Triptans in the acute treatment of migraine

Systematic Review and Network Meta-Analysis

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Efficacy and Safety Systematic Review:

The strategy for building and analyzing the evidence base for triptans in the treatment of acute migraines in adults consisted of two fundamental steps:

A broad systematic review of the available randomized evidence in the published and grey literature conducted following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions. (1)

A pair-wise meta-analysis and Bayesian network meta-analysis of randomized evidence conducted relating the triptans to other acute pharmacologic migraine treatments in a network, for each of the benefit and harm outcomes specified a priori. The methods and procedures followed are those developed by the Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (ccNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research.

A protocol was developed using guidance from the PRISMA Statement (2) and following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews for Interventions. (1) It was peer-reviewed by experts in pharmacology, statistics, and systematic review methodology.

Electronic search strategies were developed and tested through an iterative process by an experienced medical information specialist in consultation with the review team. The database searches were executed on 6 Oct 2013. Using the OVID platform, Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase Classic+Embase were searched. Also the Cochrane Database of Systematic Reviews and CENTRAL using Cochrane Library on Wiley was searched. Strategies utilized a combination of controlled vocabulary (e.g., Migraine Disorders, Triptamines) and keywords (e.g., triptans, rizatriptan, sumatriptan). Vocabulary and syntax were adjusted across databases. A filter was used for randomized clinical trials and results were restricted to English language. Additional references were also sought through hand-searching the bibliographies of relevant articles. Also a grey literature search was undertaken using Google Scholar and the clinical trial sites listed in CADTH’s Grey Matters (http://cadth.ca/resources/grey-matters).

In September 2013, the Ontario Drug Policy Research Network (ODPRN) held a stakeholder workshop in Toronto, Ontario at the Li Ka Shing Knowledge Institute at St. Michael’s Hospital. The agenda included presentations on the triptan research program, a background of research methodologies utilized, and specifically, the systematic review and network meta-analysis. Feedback was requested from all participants in attendance, including study team members and invited guests. Stakeholders from the pharmaceutical companies distributing triptan medications in Canada were present and were advised that they could present evidence submission packages to the systematic review team, as long as included studies were publicly available and no limits were placed on replication of results. In late
September and early October 2013, the review team received evidence submission packages from both Merck and Pfizer.

Studies were eligible for inclusion in the systematic review if they satisfied the population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest.

The study population consisted of adult patients with acute migraine headache, satisfying the following eligibility criteria:

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Adult patients with acute migraine headache (as defined by the International headache Society (IHS) criteria or reasonably similar classification)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index Node</td>
<td>Placebo</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Triptans: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan.</td>
</tr>
<tr>
<td></td>
<td>• Triptans vs. placebo</td>
</tr>
<tr>
<td></td>
<td>• Triptans vs. triptans (alone or in combination with other acute migraine therapies) (e.g., NSAIDs, ASA, acetaminophen, ergots, opioids, antiemetics)</td>
</tr>
<tr>
<td></td>
<td>• Triptans vs. other acute pharmacologic migraine treatment options (e.g., NSAIDs, ASA, acetaminophen, ergots, opioids, antiemetics)</td>
</tr>
<tr>
<td></td>
<td>• Self-administered</td>
</tr>
<tr>
<td></td>
<td>• Standard, low and high dose, all routes of administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>EFFICACY: All headache relief outcomes will be considered.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Time to freedom from pain</td>
</tr>
<tr>
<td></td>
<td>• Headache relief within 2/4 hrs</td>
</tr>
<tr>
<td></td>
<td>• Freedom from pain within 2 /4 hrs</td>
</tr>
<tr>
<td></td>
<td>• Sustained headache response at 24 hrs</td>
</tr>
<tr>
<td></td>
<td>• Sustained freedom from pain at 24 hrs</td>
</tr>
<tr>
<td></td>
<td>• Use of rescue medication</td>
</tr>
<tr>
<td></td>
<td>• Headache specific quality of life (QOL)</td>
</tr>
<tr>
<td></td>
<td>• Functional health status and health related QOL</td>
</tr>
<tr>
<td></td>
<td>SAFETY: All drug safety and adverse event outcomes will be considered.</td>
</tr>
<tr>
<td></td>
<td>• Participants with any adverse event during the 24 hours post-dose</td>
</tr>
<tr>
<td></td>
<td>• Participants with particular adverse events during the 24 hours post-dose</td>
</tr>
<tr>
<td></td>
<td>• Withdrawals due to adverse events</td>
</tr>
<tr>
<td></td>
<td>• Serious adverse events</td>
</tr>
</tbody>
</table>

| Study Designs    | Randomized controlled trials (RCTs). English or French language. No limits placed on sample size, study duration, and patient follow-up. |

<table>
<thead>
<tr>
<th>Exclusions</th>
<th>• Patients with cluster, tension or other headaches</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Patients with chronic or recurrent migraines who are not experiencing an acute episode</td>
</tr>
<tr>
<td></td>
<td>• Drugs used for prophylaxis or to prevent migraine headaches</td>
</tr>
<tr>
<td></td>
<td>• Comparisons of a triptan versus the same triptan of the same exact dose in combination with other drugs.</td>
</tr>
</tbody>
</table>

Studies that treated multiple migraine attacks were included, however, analysis were restricted to studies that provided data for a single migraine attack only. The first period of crossover designs were
included and, similar to the parallel studies, analysis of results from the first period of the crossover studies was conducted where data was available for a single migraine attack only.

**Results**

A total 133 unique randomized controlled trials were identified in the systematic review (Appendix A). All studies were published between 1991 and 2012 and recruited migraine sufferers who met the International Classification of Headache Disorders (ICHD) for migraine headaches, or used inclusion criteria with sufficient comparability to the ICHD criteria.(3-6) Generally, all studies included patients affected with migraine with or without aura, and a small number also included some patients with menstrual migraine. All participants self-administered their study medications. Trial participants were usually between the ages of 18 and 65 years, with an average age of approximately 40. Very few trials included participants older than 65 years. Trial participants were mostly female (on average, greater than 80%). Patients included in studies were both treatment naïve and experienced. In general, a high proportion of studies included participants with at least one previous treatment failure with a triptan.

A variety of doses and routes of administration were found in the included studies. For analysis purposes, doses were categorized into low, standard or high dose.

Exhibit 1 shows the clinical dose used to categorize each triptan.(7)

**Exhibit 1: Dose categorization for an acute migraine attack**

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Low dose (Half)</th>
<th>Standard dose (Common)</th>
<th>High dose (Double)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eletriptan</td>
<td>20 mg</td>
<td>40 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>25 mg</td>
<td>50 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>5 mg</td>
<td>10 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>--</td>
<td>2.5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>6.25 mg</td>
<td>12.5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>1.25 mg</td>
<td>2.5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>--</td>
<td>2.5 mg</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

Triptans were administered in a number of different ways in the included studies (Exhibit 2). Evidence was available for the following methods of administration: tablet, oral disintegrating tablet (ODT), skin patch (not available in Canada), subcutaneous injection, nasal spray, and rectal suppository (not available in Canada).
Exhibit 2: Summary of treatments evaluated

<table>
<thead>
<tr>
<th>Treatment Evaluated</th>
<th>Doses Available</th>
<th>Formulations Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eletriptan</td>
<td>LD, SD, HD</td>
<td>Tablet</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>LD, SD, HD</td>
<td>Tablet</td>
</tr>
<tr>
<td></td>
<td>LD,SD</td>
<td>Nasal Spray</td>
</tr>
<tr>
<td></td>
<td>SD, HD</td>
<td>Subcutaneous Injection</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>Patch</td>
</tr>
<tr>
<td></td>
<td>LD</td>
<td>Suppository</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>Oral Dissolvable Tablet</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>LD, SD, HD</td>
<td>Tablet</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>LD, SD</td>
<td>Oral Dissolvable Tablet</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>LD, SD, HD</td>
<td>Tablet</td>
</tr>
<tr>
<td></td>
<td>LD, SD, HD</td>
<td>Nasal Spray</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>Oral Dissolvable Tablet</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>LD, SD</td>
<td>Tablet</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>LD, SD, HD</td>
<td>Tablet</td>
</tr>
</tbody>
</table>

Efficacy

Network meta-analyses were conducted for five efficacy outcomes, namely: headache relief at 2 hours, freedom from pain at 2 hours, sustained freedom from pain at 24 hours, headache relief at 24 hours, and use of rescue medication. The choice of these outcomes for network meta-analysis was based on their importance and the sufficiency of the data available to derive robust and consistent network models.

The absolute risks for each outcome are provided in Exhibit 3 and Exhibit 4 for the SD triptan tablets and the different formulations available. In general:

- Standard dose (SD) triptans relieved headaches within 2 hours in 43 to 76% of patients. The number of patients needed to treat (NNT) in order for one patient to experience 2 hour headache relief ranged from 3 to 7 patients. In particular, at standard dose, eletriptan tablet, rizatriptan tablet and ODT, sumatriptan subcutaneous injection, and zolmitriptan ODT had a substantive effect on 2 hour headache relief.

- Only 18 to 50% of patients had freedom from pain within 2 hours with SD triptans. The NNT in order for one patient to experience 2 hour freedom from pain ranged from 3 to 15 patients.

- SD triptans provided sustained headache relief at 24 hours in 29 to 50% of patients. Data on sustained headache relief at 24 hours was not available for frovatriptan. The NNT in order for one patient to experience 24 hour headache relief ranged from 4 to 9 patients. Except for low dose rizatriptan tablet, all triptans had a significant effect on sustained headache relief at 24 hours.
hours compared to placebo. In particular, SD eletriptan had a substantive effect.

- Only 18 to 33% of patients had sustained freedom from pain at 24 hours. The NNT in order for one patient to experience 24 hour freedom from pain ranged from 5 to 12 patients.
- All triptans at standard dose had a significant effect on reducing the use of rescue medications compared to placebo. The NNT in order for one patient to avoid use of rescue medication ranged from 4 to 6 patients.

Exhibit 3: Percent of patients with headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications*

<table>
<thead>
<tr>
<th></th>
<th>2h headache relief (%)</th>
<th>2h freedom from pain (%)</th>
<th>24h sustained headache relief (%)</th>
<th>24h sustained freedom from pain (%)</th>
<th>Use of rescue medications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>27</td>
<td>11</td>
<td>17</td>
<td>10</td>
<td>52</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>49*</td>
<td>24*</td>
<td>36*</td>
<td>21*</td>
<td>32*</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>56*</td>
<td>39*</td>
<td>47*</td>
<td>33*</td>
<td>21*</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>43*</td>
<td>35*</td>
<td>--</td>
<td>--</td>
<td>31*</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>44*</td>
<td>18*</td>
<td>39*</td>
<td>18</td>
<td>30*</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>57*</td>
<td>37*</td>
<td>29*</td>
<td>24*</td>
<td>30*</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>50*</td>
<td>28*</td>
<td>33*</td>
<td>23*</td>
<td>34*</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>50*</td>
<td>27*</td>
<td>38*</td>
<td>22*</td>
<td>28*</td>
</tr>
<tr>
<td>ODT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>68*</td>
<td>50*</td>
<td>--</td>
<td>--</td>
<td>20*</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>66*</td>
<td>37*</td>
<td>50*</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>NASAL SPRAY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>53*</td>
<td>21</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>52*</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>23*</td>
</tr>
<tr>
<td>SUBCUTANEOUS INJECTION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>76*</td>
<td>37*</td>
<td>--</td>
<td>24*</td>
<td>26*</td>
</tr>
<tr>
<td>PATCH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>49*</td>
<td>21*</td>
<td>--</td>
<td>--</td>
<td>26*</td>
</tr>
</tbody>
</table>

*Percent of patients with outcome based on the odds ratios from the network meta-analysis and mean proportion of patients who experience the outcome in the placebo group.

Exhibit 4: Number needed to treat (NNT) to achieve headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and avoid use of rescue medications*

<table>
<thead>
<tr>
<th></th>
<th>2h headache relief</th>
<th>2h freedom from pain</th>
<th>24h sustained headache relief</th>
<th>24h sustained freedom from pain</th>
<th>Use of rescue medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>TABLET SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almotriptan</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>7</td>
<td>5</td>
<td>--</td>
<td>--</td>
<td>5</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>6</td>
<td>15</td>
<td>5</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>4</td>
<td>4</td>
<td>9</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>5</td>
<td>7</td>
<td>5</td>
<td>8</td>
<td>5</td>
</tr>
</tbody>
</table>
Headache relief at 2 hours
All seven triptans at low, standard, and high dose had a significant effect on improving 2h headache relief compared to placebo. The only exception was low dose frovatriptan tablet. In particular, at standard dose, eletriptan tablet, rizatriptan tablet and ODT, sumatriptan subcutaneous injection, and zolmitriptan ODT had a substantive effect on 2h headache relief. The percent of patients with headache relief at 2 hours exceeded 40% for all triptans considered, and reached a high of 76% for SD sumatriptan subcutaneous injection compared to 27% for placebo (Exhibit 3).

Freedom from pain at 2 hours
Compared to placebo, all seven triptans at low, standard, and high dose had a significant effect on improving 2h freedom from pain, with two exceptions: low dose frovatriptan tablet and SD sumatriptan nasal spray. In particular, at standard dose, eletriptan tablet, rizatriptan tablet and ODT, frovatriptan tablet, and zolmitriptan ODT had a substantive effect on 2h freedom from pain. The percent of patients with freedom from pain at 2 hours ranged from 18 to 50%, with a high of 50% for rizatriptan ODT compared to 10% for placebo (Exhibit 3).

Sustained headache relief at 24 hours
Data on sustained headache relief at 24 hours was not available for frovatriptan. Except for low dose rizatriptan tablet, all triptans had a significant effect on sustained headache relief at 24 hours compared to placebo. In particular, SD eletriptan had a substantive effect. The percent of patients with sustained headache relief at 24 hours ranged from 29% to 50% for all triptans considered, and reached a high of 50% for zolmitriptan ODT compared to 17% for placebo (Exhibit 3).

Sustained freedom from pain at hours
Data on sustained freedom of pain at 24 hours was not available for frovatriptan. Except for low dose rizatriptan tablet and SD naratriptan tablet, all triptans had a significant effect on sustained freedom from pain at 24 hours compared to placebo. In particular, SD eletriptan had a substantive effect. The percent of patients with sustained freedom from pain at 24 hours ranged from 14 to 33%, with a high of...
33% for SD eletriptan tablets compared to 10% for placebo (Exhibit 3).

**Use of rescue medications**
For the triptans considered at the standard and high dose, all had a significant effect on reducing the use of rescue medications except for high dose zolmitriptan subcutaneous injection. At low dose, for the triptans considered (all but almotriptan), all were not significantly better except for eletriptan and rizatriptan. The percent of patients using rescue medications ranged from 20 to 34%, with a low of 20% for rizatriptan ODT compared to 52% for placebo (Exhibit 3).

**Functional Status**
Functional status was evaluated by considering the proportion of patients who experienced an improvement in functional disability (usually described as the effort required to perform usual activities and a return to normal function with the use of the study medication). The meta-analyses of functional status are summarized in Exhibit 5 for the standard dose triptans involving different routes of administration. Overall, based on 55 studies involving 11,266 patients on a triptan and 7283 on placebo, functional status is significantly better on triptans compared to placebo (OR 2.54; 95% CI 2.20, 2.92).

**Exhibit 5: Functional status-odds ratios of triptans compared to placebo**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of participants (studies)</th>
<th>Heterogeneity (I²)</th>
<th>Odds ratio (OR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD Almotriptan Tablet</td>
<td>694 (2 studies)</td>
<td>0%</td>
<td>2.18 (1.60, 2.97)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Rizatriptan Tablet</td>
<td>4177 (12 studies)</td>
<td>42%</td>
<td>2.84 (2.32, 3.46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Naratriptan Tablet</td>
<td>1430 (6 studies)</td>
<td>0%</td>
<td>1.84 (1.47, 2.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Sumatriptan Subcutaneous Injection</td>
<td>1178 (6 studies)</td>
<td>43%</td>
<td>5.07 (3.50, 7.32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Sumatriptan Nasal Spray</td>
<td>923 (3 studies)</td>
<td>0%</td>
<td>1.73 (1.33, 2.26)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Eletriptan Tablet</td>
<td>4790 (10 studies)</td>
<td>92%</td>
<td>2.32 (1.43, 3.77)</td>
<td>0.0007</td>
</tr>
<tr>
<td>SD Sumatriptan Tablet</td>
<td>2400 (7 studies)</td>
<td>0%</td>
<td>2.77 (2.28, 3.36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SD Frovatriptan Tablet</td>
<td>672 (2 studies)</td>
<td>72%</td>
<td>1.38 (0.62, 3.10)</td>
<td>0.43</td>
</tr>
<tr>
<td>SD Zolmitriptan Tablet</td>
<td>741 (6 studies)</td>
<td>75%</td>
<td>2.15 (1.40, 3.30)</td>
<td>0.0004</td>
</tr>
<tr>
<td>SD Zolmitriptan Subcutaneous Injection</td>
<td>116 (1 study)</td>
<td>NA</td>
<td>5.06 (2.20, 11.61)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Comparisons among the triptans**
Summaries of the head-to-head comparisons among the SD triptan tablets are presented in Exhibit 6. The green circle in Exhibit 6 indicates that the triptan identified in the ‘row’ is significantly better than the ‘column’ triptan; the red circle indicates that the ‘row’ triptan is significantly worse than the...
‘column’ triptan; the blank circle indicates that there is no significant difference between the ‘row’ and ‘column’ triptan; and a missing circle indicates that the outcome was not available for analysis. In general, there were more favorable results observed for eletriptan and rizatriptan (as indicated by the green circles). Results were less favorable for naratriptan and sumatriptan. Data for frovatriptan at 24 hours were not available, and the results for the 2 hour data were not favourable compared to eletriptan and rizatriptan. Use of rescue medications was not significantly different between the triptans except for sumatriptan having a significantly favourable result compared to zolmitriptan.

Comparisons to active non-triptan treatments and other doses

- In general, SD triptan tablets were associated with equal or more favourable results than NSAIDs, aspirin, acetaminophen for 2 hour outcomes; the exception being naratriptan and frovatriptan.
- SD triptans were associated with more favourable results than ergots for 2 hour and 24 hour headache relief and freedom from pain outcomes.
- There was evidence of a dose-response relationship for both 2 hour and 24 hour headache relief and freedom from pain outcomes across the triptans.

Exhibit 6: Head-to-head comparisons of the triptans on the outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications*

<table>
<thead>
<tr>
<th></th>
<th>Almotriptan</th>
<th>Eletriptan</th>
<th>Frovatriptan</th>
<th>Naratriptan</th>
<th>Rizatriptan</th>
<th>Sumatriptan</th>
<th>Zolmitriptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eletriptan</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Frovatriptan</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naratriptan</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rizatriptan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The 5 contiguous circles correspond, respectively, to the five efficacy outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at hours, and use of rescue medications.
- The green circle indicates that the ‘row’ triptan is significantly better than the ‘column’ triptan.
- The red circle indicates that the ‘row’ triptan is significantly worse than the ‘column’ triptan.
- The blank circle indicates that there is no significant difference between the ‘row’ and ‘column’ triptan.
A missing circle indicates that the outcome was not available for analysis.
Safety

Withdrawals due to adverse event (WDAE)
The limited data available for withdrawals due to adverse effects makes interpretation difficult. In many cases the effect estimate is not estimable due to no WDAEs occurring in the study. Although adjustments can be made for these zeros, the results will be mostly driven by the large number of adjustments needed, making results hard to elucidate. In 50 studies involving 10,006 patients on a triptan and 7,440 patients on placebo, 20 and 34 WDAEs occurred in the triptan and placebo arms respectively. Based on the 16 studies providing estimable results, there is no significant difference in the occurrence of WDAEs between triptans and placebo (OR 1.14; 95% CI 0.65, 1.98).

Serious Adverse Events (SAE)
Again, the limited data available for serious adverse effects makes interpretation difficult and in many cases the effect estimate is not estimable due to no SAEs occurring in the study. Overall, based on 60 studies involving 11,861 patients on a triptan and 9301 on placebo, 84 and 81 SAEs occurred in the triptan and placebo arms respectively. Based on the 12 studies providing estimable results, there is no significant difference in the occurrence of SAEs between triptans and placebo (OR 1.21; 95% CI 0.65, 2.24).

Common Adverse Events (AE)
In general, AEs do not differ across triptans and the most commonly reported AEs are: chest tightness and central nervous system symptoms such as dizziness, numbness, tingling, and drowsiness. These may be more of related to tolerability than to actual safety. There is less information on AEs for frovatriptan, and the non-tablet formulations of the other triptans.
Key Messages

- In general, SD triptans relieved headaches within 2h in 43 to 76% of patients with the number of patients needed to treat in order for one patient to experience 2 hour headache relief ranged from 3 to 7 patients.
- Freedom from pain within 2h was less common, with only about 18 to 50% of patients experiencing freedom from pain within 2h with SD triptans. The NNT in order for one patient to experience 2h freedom from pain ranged from 3 to 15 patients.
- In general, SD triptans provided sustained headache relief at 24h in 29 to 50% of patients. The NNT in order for one patient to experience 24h headache relief ranged from 4 to 9 patients.
- Sustained freedom from pain at 24h was less common, with only about 18 to 33% of patients having sustained freedom from pain at 24h. The NNT in order for one patient to experience 24 h freedom from pain ranged from 5 to 12 patients.
- All triptans at SD had a significant effect on reducing the use of rescue medications compared to placebo. Use of rescue medications in SD triptans ranged from 20 to 34%, and the NNT in order for one patients to avoid use of rescue medication ranged from 4 to 6 patients.
- In general, there were more favorable observed for rizatriptan and eletriptan.
- There were less favorable results for frovatriptan for 2h headache relief and no data at 24h.
- There were less favorable results for naratriptan for most outcomes.
- Certain modes of administration yielded better results (e.g., rizatriptan ODT, sumatriptan subcutaneous injection).
- SD triptan tablets were associated with equal or more favorable results than NSAIDs, aspirin, acetaminophen for 2h outcomes; the exception being naratriptan and frovatriptan.
- SD triptans were associated with more favorable results than ergots for 2h and 24h outcomes.
- Sumatriptan offers the widest choice for mode of delivery —tablet, nasal spray, injection, patch, suppository; these can complement or supplement one another.
- There was evidence of a dose-response relationship for both 2h and 24h outcomes across triptans.
- There was limited data for sub-groups.
- There was limited data for side effects.
References


Appendix A: Included Study List

Included Studies (with single attack data) n = 133


73. Loder E, Freitag FG, Adelman J, Pearlman S, Abu-Shakra S. Pain-free rates with zolmitriptan 2.5 mg ODT in the acute treatment of migraine: results of a large double-blind placebo- controlled...


102. Schulman EA. Transdermal sumatriptan for acute treatment of migraineurs with baseline


Included studies (no single attack data) n = 69


158. Facchinetti F, Bonellie G, Kangasniemi P, Pascual J, Shuaib A. The efficacy and safety of


173. Mathew NT, Asgharnejad M, Peykamian M, Laurenza A. Naratriptan is effective and well tolerated in the acute treatment of migraine. Results of a double-blind, placebo-controlled,


187. Ryan RE, Elkind A, Goldstein J. Twenty-four-hour effectiveness of BMS 180048 in the acute


