 participants) compared subcutaneous sumatriptan with placebo or an active comparator.[14] The majority of included studies were of good methodological quality, Most of the data were for the 6 mg dose. Sumatriptan surpassed placebo for all efficacy outcomes (NNTs were 2.9, 2.3, 2.2, and 2.1 for pain-free at one and two hours, and headache relief at one and two hours, respectively). Results for the 4 mg and 8 mg doses were similar to the 6 mg dose. There was no evidence of increased migraine relief if a second dose of sumatriptan 6 mg was given after an inadequate

response to the first. Sumatriptan was compared directly with a number of active treatments, including other triptans, but there were insufficient data for any pooled analyses or to make firm conclusions for any outcomes of interest. Withdrawals due to adverse events were uncommon. In placebo-controlled studies the rate of adverse event withdrawal after treating with sumatriptan (1.2%) was marginally higher than that after placebo (0.40%).[14]

Sixty-one studies (37,250 participants) compared oral sumatriptan with placebo or an active comparator.[15] Most of the data were for the 50 mg and 100 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes (NNTS were 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively for 50mg versus placebo and 4.7, 6.8, 3.5 for sumatriptan 100mg). Results for the 25 mg dose were similar to the 50 mg dose, while sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at two hours, and for sustained pain-free during 24 hours. Sumatriptan was compared directly with a number of active treatments, including other triptans. For the outcome of pain-free at two hours, there was no significant difference between sumatriptan 50mg and rizatriptan 5mg or 10mg, sumatriptan 100mg and almotriptan 12.5mg. Rizatriptan 5mg and 10mg were superior to sumatriptan 25mg (NNT 18, 8.5 respectively), and eletriptan 40mg and 80mg were superior to sumatriptan 50mg (NNT 16, 8 respectively). For zolmitriptan 2.5 mg and 5 mg compared with sumatriptan 50 mg, there was no significant difference for headache relief at either one or two hours, There was insufficient comparative evidence to calculate relative risk or NNH for serious adverse events or withdrawals due to adverse events, but for the majority of adverse events, there was no significant difference between sumatriptan and any active comparator.[15]

Guidelines:
Guidelines from the European Federation of Neurological Societies published in 2009 recommend either triptans or NSAIDs for the treatment of acute migraine.[5] The use of subcutaneous sumatriptan is recommended for very severe attacks. These guidelines indicated the minor differences between the triptans including onset of efficacy of pain relief and recurrence rate. There is no evidence that different oral formulations such as rapidly dissolving tablets, wafer forms, or rapid release forms act earlier than others.

In 2011, the guidelines for the diagnosis and treatment of headache were updated by the Institute for Clinical Systems Improvement (ICSI) and recommend triptans as effective for mild to severe migraine headaches. Given a longer half-life of naratriptan, headache response is delayed when compared with other triptans. However, headache recurrence may be less frequent. Also, second doses of triptans have not been shown to relieve headache more if the first dose has been ineffective. Studies show that sumatriptan and naproxen sodium in combination may be more effective than either drug alone. However there are no studies that demonstrate that sumatriptan 85mg/naproxen sodium 500mg is more effective than sumatriptan and naproxen sodium taken together. These guidelines also state that use of drugs for acute treatment of headache for more than nine days per month is associated with an increased risk of chronic daily headache and second doses of triptans have not been shown to relieve headache more if the first dose has been ineffective. Studies show that sumatriptan and naproxen sodium in combination may be more effective than either drug alone.

Recommendations:

- Accept scan as is; no further research or review needed at this time.
- Further review comparative costs due to limited evidence of a difference in effectiveness or safety between agents.

Appendix 1: New Trials

1. **Seeburger JL, Taylor FR, Friedman D, Newman L, Ge Y, Zhang Y, Hustad CM, Lasorda J, Fan X, Hewitt D, Ho T, Connor KM. Efficacy and tolerability of rizatriptan for the treatment of acute migraine in sumatriptan non-responders. Cephalalgia. 2011 May;31(7):786-96. Epub 2010 Nov 15.**

Objective: The study was carried out to assess the efficacy and tolerability of rizatriptan orally disintegrating tablet (ODT) for treating acute migraine in patients who are non-responders to sumatriptan.
Background: Many migraineurs report dissatisfaction with sumatriptan efficacy. It is unclear whether sumatriptan 100 mg non-responders will respond to other triptans.
Methods: This was a randomized, placebo-controlled, double-blind study in adults with >1-year history of ICHD-II (International Classification of Headache Disorders, second edition) migraine who reported that they generally do not respond to sumatriptan (≥50% unsatisfactory response). In the baseline phase, participants treated a single moderate/severe migraine attack with open-label generic sumatriptan 100 mg. Those who continued to experience moderate/severe pain at two hours post-dose were eligible to enter the double-blind treatment phase, during which participants treated three migraine attacks in crossover fashion (two with rizatriptan 10-mg ODT, one with placebo) after being randomly assigned to one of three treatment sequences (1 : 1 : 1 ratio). The primary endpoint was two-hour pain relief.
Results: A total of 102 (94%) participants treated at least one study migraine. Pain relief at two hours was significantly greater with rizatriptan compared with placebo (51% vs. 20%, $p < .001$). Response rates also favored rizatriptan on two-hour pain freedom (22% vs. 12%, $p = .013$) as well as 24-hour sustained pain relief (38% vs. 14%, $p < .001$) and sustained pain freedom (20% vs. 11%, $p = .036$). Treatment was generally well tolerated.
Conclusion: Rizatriptan 10-mg ODT was superior to placebo at providing two-hour pain relief and two-hour pain freedom in the treatment of acute migraine in those who do not respond to sumatriptan 100 mg. Rizatriptan was generally well tolerated in this population.

2. **Bartolini M, Giamberardino MA, Lisotto C, Martelletti P, Moscato D, Panascia B, Savi L, Pini LA, Sances G, Santoro P, Zanchin G, Omboni S, Ferrari MD, Brighina F, Fierro B. A double-blind, randomized, multicenter, Italian study of frovatriptan versus almotriptan for the acute treatment of migraine. J Headache Pain. 2011 Jun;12(3):361-8. Epub 2011 Mar 25.**

Objective: The objective of this study was to evaluate patients' satisfaction with acute treatment of migraine with frovatriptan or almotriptan by preference questionnaire.
Methods: One hundred and thirty three subjects with a history of migraine with or without aura (IHS 2004 criteria), with at least one migraine attack in the preceding 6 months, were enrolled and randomized to frovatriptan 2.5 mg or almotriptan 12.5 mg, treating 1-3 attacks. The study had a multicenter, randomized, double blind, cross-over design, with treatment periods lasting <3 months. At study end patients assigned preference to one of the treatments using a questionnaire with a score from 0 to 5 (primary endpoint). Secondary endpoints were pain free and pain relief episodes at 2 and 4 h, and recurrent and sustained pain free episodes within 48 h.
Results: Of the 133 patients (86%, intention-to-treat population) 114 of them expressed a preference for a triptan. The average preference score was not significantly different between frovatriptan (3.1 ± 1.3) and almotriptan (3.4 ± 1.3). The rates of pain free (30% frovatriptan vs. 32% almotriptan) and pain relief (54% vs. 56%) episodes at 2 h did not significantly differ between treatments. This was the case also at 4 h (pain free: 56% vs. 59%; pain relief: 75% vs. 72%). Recurrent episodes were significantly ($P < 0.05$) less frequent under frovatriptan (30% vs. 44%), also for the attacks treated within 30 min. No significant differences were observed in sustained pain free episodes (21% vs. 18%). The tolerability profile was similar between the two drugs.
Conclusions: In conclusion, our study suggests that frovatriptan has a similar efficacy of almotriptan in the short-term, while some advantages are observed during long-term treatment.

3. **Allais G, Bussone G, D'Andrea G, Moschiano F, d'Onofrio F, Valguarnera F, Manzoni GC, Grazzi L, Allais R, Benedetto C, Acuto G. Almotriptan 12.5 mg in menstrually related migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia. 2011 Jan;31(2):144-51. Epub 2010 Jul 26.**

Background: Menstrually related migraine (MRM) affects more than half of female migraineurs. Because such migraines are often predictable, they provide a suitable target for treatment in the mild pain phase. The present study was designed to provide prospective data on the efficacy of almotriptan for treatment of MRM.
Methods: Premenopausal women with MRM were randomized to almotriptan (N = 74) or placebo (N = 73), taken at onset of the first perimenstrual migraine. Patients crossed over to the other treatment for the first perimenstrual migraine of their second cycle, followed by a two-month open-label almotriptan treatment period.
Results: Significantly more patients were pain-free at two hours (risk ratio [RR] = 1.81; p = .0008), pain-free from 2-24 hours with no rescue medication (RR = 1.99; p = .0022), and pain-free from 2-24 hours with no rescue medication or adverse events (RR = 1.94; p = .0061) with almotriptan versus placebo. Nausea (p = .0007) and photophobia (p = .0083) at two hours were significantly less frequent with almotriptan. Almotriptan efficacy was consistent between three attacks, with 56.2% of patients pain-free at two hours at least twice. Adverse events were similar with almotriptan and placebo.

Conclusions: Almotriptan was significantly more effective than placebo in women with MRM attacks, with consistent efficacy in longer-term follow-up.

4. **Allais G, Tullo V, Benedetto C, Zava D, Omboni S, Bussone G. Efficacy of frovatriptan in the acute treatment of menstrually related migraine: analysis of a double-blind, randomized, multicenter, Italian, comparative study versus zolmitriptan. Neurol Sci. 2011 May;32 Suppl 1:S99-104.**

Menstrually related migraine (MRM) is a particularly difficult-to-treat pain condition, associated with substantial disability. Aim of this study was to compare the efficacy and safety of frovatriptan and zolmitriptan in the treatment of MRM attacks, analyzing data from a multicenter, randomized, double blind, cross-over study. We analyzed the subset of 76 regularly menstruating women who participated in one head-to-head multicenter, randomized, double blind, cross-over clinical trial and who took the study drugs to treat MRM attacks. In a randomized sequence, each patient received frovatriptan 2.5 mg or zolmitriptan 2.5 mg: after treating three episodes of migraine in no more than 3 months with the first treatment, the patient had to switch to the other treatment. MRM was defined according to the criteria listed in the Appendix of the last Classification of Headache disorders of the International Headache Society. A total of 73 attacks, classified as MRM, were treated with frovatriptan and 65 with zolmitriptan. Rate of pain relief at 2 h was 52% for frovatriptan and 53% for zolmitriptan (p = NS), while rate of pain free at 2 h was 22 and 26% (p = NS), respectively. At 24 h, 74 and 83% of frovatriptan-treated and 69 and 82% of zolmitriptan-treated patients were pain free and had pain relief, respectively (p = NS). Recurrence at 24 h was significantly ($p < 0.05$) lower with frovatriptan (15 vs. 22% zolmitriptan). Frovatriptan proved to be effective in the immediate treatment of MRM attacks, similarly to zolmitriptan, but showed lower recurrence rates, and thus a better sustained relief.

5. **Tullo V, Allais G, Ferrari MD, Curone M, Mea E, Omboni S, Benedetto C, Zava D, Bussone G. Frovatriptan versus zolmitriptan for the acute treatment of migraine: a double-blind, randomized, multicenter, Italian study. Neurol Sci. 2010 Jun;31 Suppl 1:S51-4.**

Objective: The objective of this study is to assess patients' satisfaction with migraine treatment with frovatriptan (F) or zolmitriptan (Z), by preference questionnaire. 133 subjects with a history of migraine with or without aura (IHS criteria) were randomized to F 2.5 mg or Z 2.5 mg.

Methods: The study had a multicenter, randomized, double-blind, cross-over design, with each of the two treatment periods lasting no more than 3 months. At the end of the study, patients were asked to assign preference to one of the treatments (primary endpoint). The number of pain-free (PF) and pain-relief (PR) episodes at 2 h, and number of recurrent and sustained pain-free (SPF) episodes within 48 h were the secondary study endpoints.
Results: Seventy-seven percent of patients expressed a preference. Average score of preference was 2.9 +/- 1.3 (F) versus 3.0 +/- 1.3 (Z; p = NS). Rate of PF episodes at 2 h was 26% with F and 31% with Z (p = NS). PR episodes at 2 h were 57% for F and 58% for Z (p = NS). Rate of recurrence was 21 (F) and 24% (Z; p = NS). Time to recurrence within 48 h was better for F especially between 4 and 16 h ($p < 0.05$). SPF episodes were 18 (F) versus 22% (Z; p = NS). Drug-related adverse events were significantly ($p < 0.05$) less under F (3 vs. 10).
Conclusions: In conclusion, our study suggests that F has a similar efficacy of Z, with some advantage as regards tolerability and recurrence.

6. Spierings, E. L. H. and C. Keywood (2009). "Rapid responders to frovatriptan in acute migraine treatment: results from a long-term, open-label study." Pain Medicine 10(4): 633-8.

Objectives: First, assessment of the tolerability and safety of frovatriptan, 2.5-7.5 mg taken orally over 24 hours, for the acute treatment of migraine, repeatedly over a 12-month period. Second, assessment of the efficacy and tolerability of a second, double-blind dose of 2.5-mg frovatriptan, compared with placebo, for nonresponse at 2 hours after treatment of moderate or severe headache with 2.5-mg frovatriptan.
Results: With regard to the first attack treated, 173 (36%) of the 486 subjects in the study did not take a second dose at 2 hours for nonresponse. At 2 hours and 4 hours, these "rapid responders" experienced a decrease in headache intensity from moderate or severe to mild or no pain in 84% and 98%, respectively ("headache response"). Six percent of them experienced recurrence of moderate or severe headache within 24 hours following a response at 4 hours and 12% took rescue medication. The response, measured in terms of median time to "complete migraine relief," was maintained over 30 subsequent migraine attacks, treated from attack 2 onwards over the course of 12 months.
Conclusion: Frovatriptan provides a remarkably fast and high headache response in a subgroup of more than one-third of migraineurs, with a very low 24-hour headache recurrence and low rescue medication intake.

7. Mathew, N. T., S. Landy, et al. (2009). "Fixed-dose sumatriptan and naproxen in poor responders to triptans with a short half-life." Headache 49(7): 971-82.

Objective: To evaluate efficacy and tolerability of a single, fixed-dose tablet of sumatriptan 85 mg/naproxen sodium 500 mg (sumatriptan/naproxen sodium) vs. placebo in migraineurs who had discontinued treatment with a short-acting triptan because of poor response or intolerance.
Background: Triptan monotherapy is ineffective or poorly tolerated in 1 of 3 migraineurs and in 2 of 5 migraine attacks. In April, 2008, the Food and Drug Administration approved the combination therapy sumatriptan/naproxen sodium, developed specifically to target multiple migraine mechanisms. This combination product offers an alternative migraine therapy for patients who have reported poor response or intolerance to short-acting triptans.
Methods: Two replicate, randomized, multicenter, double-blind, placebo-controlled, 2-attack crossover trials evaluated migraineurs who had discontinued a short-acting triptan in the past year because of poor response or intolerance. Patients were instructed to treat within 1 hour and while pain was mild. RESULTS: Patients (n = 144 study 1; n = 139 study 2) had discontinued an average of 3.3 triptans before study entry. Sumatriptan/naproxen sodium was superior ($P < .001$) to placebo for 2- through 24-hour sustained pain-free response (primary end point) (study 1, 26% vs 8%; study 2, 31% vs 8%) and pain-free response 2 hours post dose (key secondary end point) (study 1, 40% vs 17%; study 2, 44% vs 14%). A similar pattern of results was observed for other end points that evaluated acute (2- or 4-hour), intermediate (8-hour), or 2- through 24-hour sustained response for migraine (i.e., pain and associated symptoms), photophobia, phonophobia, or nausea (with the exception of nausea 2 and 4 hours post dose). The percentage of patients with at least 1 adverse event (regardless of causality) was 11% with sumatriptan/naproxen sodium compared with 4% with placebo in study 1 and 9% with sumatriptan/naproxen sodium compared with 5% with placebo in study 2. Only 1

adverse event in 1 study was reported in > or =2% of patients after treatment with sumatriptan/naproxen sodium and reported more frequently with sumatriptan/naproxen than placebo: chest discomfort was reported in 2% of subjects in study 1, and no events met this threshold in study 2. No serious adverse events attributed to study medication were reported in either study.
Conclusion: In migraineurs who reported poor response to a short-acting triptan, sumatriptan/naproxen sodium was generally well tolerated and significantly more effective than placebo in conferring initial, intermediate, and sustained efficacy for pain and migraine-associated symptoms of photophobia and phonophobia.

8. Cady, R. K., V. T. Martin, et al. (2009). "Rizatriptan 10-mg ODT for early treatment of migraine and impact of migraine education on treatment response." Headache 49(5): 687-96.

Objective: To examine the efficacy of rizatriptan 10-mg orally disintegrating tablet (ODT) for treating migraines of mild intensity soon after onset, with or without patient-specific migraine education.
Background: Studies have shown rizatriptan tablet efficacy in early migraine treatment.
Methods: In this randomized, placebo-controlled, double-blind, factorial design study, adults with a history of migraine were assigned to rizatriptan 10-mg ODT patient education (personalized summary of early migraine signs and symptoms) or placebo patient education in a 1 : 1 : 1 : 1 ratio. Patients were instructed to treat 1 attack at the earliest time they knew that their headache was a migraine, while pain was mild. During the next 24 hours, patients assessed pain severity, associated symptoms, functional disability, use of rescue medication, and treatment satisfaction. The primary endpoint was pain freedom at 2 hours; a key secondary endpoint was 24-hour sustained pain freedom. Results: Of 207 patients randomized to treatment, 188 (91%) treated a study migraine. Significantly more patients taking rizatriptan reported pain freedom at 2 hours compared with placebo (66.3% vs 28.1%, P < .001). Similarly, significantly more patients taking rizatriptan reported 24-hour sustained pain freedom (52.2% vs 17.7%, P < .001). A greater proportion of patients in the rizatriptan + education group reported pain freedom at 2 hours compared with those in the rizatriptan + no education group (71.7% vs 60.9%, P = .430). Few adverse events were reported. Conclusion: Rizatriptan 10-mg ODT, when taken early, while headache pain is mild, was superior to placebo at providing pain freedom at 2 hours and 24-hour sustained pain freedom.

9. Ng-Mak, D. S., X. H. Hu, et al. (2009). "Migraine treatment with rizatriptan and almotriptan: a crossover study." Headache 49(5): 655-62.

Background: Rizatriptan and almotriptan are effective and well-tolerated triptans that have not been compared directly.
Objective: To evaluate the effectiveness of rizatriptan 10 mg and almotriptan for the acute treatment of migraine, in a real-world setting.
Methods: Of a large, multicenter, open-label, crossover study, we conducted a substudy to contrast the effectiveness of rizatriptan 10 mg and almotriptan 12.5 mg for the acute treatment of 2 migraine attacks in a sequential, crossover manner. Time to outcome was assessed using stopwatches. Mean and median times to onset of pain relief (PR) and pain freedom (PF) for rizatriptan and almotriptan were compared. The
effect of rizatriptan on times to onset of PR and PF, adjusting for potential confounding factors (treatment sequence, treatment order, and use of rescue medication), was computed via a Cox proportional hazard model.
Results: Out of the 146 patients taking almotriptan as their usual care medication, 79 used stopwatch for both attacks. Significantly more patients taking rizatriptan achieved onset of PR within 2 hours after dosing than those taking almotriptan (88.6% vs 73.4%, P = .007). A higher proportion of patients taking rizatriptan achieved PF within 2 hours after dosing than those taking almotriptan (55.7% vs 45.6%, P = .10). Times to onset of PR and PF were significantly shorter with those patients taking rizatriptan than with those taking almotriptan (median time to PR: 45 vs 60 minutes, P = .002; median time to PF: 100 vs 135 minutes, P = .004). The adjusted proportional hazard ratios (rizatriptan vs almotriptan) for times to onset of PR and PF were 1.51 (95% confidence interval 1.20 to 1.88) and 1.42 (95% confidence interval 1.15 to 1.76), respectively. More patients were very satisfied when treating their attacks with rizatriptan than with almotriptan. Rizatriptan was preferred by most patients. Conclusions: Times to achieve PR and PF were significantly shorter for patients using rizatriptan, as compared with those using almotriptan

12. **Christopher J Derry, Sheena Derry, R Andrew Moore Sumatriptan (rectal route of administration) for acute migraine attacks in adults: Cochrane Pain, Palliative and Supportive Care Group Published Online: 15 FEB 2012 DOI: 10.1002/14651858.CD009664**

Background: Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family. Rectal administration may be preferable to oral for individuals experiencing nausea and/or vomiting. To determine the efficacy and tolerability of rectal sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011. We included randomised, double-blind, placebo- and/or active-controlled studies using rectally administered sumatriptan to treat a migraine headache episode, with at least 10 participants per treatment arm. Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate relative risk (or 'risk ratio') and numbers needed to treat to benefit (NNT) or harm (NNH) compared to placebo or a different active treatment.

Results: Three studies (866 participants) compared rectally administered sumatriptan with placebo or an active comparator. Most of the data were for the 12.5 mg and 25 mg doses. For the majority of efficacy outcomes, sumatriptan surpassed placebo. For sumatriptan 12.5 mg versus placebo the NNTs were 5.2 and 3.2 for headache relief at one and two hours, respectively. Results for the 25 mg dose were similar to the 12.5 mg dose, and there were no significant differences between the two doses for any of the outcomes analysed. The NNTs for sumatriptan 25 mg versus placebo were 4.2, 3.2, and 2.4 for pain-free at two hours, headache relief at one hour, and headache relief at two hours, respectively. Relief of functional disability was greater with sumatriptan than with placebo, with NNTs of 8.0 and 4.0 for the 12.5 mg and 25 mg doses, respectively. For the most part, adverse events were transient and mild and were more common with sumatriptan than with placebo, but there were insufficient data to perform any analyses. Direct comparison of sumatriptan with active treatments was limited to one study comparing sumatriptan 25 mg with ergotamine tartrate 2 mg + caffeine 100 mg.

Conclusions: Based on limited amounts of data, sumatriptan 25 mg, administered rectally, is an effective treatment for acute migraine attacks, with participants in these studies experiencing a significant reduction in headache pain and functional disability within two hours of treatment. The lack of data on relief of headache-associated symptoms or incidence of adverse events limits any conclusions that can be drawn.

13. **Christopher J Derry, Sheena Derry, R Andrew Moore Sumatriptan (intranasal route of administration) for acute migraine attacks in adults: Cochrane Pain, Palliative and Supportive Care Group Published Online: 15 FEB 2012 DOI: 10.1002/14651858.CD009663**

Background: Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family. Intranasal administration may be preferable to oral for individuals experiencing nausea and/or vomiting, although it is primarily absorbed in the gut, not the nasal mucosa. To determine the efficacy and tolerability of intranasal sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Methods: We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011. We included randomised, double-blind, placebo- and/or active-controlled studies using intranasal sumatriptan to treat a migraine headache episode, with at least 10 participants per

treatment arm. Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate relative risk (or 'risk ratio') and numbers needed to treat to benefit (NNT) or harm (NNH) compared to placebo or a different active treatment.

Results: Twelve studies (4755 participants) compared intranasal sumatriptan with placebo or an active comparator. Most of the data were for the 10 mg and 20 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes. For sumatriptan 10 mg versus placebo the NNTs were 7.3, 7.4, and 5.5 for pain-free at two hours, and headache relief at one and two hours, respectively. For sumatriptan 20 mg versus placebo the NNTs were 4.7, 4.9, and 3.5, respectively, for the same outcomes. The 20 mg dose was significantly better than the 10 mg dose for each of these three primary efficacy outcomes. Relief of headache-associated symptoms, including nausea, photophobia, and phonophobia, was greater with sumatriptan than with placebo, and use of rescue medication was lower with sumatriptan than placebo. For the most part, adverse events were transient and mild and were more common with sumatriptan than placebo. Direct comparison of sumatriptan with active treatments was limited to two studies, one comparing sumatriptan 20 mg and dihydroergotamine (DHE) 1 mg, and one comparing sumatriptan 20 mg with rizatriptan 10 mg.

Conclusions: Intranasal sumatriptan is effective as an abortive treatment for acute migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased adverse events compared with placebo.

14. Christopher J Derry, Sheena Derry, R Andrew Moore Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults: Cochrane Pain, Palliative and Supportive Care Group Published Online: 15 FEB 2012 DOI: 10.1002/14651858.CD009665

Background: Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family. Subcutaneous administration may be preferable to oral for individuals experiencing nausea and/or vomiting. To determine the efficacy and tolerability of subcutaneous sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Methods: We searched Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011. We included randomised, double-blind, placebo- and/or active-controlled studies using subcutaneous sumatriptan to treat a migraine headache episode, with at least 10 participants per treatment arm. Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate relative risk (or 'risk ratio') and numbers needed to treat to benefit (NNT) or harm (NNH) compared to placebo or a different active treatment.

Results: Thirty-five studies (9365 participants) compared subcutaneous sumatriptan with placebo or an active comparator. Most of the data were for the 6 mg dose. Sumatriptan surpassed placebo for all efficacy outcomes. For sumatriptan 6 mg versus placebo the NNTs were 2.9, 2.3, 2.2, and 2.1 for pain-free at one and two hours, and headache relief at one and two hours, respectively, and 6.1 for sustained pain-free at 24 hours. Results for the 4 mg and 8 mg doses were similar to the 6 mg dose, with 6 mg significantly better than 4 mg only for pain-free at one hour, and 8 mg significantly better than 6 mg only for headache relief at one hour. There was no evidence of increased migraine relief if a second dose of sumatriptan 6 mg was given after an inadequate response to the first. Relief of headache-associated symptoms, including nausea, photophobia, and phonophobia, was greater with sumatriptan than with placebo, and use of rescue medication was lower with sumatriptan than placebo. For the most part, adverse events were transient and mild and were more common with sumatriptan than placebo. Sumatriptan was compared directly with a number of active treatments, including other triptans, acetylsalicylic acid plus metoclopramide, and dihydroergotamine, but there were insufficient data for any pooled analyses.

Conclusion: Subcutaneous sumatriptan is effective as an abortive treatment for acute migraine attacks, quickly relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased adverse events.

15. Christopher J Derry, Sheena Derry, R Andrew Moore Sumatriptan (oral route of administration) for acute migraine attacks in adults: Cochrane Pain, Palliative and Supportive Care Group Published Online: 15 FEB 2012 DOI: 10.1002/14651858.CD008615.pub2

Background: Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family. To determine the efficacy and tolerability of oral sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011. We included randomised, double-blind, placebo- and/or active-controlled studies using oral sumatriptan to treat a migraine headache episode, with at least 10 participants per treatment arm. Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate relative risk (or 'risk ratio') and numbers needed to treat to benefit (NNT) or harm (NNH) compared to placebo or a different active treatment.

Results: Sixty-one studies (37,250 participants) compared oral sumatriptan with placebo or an active comparator. Most of the data were for the 50 mg and 100 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes. For sumatriptan 50 mg versus placebo the NNTs were 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively. NNTs for sustained pain-free and sustained headache relief during the 24 hours postdose were 9.5 and 6.0, respectively. For sumatriptan 100 mg versus placebo the NNTs were 4.7, 6.8, 3.5, 6.5, and 5.2, respectively, for the same outcomes. Results for the 25 mg dose were similar to the 50 mg dose, while sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at two hours, and for sustained pain-free during 24 hours. Treating early, during the mild pain phase, gave significantly better NNTs for pain-free at two hours and sustained pain-free during 24 hours than did treating established attacks with moderate or severe pain intensity. Relief of associated symptoms, including nausea, photophobia, and phonophobia, was greater with sumatriptan than with placebo, and use of rescue medication was lower with sumatriptan than with placebo. For the most part, adverse events were transient and mild and were more common with the sumatriptan than with placebo, with a clear dose response relationship (25 mg to 100 mg). Sumatriptan was compared directly with a number of active treatments, including other triptans, paracetamol (acetaminophen), acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), and ergotamine combinations.

Conclusion: Oral sumatriptan is effective as an abortive treatment for migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased adverse events.

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