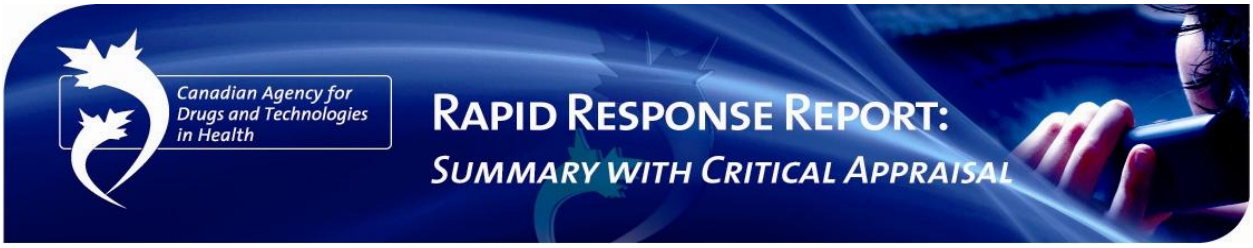

TITLE: Triptans for Migraine Headaches: A Review of Clinical Evidence on Safety

DATE: 23 March 2012

CONTEXT AND POLICY ISSUES

Three million Canadians suffer from migraine headaches; characterized by intense headaches, nausea, vomiting, and sensitivity to light, sound or movements as defined by the International Headache Society.[1] Migraine attacks last from four to 72 hours and are preceded or accompanied by transient focal neurological symptoms known as aura in 10% to 20% of patients.[1] More common in women than men, migraines are costly in terms of health care resources, lost productivity and impact on quality of life. Triptans have become the treatment of choice for moderate to severe migraine attacks. While six triptans are available for use in Canada, sumatriptan, rizatriptan, naratriptan, zolmitriptan and almotriptan are currently listed on the formulary.[1] Most formularies have a limit on the number of tablets covered per month. This review evaluates the safety and harms of triptans to identify whether triptan overuse is unsafe and limits are clinically valid.

RESEARCH QUESTION

What is the clinical evidence on the safety and harms of triptans for migraine headaches?

KEY MESSAGE

While no consistent differences were found between triptans in the rates of overall AEs, a small number of studies suggest oral, intranasal and subcutaneous sumatriptan are associated with chest pain and tachycardia. The most common AEs include dizziness, drowsiness, paresthesia, nausea and fatigue. One study suggests that providing a clinical limit of 27 rizatriptan ODT 10 mg/month did not reduce the number of migraine days compared with providing a formulary limit of 9 tablets per month. Regardless of quantity, rizatriptan ODT 10 mg was well tolerated as AEs were similar between groups.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. A focused search (with main concepts appearing in title or subject heading) was also conducted in Ovid EMBASE. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2008 and February 24, 2012.

Selection Criteria and Methods

One reviewer screened citations to identify health technology assessments, systematic reviews, meta-analyses, randomized and non-randomized studies on the safety of triptans for migraine headache. Potentially relevant articles were ordered based on titles and abstracts, where available. One reviewer considered full-text articles for inclusion according to the selection criteria listed in Table 1.

Population	Individuals with migraine headaches
Intervention	Triptans: sumatriptan, rizatriptan, naratriptan, zolmitriptan and almotriptan
Comparator	Triptans: sumatriptan, rizatriptan, naratriptan, zolmitriptan and almotriptan None (for non-randomized studies)
Outcomes	Harms Harms including cardiovascular adverse events Harms stemming from overuse
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCT), and non-randomized studies.

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, if they had incomplete methods, were included in a selected systematic review, or were narrative reviews or case reports.

Critical Appraisal of Individual Studies

Critical appraisal of the included studies was performed based on study design. Systematic reviews were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) criteria.[2] Randomized studies were assessed for quality using the Down's and Black instrument.[3] Instead of calculating numeric scores, the strengths and limitations of each study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 475 citations. Upon screening titles and abstracts, 18 potentially relevant articles were retrieved for full-text review. Three potentially relevant reports were retrieved from grey literature and hand searching. Of the 21 potentially relevant reports, one contained an irrelevant population, three contained an irrelevant outcome, and nine had incomplete methods, were narrative reviews or case reports. Eight publications were included in this review. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Clinical Evidence on the Safety of Triptans for Migraine Headache

Summary of Study Characteristics

The safety of triptans for migraine headache was reported in six systematic reviews and meta-analyses,[4-9] one RCT,[10] and an observer-blind, randomized, parallel-group study.[11] The Drug Effectiveness Review Project reported a class review of all formulations of triptans and triptan fixed dose combination products used to treat acute migraine with or without aura.[4] Four systematic reviews with meta-analyses reported on the use of sumatriptan administered orally,[7] intranasally,[5] subcutaneously[6] or rectally[8] for the treatment of acute migraine. One systematic review and meta-analysis reported on the efficacy and safety of three formulations of zolmitriptan for acute migraine.[9] A multicentre RCT reported on the use of almotriptan for migraine in adolescents.[10] An observer-blind, randomized, parallel-group study comparing a formulary limit versus a clinical limit of rizatriptan orally disintegrating tablets (ODT) was also selected for review.[11] Studies were conducted in the United States[4,10,11] and the United Kingdom.[5-9] Summaries of study characteristics, critical appraisal and study findings can be found in Appendices 2, 3, and 4, respectively. A summary of the clinical evidence on the safety and harms of triptans for migraine headaches can be found in Table 2.

Systematic reviews and meta-analyses

Systematic reviews contained as few as three[8] and as many as 134 studies.[4] All six systematic reviews included adults with migraine with or without aura but five reviews specified the International Headache Society definition for migraine.[5-9] The class review by DERP compared all formulations of almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatripta-naproxen, and zolmatriptan as monotherapy or in combination versus an active comparator or placebo.[4] Four systematic reviews compared sumatriptan administered orally,[7] intranasally,[5] subcutaneously,[6] or rectally[8] versus an active comparator or placebo. One systematic review compared zolmitriptan oral tablets, orally disintegrating tablets (ODT), and nasal spray versus an active comparator or placebo.[9] Overall, the reviews reported withdrawals,[4] withdrawals due to AEs,[4-8] withdrawals by specific AEs,[4] 24 hour AEs,[5-9] and particular AEs.[5-9]

RCTs

One multicentre double-blind RCT[10] compared oral almotriptan versus placebo in 866 adolescents with migraine with or without aura.[10] An observer-blind, randomized parallel-group study comparing a limit of 9 rizatripan ODT per month versus 27 rizatriptan ODT per month in 197 adults with migraine was also included in this review.[11] Both studies reported AEs.[10,11]

Summary of Critical Appraisal

Systematic reviews and meta-analyses

All systematic reviews with meta-analyses[4-9] were based on a comprehensive literature search using pre-defined criteria. Study selection and data extraction was performed by two independent reviewers in all but one review.[4] A list of included and excluded studies was provided in all but one systematic review.[9] There were possible discrepancies in reporting the number and nature of studies in text versus appendices of the DERP report.[4] Most reviews reported significant variability in the details of reporting AEs within included studies.[5,6,8,9] All reviews used appropriate methods for pooling studies but the small number of events and varying time periods over which some data were collected prohibited pooling in one review.[8] Two reviews did not assess publication bias.[4,9]

RCTs

Both studies clearly described their research questions, eligibility criteria, interventions, outcomes and patient characteristics.[10,11] The RCT calculated sample size and used an intent to treat analysis. However, the method of randomization was not reported and it is difficult to ensure people were randomized to almotriptan and placebo.[10] In the observer-blind randomized parallel group study, industry generated the allocation schedule and patients were stratified into two groups according to the number of days of migraine per month during baseline. While subjects and investigators were blind at randomization, subjects were unblinded upon receiving nine or 27 rizatriptan ODT.[11]

Summary of Findings

Systematic reviews and meta-analyses

Triptans and Triptan Fixed-dose Combinations

The Drug Effectiveness Review Project reported that chest pain was more frequent in patients taking sumatriptan100 mg than rizatriptan 5 mg (6% compared with 1%; $P < 0.05$) but did not differ from rizatriptan 10 mg (6% compared with 3%). Treatment-emergent chest pain was significantly greater for oral sumatriptan 50 mg recipients compared with almotriptan 12.5 mg recipients (2.2% versus 0.3%; $P = 0.004$). Patients taking subcutaneous sumatriptan 6 mg had higher rates of chest pain than those taking eletriptan 80 mg in one open trial of 1696 migraines. No significant differences were reported in trials assessing dizziness, paresthesias, or somnolence. One trial showed that fatigue was more frequent in patients using sumatriptan 100 mg than those using rizatriptan 5 mg (8% versus 2%; $P < 0.05$) but no difference was found between sumatriptan 100 mg and rizatriptan 10 mg (8% versus 8%). No consistent differences were reported between Treximet (a sumatriptan-naproxen combination) versus reformulated sumatriptan 85 mg in the rates of dizziness, paresthesia, or somnolence.[4]

Oral Sumatriptan

A dose response relationship was observed in the systematic review of oral sumatriptan.[7] Compared to placebo, significantly more sumatriptan recipients experienced an AE 24 hours post dose with increasing dosage (number needed to harm (NNH): 5.2, 13, and not statistically significant for sumatriptan 100 mg, 50 mg, and 25 mg, respectively). No significant differences

were found between sumatriptan 25 mg, 50 mg, or 100 mg and rizatriptan 5 mg or 10 mg. Similarly, there was no significant difference between sumatriptan 50 mg and effervescent acetylsalicylic acid (ASA) 1000 mg, or zolmitriptan 2.5 mg and 5 mg. The relative risk (RR) of chest pain with sumatriptan 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg was 1.8 (95% confidence interval [CI] 0.7 to 4.3), 2.1 (95% CI 1.1 to 3.9), 3.0 (95% CI 1.7 to 5.4), 4.4 (95% CI 0.54 to 36), and 17 (95% CI 2.4 to 127), respectively. Corresponding NNHs for sumatriptan 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg were not reported, 69 (95% CI 40, 260), 44 (95% CI 31, 73), not reported, and 16 (95% CI 11, 27), respectively. The RR of tachycardia using sumatriptan 100 mg was 3.5 (0.75, 17). Sumatriptan caused significantly less fatigue, nausea and vomiting than eletriptan 80 mg (NNH: -17 and -24, respectively). Sumatriptan 25 mg caused less dizziness and drowsiness than rizatriptan 10 mg (NNH 20 and -34, respectively). Sumatriptan 50 mg caused significantly more headache than rizatriptan (5 mg or 10 mg) (NNH: 38 and 34, respectively).

The overall incidence of withdrawals due to AEs was 1.6% (113/7133) for all doses of sumatriptan and 0.65% (19/2926) for placebo.[7] Overall withdrawals were 2.5% (31/1229) for all doses of sumatriptan, and 2.9% (52/1775) for all doses of zolmitriptan. Withdrawal incidence was 1.2% (10/841) for sumatriptan and 1.3% (12/938) for eletriptan while withdrawals were 0.38% (4/1048) for sumatriptan versus 0.28% (4/1434) for rizatriptan.

Sumatriptan Nasal Spray

In another systematic review by Derry et al,[5] a meta-analysis of two trials showed that 38% (125/331) of sumatripan nasal spray (NS) 20 mg recipients and 15% (27/185) of placebo recipients experienced an AE 24 hours after dosing. The relative harm of treatment compared to placebo was 2.9 (95% CI 2.0 to 4.2) and the NNH was 4.3 (3.3, 6.3). One study reported that 46% (17/37) of sumatritan NS 40 mg recipients experienced an AE compared to 14% (5/37) placebo recipients. Another study reported that patients receiving sumatriptan NS 10 mg and 20 mg experienced 18% (7/39) and 23% (9/39) AEs compared to 5% (2/39) of placebo participants. A meta-analysis of two trials suggested that the rates of chest pain and tachycardia were similar between sumatriptan NS 20 mg and placebo recipients [RR: 2.0 (95% CI 0.32 to 12) and RR: 0.73 (95% CI 0.11 to 4.9), respectively]. Overall withdrawals were 0.1% (3/1609) for sumatriptan NS and 0.23% (1/431) for placebo. The NNH was not calculated because there were too few events.

Subcutaneous Sumatriptan

In a third systematic review by Derry et al,[6] meta-analysis of three studies showed that 71% (313/442) of subcutaneous (SC) sumatriptan 4 mg recipients and 41% (113/278) of placebo recipients experienced an AE 24 hours after dosing. The relative harm of treatment compared to placebo was 1.8 (95% CI 1.6 to 2.2) and the NNH was 3.3 (2.7, 4.4). Meta-analysis of nine studies showed that 44% (341/767) of sumatriptan SC 6 mg recipients and 24% (137/575) of placebo recipients experience an AE 24 hours after dosing. The relative harm of treatment compared with placebo was 2.1 (95% CI 1.8 to 2.5) and the NNH was 4.9 (3.9, 6.4). One study reported that the proportion of participants experiencing an AE 24 hours after sumatriptan SC 1 mg, 2 mg, 3 mg, and 8 mg was 63%, 67%, 80%, and 97%, respectively, compared to 55% of placebo recipients. Meta-analyses of two and six studies suggested rates of 5% and 4% for chest pain in sumatriptan SC 2 mg and 6 mg recipients, respectively compared to 1% in placebo recipients. Of the patients receiving sumatriptan SC 6 mg, 4% experienced fatigue, 6% experienced dizziness, and 7% experienced nausea and vomiting compared to 4%, 4% and 5%

of placebo recipients, respectively. The overall incidence of withdrawals due to AE was 1.2% (41/3451) for sumatriptan SC and 0.4% (10/2474) for placebo recipients. There were too few events to calculate NNH.

Rectal Sumatriptan

In a fourth systematic review by Derry et al,[8] two studies reported a similar incidence of AE with low doses of sumatriptan <12.5 mg and placebo, and a greater incidence with higher doses >25 mg. In these two studies involving 654 patients, one rectal sumatriptan 100 mg recipient was hospitalized for migraine. Due to the varying time periods for data collection and differing means of reporting, data was not pooled. No significant differences in the rates of fatigue, nausea, or vomiting were reported for any dose of rectal sumatriptan compared to placebo. The overall incidence of withdrawals due to AE for two studies was 0.4% (2/520) for all doses of rectal sumatriptan and 0% (0/95) for placebo.

Zolmitriptan Oral Tablets, Orally Disintegrating Tablets and Nasal Spray

A meta-analysis by Chen[9] pooled risks of AEs from 24 studies and reported that all three formulations of zolmitriptan were associated with significantly more patients reporting AEs than placebo. Zolmitriptan 2.5 mg and 5 mg tablets and zolmitriptan NS 5 mg were also associated with significantly higher risks of dizziness, somnolence, and asthenia than placebo. No significant difference was found in the risk of chest related symptoms when zolmitriptan 2.5 mg and 5 mg were compared with placebo. Single trials showed that there was no significant difference in the risk of dizziness associated with zolmitriptan NS 2.5 mg and somnolence associated with zolmitriptan ODT 2.5 mg compared to placebo. A study of 693 patients reported fewer AEs in zolmitriptan tablet 2.5 mg recipients compared with zolmitriptan NS 5 mg (RR: 0.8; 95% CI 0.65 to 0.99). Significantly more patients taking zolmitriptan 2.5 mg tablets reported AEs than those taking naratriptan 2.5 mg (RR: 1.59; 95% CI 1.10 to 2.30) or rizatriptan 10 mg (RR: 1.27; 95% CI 1.02 to 1.58). In contrast, zolmitriptan tablet 2.5 mg resulted in significantly fewer patients reporting AEs compared with eletriptan 80 mg (RR: 0.80; 95% CI 0.67 to 0.95). There was no significant difference in patients reporting AEs when zolmitriptan tablet 2.5 mg was compared with almotriptan 12.5 mg eletriptan 40 mg, and sumatripan 50 mg. Similarly, no significant difference was found between zolmitriptan tablet 5 mg versus sumatriptan 50 mg or 100 mg.

Randomized controlled trials (RCTs)

Almotriptan for Migraine in Adolescents

According to one RCT,[10] the proportion of adolescents aged 12 to 17 years with ≥1 AE was 18.6% for placebo, 15% for almotriptan 6.25 mg, 23.6% for almotriptan 12.5 mg, and 25.8% for almotriptan 25 mg. The incidences of AEs in almotriptan 6.25 mg, 12.5 mg, and 25 mg groups were 6.7%, 12.1%, and 12.4%, respectively, compared with 5.8% in the placebo group. AEs with an incidence >2% in any treatment group were dizziness, somnolence, and nausea. No deaths, serious AE, or discontinuations due to AE occurred, and no clinically significant changes in vital signs or electrocardiograms were noted.

Observer-blind Randomized Parallel Group Study

Rizatriptan Orally Disintegrating Tablet

An observer-blind, randomized parallel-group study, showed that while rizatriptan is well tolerated, providing a clinical limit of 27 rizatriptan ODT 10 mg did not reduce the number of migraine days compared to patients receiving a formulary limit of 9 tablets.[11] AEs were similar for subjects receiving clinical and formulary limits of rizatriptan. Three subjects discontinued due to abdominal cramping and somnolence during baseline, and heart palpitations during treatment. Overall, rizatriptan was generally well tolerated and fewer AEs were reported during treatment than baseline periods. There were six serious AEs involving cholelithiasis, appendicitis, chest pain, paresthesia, hypoesthesia and ketoacidosis in four subjects during baseline. None were considered treatment-related.

Table 2. Summary of the Safety and Harms of Triptans for Migraine Headache

Intervention	Evidence	Results
Safety and Harms of Triptans for Migraine Headache		
Triptan Fixed-dose combinations	Systematic review[4]	• No consistent differences in rates of dizziness, parethesia, or somnolence between Trexmet (sumatriptan 85 mg+naproxen sodium 500 mg) and reformulated sumatriptan 85 mg.[4]
Sumatriptan (oral, intranasal, subcutaneous, rectal)	5 Systematic reviews[4-8]	Oral • Increasing AEs with increasing oral sumatriptan dosage (NNH: 5, 13 and NS for 100 mg, 50 mg, and 25 mg, respectively).[7] • Oral sumatriptan 100 mg resulted in more chest pain and fatigue than rizatriptan 5 mg (6% versus 1%; P<0.05; and 8% versus 2%; P<0.05)[4] but NSD from rizatriptan 10 mg. • RR of chest pain increased with oral sumatriptan 25 mg, 50 mg, 100 mg, 200 mg and 300 mg were 1.8 (95%CI 0.7, 4.3), 2.1 (95% CI 1.1, 3.9), 3.0 (95% CI 1.7, 5.4), 4.4 (95% CI 0.54, 36) and 17 (95%CI 2.4, 127), respectively.[7] NNH: NR, 69, 44, NR, 16, respectively.[7] • Treatment-emergent chest pain was significantly greater for oral sumatriptan 50 mg compared with almotriptan 12.5 mg (2.2% versus 0.3%; P=0.004)[4] • RR of tachycardia for oral sumatriptan 100 mg was 3.5 (0.75, 17). • Sumatriptan caused less fatigue, nausea and vomiting than eletriptan 80 mg (NNH: -17 and -24, respectively).[7] Nasal Spray • More sumatriptan NS 20 mg users experienced 24 hour AEs than placebo (38% versus 15%, respectively). RR of harm: 2.9 (95% CI 2.0, 4.2); NNH: 4.3.[5] • More sumatriptan NS 40 mg users experienced 24 hour AEs than placebo recipients (46% versus14%, respectively). More patients receiving sumatriptan NS 10 mg and 20 mg experienced AEs than placebo recipients (18% and 23% versus 5%).[5] • Chest pain and tachycardia were similar between sumatriptan NS 20 mg and placebo [RR: 2.0; (95% CI 0.32, 12) and RR: 0.73: (95% CI 0.11, 4.9) respectively].[5] Subcutaneous • More sumatriptan SC 4 mg recipients experienced 24 hour AEs than placebo recipients (71% versus 41%, respectively).[6] • Subcutaneous sumatriptan resulted in higher rates of chest pain than eletriptan 80 mg.[4]

Intervention	Evidence	Results
Safety and Harms of Triptans for Migraine Headache		
		Rectal • Low incidence of AEs with low dose sumatriptan<12.5; higher incidence with higher doses>25 mg.[8] • NSD in fatigue, nausea, or vomiting between sumatriptan and placebo.[8]
Zolmitriptan	Systematic review[9]	• More zolmitriptan recipients (all formulations) experienced 24 hour AEs than placebo recipients.[9] • Zolmitriptan 2.5 and 5 mg tablets and NS 5 mg were associated with higher risks of dizziness, somnolence, and asthenia than placebo.[9] • NSD in chest-related symptoms between zolmitriptan 2.5 mg or 5 mg versus placebo.[9] • NSD in dizziness with zolmitriptan 2.5 mg and somnolence with ODT 2.5 mg compared to placebo.[9] • Fewer zolmitriptan 2.5 mg had AEs than zolmitriptan NS 5 mg (RR: 0.8; 95% CI 0.65, 0.99).[9] • More zolmitriptan 2.5 mg users reported AEs than naratriptan 2.5 mg (RR: 1.59; 95% CI 1.10, 2.30) or rizatriptan 10 mg (RR: 1.27; 95% CI 1.02, 1.58).[9] • Fewer zolmitriptan 2.5 mg users reported AEs than eletriptan 80 mg (RR: 0.8; 95% CI 0.67, 0.95).[9] • NSD in AEs between zolmitirptan 2.5 mg, almotriptan 12.5 mg, eletriptan 40 mg, and sumatriptan 50 mg.[9]
Almotriptan	RCT[10]	• More adolescent almotriptan recipients experienced an AE than placebo recipients with the exception of 6.5 mg recipients (23.6%, 25.8%, 18.6% and 15%, respectively).[10] • Incidence of AEs in almotriptan 6.25 mg, 12.5 mg, and 25 mg groups were 6.7%, 12.1%, and 12.4%, respectively, compared with 5.8% in the placebo group.
Rizatriptan	Observer-blind randomized parallel group study[11]	• While rizatriptan is well tolerated, providing 27 ODT 10 mg did not reduce the number of migraine days compared to patients receiving 9 ODT/month.[11] • AE were similar between groups.[11]

AE: adverse event; CI: confidence interval; NNH: number needed to harm; NSD: no significant difference; ODT: oral disintegrating tablets, RR: relative risk

Limitations

The evidence included in this review has inherent limitations that limit its usefulness in drawing conclusions regarding the safety and harms of triptans for migraine headaches. While one class review, 4 systematic reviews on sumatriptan, a systematic review of all formulations of zolmitriptan, an RCT of almotriptan in adolescents and an observer-blind parallel group study were reviewed, large retrospective database case-controlled studies are more likely to accurately reflect the incidence of rare cardiovascular events. While cardiovascular AE are of interest, with the exception of the electrocardiograms reported in the RCT,[10] it is difficult to tell whether chest pain or chest related events are cardiovascular related if no diagnostic test is specified. The systematic reviews cited significant variability in the details of reporting of outcomes in the included studies,[5,8,9] and specific AEs were often reported as in terms of number of patients experiencing any AE as opposed to number of adverse events experienced[6] which could underestimate their occurrence. There is likely some overlap between the studies

included in the DERP class review and other systematic reviews and meta-analysis. While one blind-observer randomized parallel group study reported on the use of a formulary limit of nine versus a clinical limit of 27 rizatriptan ODT,[11] no evidence was found regarding AE and harms due to triptan overuse.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

A drug class review suggests there are no consistent differences between triptan monotherapies in rates of overall AEs.[4] The most common AEs include dizziness, drowsiness, paresthesia, nausea and fatigue.[4-7,9-11] Systematic reviews of sumatriptan and zolmitriptan suggest AEs are transient, mild and increase with dose but there is no significant difference between triptans and comparators for most AEs.[5-7,9] Oral, intranasal and subcutaneous sumatriptan were associated with chest pain[5-7] and tachycardia.[5,7] One in every 44 people treated with oral sumatriptan 100 mg experience chest pain. While no evidence was found regarding AEs as a result of triptan overuse, an observer-blind randomized parallel group study showed that providing a clinical limit of 27 rizatriptan ODT 10 mg/month did not reduce the number of migraine days compared with providing 9 tablets/month.[11] Regardless of quantity, rizatriptan was well tolerated as AEs were similar between groups.[11]

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REFERENCES

1. Membe S, McGahan L, Cimon K, Gawel M, Giammarco R, Mierzwinski-Urban M. Triptans for acute migraine: comparative clinical effectiveness and cost-effectiveness [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2007. [cited 2012 Feb 24]. (Technology report no. 76). Available from: http://www.cadth.ca/en/products/health-technology-assessment/publication/690

2. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2012 Feb 24];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

3. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2012 Feb 24];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

4. Helfand M, Peterson K. Drug class review: triptans [Internet]. Final report: update 4. Portland (OR): Drug Effectiveness Review Project, Oregon and Health & Science University; 2009. [cited 2012 Mar 9]. Available from: http://derp.ohsu.edu/final/Triptans_final_report_update%204_version%202_unshaded_09_JUN.pdf

5. Derry CJ, Derry S, Moore RA. Sumatriptan (intranasal route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012;2:CD009663.

6. Derry CJ, Derry S, Moore RA. Sumatriptan (subcutaneous route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012;2:CD009665.

7. Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012;2:CD008615.

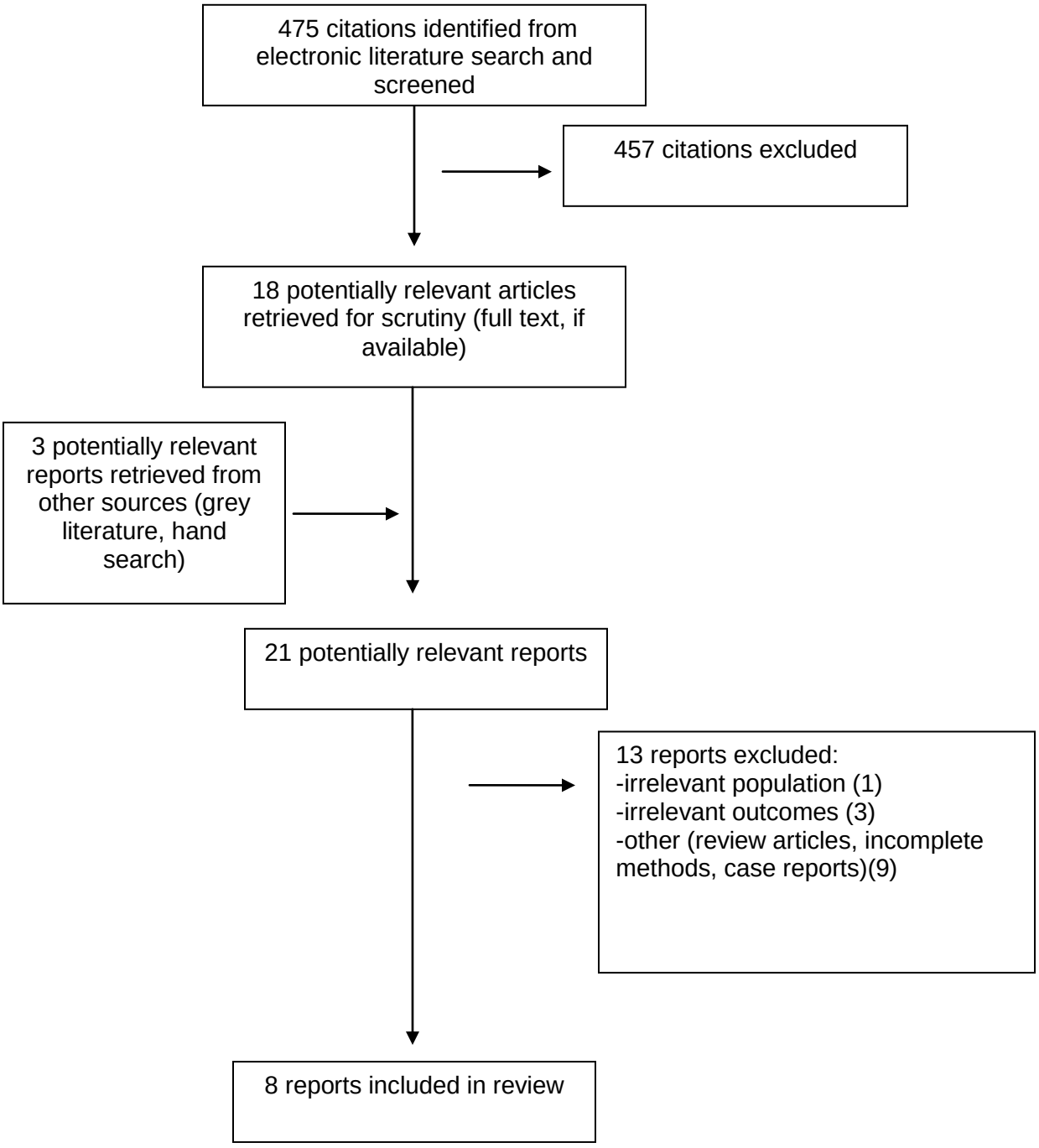
8. Derry CJ, Derry S, Moore RA. Sumatriptan (rectal route of administration) for acute migraine attacks in adults. Cochrane Database Syst Rev. 2012;2:CD009664.

9. Chen LC, Ashcroft DM. Meta-analysis of the efficacy and safety of zolmitriptan in the acute treatment of migraine. Headache. 2008 Feb;48(2):236-47.

10. Linder SL, Mathew NT, Cady RK, Finlayson G, Ishkanian G, Lewis DW. Efficacy and tolerability of almotriptan in adolescents: a randomized, double-blind, placebo-controlled trial. Headache. 2008 Oct;48(9):1326-36.

11. Cady RK, Goldstein J, Silberstein S, Juhasz M, Ramsey K, Rodgers A, et al. Expanding access to triptans: assessment of clinical outcome. Headache. 2009 Nov;49(10):1402-13.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

First Author, Publication Year Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Safety and Harms of Triptans for Migraine Headache					
Systematic Reviews and Meta-analyses					
DERP[4] 2009 United States	Systematic review of 39 head-to-head trials, 82 placebo-controlled trials, 2 non-randomized studies and 11 systematic reviews	Adults with migraine with or without aura	Oral, nasal or injectable monotherapy or combination almotriptan, eletriptan, frovatriptan naratriptan, rizatriptan, sumatriptan, sumatriptan-naproxen, zolmatriptan	Active comparator or placebo	Overall withdrawals, withdrawals due to AE, withdrawals due to specific AE (CNS effects, chest tightness)
Derry[7] 2012 United Kingdom	Systematic review, meta-analysis (61 studies, 37,250 participants)	Adults with migraine with or without aura (IHS criteria)	Sumatriptan (oral)	Active comparator or placebo	Any AE 24 hr post-dose, particular AE 24 hr post-dose, withdrawals due to AE
Derry[5] 2012 United Kingdom	Systematic review, meta-analysis (12 studies, 4755 participants)	Adults with migraine with or without aura (IHS criteria)	Sumatriptan (NS)	Active comparator or placebo	Any AE 24 hr post-dose, particular AE 24 hr post-dose, withdrawals due to AE
Derry[6] 2012 United Kingdom	Systematic review, meta-analysis (35 studies, 9365 participants)	Adults with migraine with or without aura (IHS criteria)	Sumatriptan (SC)	Active comparator or placebo	Any AE 24 hr post-dose, particular AE 24 hr post-dose, withdrawals due to AE
Derry[8] 2012 United Kingdom	Systematic review, meta-analysis (3 studies, 866 participants)	Adults with migraine with or without aura (IHS criteria)	Sumatriptan (rectal)	Active comparator or placebo	Any AE 24 hr post-dose, particular AE 24 hr post-dose, withdrawals due to AE
Chen[9] 2008 United Kingdom	Systematic review, meta analysis (24 RCTs,	Adults with migraine with or without aura (IHS criteria)	Zolmitriptan (oral tablet, ODT, NS)	Active comparator or placebo	Any AE 24 hr post-dose; dizziness, somnolence,

First Author, Publication Year Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
	15,408 patients)				asthenia, or chest-related symptoms
Randomized Controlled Trials (RCTs)					
Linder[10] 2008 United States	DB MC RCT (n=866)	Adolescents aged 12 to 17 yr with >1 yr history of migraine, having a migraine with or without aura	Almotriptan (oral)	Placebo	AE, vital signs, electrocardiograms
Randomized Observer-blind Parallel-Group Study					
Cady[11] 2009 United States	Observer-blind, randomized, parallel-group; 3 months (n=197)	Adults with migraine with or without aura	Rizatriptan (formulary limit of 9 ODT/month)	Rizatriptan (clinical limit of 27 ODT/month)	AE

AE: adverse events; CNS: central nervous system; DB: double blind; DERP: Drug Effectiveness Review Project; IHS: International Headache Society criteria; MC: multicentre; NS: nasal spray; ODT: orally disintegrating tablet; SC: subcutaneous: RCT: randomized controlled trial

APPENDIX 3: Summary of Critical Appraisal

First Author, Publication Year	Strengths	Limitations
Safety and Harms of Triptans for Migraine Headache		
Systematic Reviews and Meta-Analyses		
DERP[4] 2009 United States	• Comprehensive literature search based on pre-defined criteria • Study selection was performed using well defined criteria • A list of included and excluded studies was provided • Trial quality assessed based on predefined criteria. • Conflict of interest statement	• Search restricted to English language articles • Unclear if study selection and data extraction was in duplicate • Possible discrepancies in reporting the number and nature of studies in text versus appendices • Publication bias not assessed
Derry[7] 2012 United Kingdom	• Comprehensive literature search based on pre-defined criteria • Study selection was performed by two independent reviewers • A list of included and excluded studies was provided • Data extraction was performed in duplicate by two reviewers • Characteristics of included studies were well reported • Methods of pooling studies were appropriate and publication bias was assessed	• No conflict of interest statement provided
Derry[5] 2012 United Kingdom	• Comprehensive literature search based on pre-defined criteria • Study selection was performed by two independent reviewers • A list of included and excluded studies was provided • Data extraction was performed in duplicate by two reviewers • Characteristics of included studies were well reported • Methods of pooling studies were appropriate and publication bias was assessed	• No conflict of interest statement provided • Significant variability in the details of reporting of included studies (diary cards, spontaneous reports, follow-up reviews)
Derry[6] 2012 United Kingdom	• Comprehensive literature search based on pre-defined criteria • Study selection was performed by two independent reviewers • A list of included and excluded studies was provided • Data extraction was performed in duplicate by two reviewers • Characteristics of included studies were well reported	• No conflict of interest statement provided • Individual AE were reported inconsistently between included studies. Specific AEs were reported as proportions of participants experiencing AEs as the low number of AE prevented pooled analysis.

First Author, Publication Year	Strengths	Limitations
Safety and Harms of Triptans for Migraine Headache		
	• Methods of pooling studies were appropriate and publication bias was assessed	
Derry[8] 2012 United Kingdom	• Comprehensive literature search based on pre-defined criteria • Study selection was performed by two independent reviewers • A list of included and excluded studies was provided • Data extraction was performed in duplicate by two reviewers • Characteristics of included studies were well reported • Methods of pooling studies were appropriate and publication bias was assessed	• No conflict of interest statement • Significant variability in the details of reporting of included studies (spontaneous reports in diary cards, follow-up review and duration over which data was collected was not always specified) • Different time periods over which data were collected prohibited pooling studies for analysis
Chen[9] 2008 United Kingdom	• Comprehensive literature search based on pre-defined criteria • Study selection and data extraction was performed by two independent reviewers • Included studies were listed • Data extraction was performed in duplicate by two reviewers • Characteristics of included studies were well reported • Methods of pooling studies were appropriate • Funding and conflict of interest reported	• While reasons for exclusion were given a list of excluded studies was not provided • Publication bias was not assessed • AE were reported differently in included studies
Randomized Controlled Trials (RCTs)		
Linder[10] 2008 United States	• Clearly described research question, eligibility criteria, interventions, outcomes and patient characteristics • Sample size was calculated assuming a placebo response rate of 45% and almotriptan response rate of 60% • Intent to treat analysis • Conflicts of interest were reported	• Method of randomization was not reported, difficult to ensure random allocation to almotriptan and placebo
Randomized Observer-blind Parallel-Group Study		
Cady[11] 2009 United States	• Clearly described research question, eligibility criteria, interventions, outcomes and patient characteristics • Computer generated randomization • Outcome assessors blinded	• Allocation schedule from industry • Patients stratified into 2 groups according to number of days of migraine per month during baseline (<6/>6 days/month) • Subjects were blind at

First Author, Publication Year	Strengths	Limitations
Safety and Harms of Triptans for Migraine Headache		
		randomization, but unblinded upon receiving drug • Subjects recorded number of tablets taken and responses in monthly diaries • Industry funded

AE: adverse event

APPENDIX 4: Summary of Findings

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Safety and Harms of Triptans for Migraine Headache		
Systematic Reviews and Meta-Analyses		
DERP[4] 2009 United States	***Monotherapy versus Monotherapy***	
	• A review of post marketing surveillance data reported 16 cardiovascular events following subcutaneous and 11 following oral sumatriptan. • Chest pain was more frequent in patients taking sumatriptan100 mg than rizatriptan 5 mg (6% compared with 1%; P<0.05) but did not differ from rizatriptan 10 mg (6% compared with 3%). • Treatment-emergent chest pain was significantly greater for oral sumatriptan 50 mg compared with almotriptan 12.5 mg (2.2% versus 0.3%; P=0.004). • Subcutaneous sumatriptan 6 mg had higher rates of chest pain than eletriptan 80 mg in one open trial of 1696 migraines. • No significant differences were reported in trials assessing dizziness, paresthesias, or somnolence. • Fatigue was more frequent in patients using sumatriptan 100 mg than those using rizatriptan 5 mg (8% versus 2%; P<0.05) but no difference was found between sumatriptan 100 mg and rizatriptan 10 mg (8% versus 8%) based on one trial.	• "There were no consistent differences between triptan monotherapies in rates of overall AE.." (pg 20)[4]
	Fixed-dose Combination Tablet versus Triptan	
	• Chest discomfort was 2% for Trixmet (reformulated sumatripan,85 mg/naproxen 500 mg) versus 1% for reformulated sumatriptan 85 mg in one study while another study suggested rates were below 2% in both groups. • No significant difference between Trixmet versus reformulated sumatriptan 85 mg on rates of AE dizziness, paresthesia, somnolence	• "No consistent differences in rates of overall AE, dizziness, paresthesia, or somnolence." (pg 20)[4]
	Fixed-dose Combination Tablet versus Co-administration of Individual Component	
	• No evidence was found comparing Treximet versus co-administration of individual components.	"No head-to-head trials were found reporting harms." (pg 21)[4]
Derry[7] 2012 United Kingdom	**AE 24 hours Post Dose** • Compared to placebo, significantly more sumatriptan recipients experience AE with dose increment (NNH: 5.2, 13, and not statistically significant for sumatriptan 100 mg, 50 mg, and 25 mg, respectively) (54 trials). • NSD between sumatriptan 25 mg, 50 mg or 100 mg and rizatriptan 5 mg or 10 mg (10 trials). • NSD between sumatriptan 50 mg and effervescent ASA 1000 mg (2 trials), or zolmitriptan 2.5 mg and 5 mg in 24 hour AE (4 trials).	"AE were transient and mild and were more common with sumatriptan than placebo, with a clear dose response relationship (25-100 mg). AE were experienced by 4 in 10 (43%) of people taking sumatriptan 100 mg and by 2 in 10 (23%) taking

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	• Sumatriptan 100 mg was worse than ASA 900 mg+MCP 10 mg (NNH: 7.7) (2 trials). **Chest Pain on Sumatriptan** • 25 mg, RR: 1.8 (95% CI: 0.7, 4.3); NNH: NR (3 trials) • 50 mg, RR: 2,1 (95% CI: 1.1, 3.9); NNH: 69 (95% CI: 40, 260) (7 trials) • 100 mg, RR: 3.0 (95% CI: 1.7, 5.4); NNH: 44 (95% CI: 31, 73) (12 trials) • 200 mg, RR: 4.4 (95% CI: 0.54, 36); NNH: NR (2 trials) • 300 mg, RR: 17 (95% CI: 2.4, 127); NNH: 16 (95% CI: 11, 27) (2 trials) **Palpitations/tachycardia on Sumatriptan** • 100 mg, RR: 3.5 (95% CI: 0.75, 17); NNH: NR (2 trials) **Specific AE** • Sumatriptan caused significantly less fatigue and nausea/vomiting than eletriptan 80 mg (NNH: -17 and -24, respectively. • Sumatriptan 25 mg caused less dizziness and drowsiness than rizatriptan 10 mg (NNH 20 and -34, respectively). • Sumatriptan 50 mg caused significantly more headache than rizatriptan (5 mg or 10 mg) (NNH: 38 and 34, respectively). • Sumatriptan 100 mg caused significantly more nausea/vomiting, chest pain/tightness, and paraesthesia/numbness than ASA 900 mg+MCP 10 (NNH: 19, 33, 33, and 37, respectively). **Withdrawals due to AE** • Sumatriptan 1.6% (113/7133) versus placebo 0.65% (19/2926) • Sumatriptan 2.5% (31/1229) versus zolmitriptan 2.9% (52/1775) • Sumatriptan 1.2% (10/841) versus eletriptan 1.3% (12/938) • Sumatriptan 0.38% (4/1048) versus rizatriptan 0.28% (4/1434)	placebo. NSD between sumatriptan and comparator for majority of AE." (pg 2)[7]

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Derry[5] 2012 United Kingdom	**AE 24 hours Post Dose** • Overall withdrawals were 0.1% (3/1609) for sumatriptan NS and 0.23% (1/431) for placebo. The NNH was not calculated because there were too few events. • Sumatriptan NS 20 mg 38% (125/331) versus placebo 15% (27/185) • RR: 2.9 (95% CI 2.0, 4.2); NNH: 4.3 (95% CI: 3.3, 6.3) • Sumatriptan NS 40 mg 46% (17/37) versus placebo 14% (5/37) • Sumatriptan NS 10 mg, 20 mg 18%(7/39), 23% (9/39) versus placebo 5% (2/39) **Chest Pain on Sumatriptan NS** • 20 mg, RR: 2.0 (95% CI: 0.32, 12); NNH: NR (2 trials) **Palpitations/tachycardia on Sumatriptan NS** • 20 mg, RR: 0.73 (95% CI 0.11, 4.9); NNH: NR (2 trials) **Specific AE** • NSD between sumatriptan NS and comparator for fatigue, nausea, vomiting, paresthesia or dizziness. **Withdrawals due to AE** • Sumatriptan 1.6% (113/7133) versus placebo 0.65% (19/2926)	"AE were transient and mild but more common with sumatriptan than placebo." (pg 2)[5] NSD between sumatriptan NS and comparator for chest pain, palpitations or tachycardia.
Derry[6] 2012 United Kingdom	**AE 24 hours Post Dose** • Sumatriptan SC 4 mg 71% (313/442) versus placebo 41% (113/278) • RR 4 mg: 1.8 (95% CI 1.6, 2.2); NNH: 3.3 (95% CI: 2.7, 4.4) • Sumatriptan SC 6 mg 44% (341/767) versus placebo 24% (137/575) • RR 6 mg: 2.1 (95% CI 1.8, 2.5); NNH: 4.9 (95% CI: 3.9, 6.4) • Proportion of participants sumatriptan SC 1, 2, 3, and 8 mg was 63%, 67%, 80%, and 97%, respectively, compared to 55% of placebo recipients. **Chest Pain on Sumatriptan SC** • 2 mg and 6 mg, 5% and 4%, respectively; placebo 1% **Specific AE** • SC 6 mg: 4% fatigue, 6% dizziness, 7% nausea versus 4%, 4%, and 5%, respectively in placebo **Withdrawals due to AE** Sumatriptan SC 1.2% (41/3451) versus placebo 0.4% (10/2474); NNH: NR	"Adverse events were transient and mild and were more common with sumatriptan than placebo." (pg 2)[6]

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Derry[8] 2012 United Kingdom	**AE 24 hours Post Dose** • NSD in AE between sumatriptan<12.5 mg and placebo, greater incidence with doses >25 mg. **Chest Pain on Rectal Sumatriptan** • None reported in sumatriptan versus placebo trials **Specific AE** • One rectal sumatriptan 100 mg patient hospitalized for migraine • NSD in rates of fatigue, nausea or vomiting for any dose of rectal sumatriptan compared to placebo **Withdrawals due to AE** • The overall incidence of withdrawals due to AE for two studies was 0.4% (2/520) for all doses of rectal sumatriptan and 0% (0/95) for placebo.	"There was not enough evidence to draw conclusions about the incidence of AE or to compare rectal sumatriptan directly with any other active comparators." (pg 2)[8]
Chen[9] 2007 United Kingdom	**AE 24 hours Post Dose** • Fewer AE in zolmitriptan tablet 2.5 mg recipients compared with zolmitriptan NS 5 mg (RR: 0.8; 95% CI 0.65, 0.99). • Significantly zolmitriptan 2.5 mg tablets recipients reported AE than naratriptan 2.5 mg (RR: 1.59; 95% CI 1.10, 2.30) or rizatriptan 10 mg recipients (RR: 1.27; 95% CI 1.02, 1.58). • In contrast, zolmitriptan tablet 2.5 mg resulted in significantly fewer patients reporting AE compared with eletriptan 80 mg (RR: 0.80; 95% CI 0.67, 0.95). • NSD in patients reporting AE when zolmitriptan tablet 2.5 mg was compared with almotriptan 12.5 mg eletriptan 40 mg, and sumatripan 50 mg. • Similarly, NSD between zolmitriptan tablet 5 mg versus sumatriptan 50 mg or 100 mg. **Chest Pain on Zolmitriptan** • NSD in the risk of chest related symptoms between zolmitriptan 2.5 mg, 5 mg and placebo. **Specific AE** • Zolmitriptan 2.5 mg and 5 mg and zolmitriptan NS 5 mg showed significantly higher risks of dizziness, somnolence, and asthenia than placebo. • Single trials showed NSD in the risk of dizziness with zolmitriptan NS 2.5 mg and somnolence with zolmitriptan ODT 2.5 mg compared to placebo.	"Zolmitriptan 2.5 mg tablet had a similar AE profile to almotriptan 12.5 mg, eletriptan 40 mg, and sumatriptan 50 mg. Zolmitriptan 5 mg tablet had a similar AE profile to sumatriptan 50 mg and 100 mg. Zolmitriptan 2.5 mg tablet had a higher risk of AE than naratriptan 2.5 mg and rizatriptan 10 mg but a lower risk of AE than eletriptan 80 mg." (pg 242)[9]
Randomized Controlled Trials (RCTs)		
Linder[10] 2008 United States	**AE** • Proportion with ≥1 AE: placebo: 18.6%, almotriptan 6.25 mg, 12.5 mg, 25 mg were 15%, 23.6% and	"Almotriptan was well tolerated, with the most common AE (>2%) of

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	25.8%, respectively • AEs in almotriptan 6.25 mg, 12.5 mg, and 25 mg groups were 6.7%, 12.1%, and 12.4%, respectively, compared with 5.8% in the placebo group. • AE with an incidence >2% in any treatment group were dizziness, somnolence, and nausea. No deaths, serious AE, or discontinuations due to AE occurred, and no clinically significant changes in vital signs or electrocardiograms were noted. **Chest Pain in Adolescents using Almotriptan** • No clinically significant changes in vital signs or electrocardiograms were noted. **Specific AE** • AE with an incidence >2% in any treatment group were dizziness, somnolence, and nausea. • No deaths, serious AE, or discontinuations	nausea, dizziness, and somnolence." (pg 1326)[10]
Randomized Observer-blind Parallel-Group Study		
Cady[11] 2009 United States	**AE** • Rizatriptan well tolerated but 27 rizatriptan ODT 10 mg did not reduce migraine days compared to 9 tablets. • AE were similar for subjects receiving clinical and formulary limits of rizatriptan. • Overall, rizatriptan was generally well tolerated and fewer AE were reported during treatment than baseline periods. **Palpitations on Rizatriptan OTD** • One subject discontinued due to heart palpitations during treatment. **Specific AE** • 6 Serious AEs: cholelithiasis, appendicitis, chest pain, paresthesia, hypoesthesia and ketoacidosis in four subjects during baseline. None were considered treatment-related. **Discontinuation** • Three subjects had abdominal cramping and somnolence during baseline and heart palpitations during treatment.	"Providing a greater quantity of rizatriptan ODT 10 mg did not reduce the number of migraine days compared with providing 9 tablets/month for this population with epidosic migraine with a frequency of 3-4 migraines /month. Regardless of quantity provided, rizatriptan was generally well tolerated." (pg 1402)[11]

AE: adverse event; ASA: acetylsalicylic acid; CI: confidence interval; NSD: no significant difference; MCP: metoclopramide; NNH: number needed to harm; NR: not reported; ODT: orally disintegrating tablet; RR: relative risk;