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Are Triptan drugs safe and effective for use in the prevention of Menstrually Related Migraines (MRMs)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not Triptan drugs are safe and effective for use in the prevention of menstrually related migraines (MRMs).

Study Design: Review of two English language randomized controlled trials and one pilot randomized control trial

Data Sources: Randomized controlled trials comparing Triptan drugs to a placebo group were found using Medline, PubMed, and OVID

Outcomes Measured: Incidence of MRM based on patient self-report; number of relapses; patients’ subjective evaluations of effectiveness based on questionnaire; adverse effects of Triptan treatment

Results: Two randomized controlled trials and one pilot study were included in this review. Oral Triptan drugs were shown to be of benefit in the prevention of menstrually related migraines (MRMs).

Conclusions: The results of the randomized controlled trials reviewed demonstrate that oral Triptan drugs, given short-term, were safe and effective at preventing menstrually related migraines (MRMs). However, in one of the RCTs, some migraineurs experienced post-treatment attacks. There is not a clear explanation for these post-treatment attacks; further studies need to be conducted to allow for more flexible dosing in order to ensure that the migraineurs are being treated during their perimenstrual period (PMP). Additionally, further studies should be conducted comparing Triptan dosing schedules, dosages, duration of treatment, routes of administration as well as the efficacy of the drugs within the Triptan class in preventing MRMs.

Key Words: migraine, Triptan, menstruation
Introduction

Menstrually related migraine (MRM) is a common disorder among women migraineurs. Approximately 60% of women with migraines report an increase in frequency and/or severity of migraine attacks around the time of their menstrual period. The generally accepted definition of a menstrually related migraine is a migraine that occurs during the perimenstrual period (PMP), which is equated to two days before menses through 2-4 days of menstruation. In MRMs, attacks may occur at other times of the cycle. Attacks that occur exclusively with menses are reported in 15% of female migraine patients. According to the International Headache Society (IHS), the criteria for diagnosing a menstrual migraine is that it must occur on days -2 to +3 of menstruation in at least two of three consecutive cycles.

MRMs are similar to migraine without aura but MRMs tend to be longer in duration, more intense in severity, less responsive to treatment, and more subject to recurrence after initial treatment. The symptoms of MRMs occur two days before onset of menstruation to 2-4 days during menstruation and are unilateral in location, pulsatile in quality, moderate to severe in intensity, made worse by physical activity, and associated with nausea, photophobia, and phonophobia.

The exact pathophysiology of MRMs is not understood but it is of the general belief that they are related to the decrease in estrogen levels at menstruation. The trigger of the MRMs may be related to either the level of estrogen before decline, the rate of decline, or the magnitude of decline.

Although there is no recent data, in 2003 there were 10.4 million US physician office visits for headache. “More than 50% of migraine sufferers report a clear relationship
between migraine attacks and menstrual flow and 10% of patients show migraine symptomatology exclusively during the PMP.” Medical costs of patients with migraine are estimated to be $2,571/person/year higher than in non-migraine patients. The direct cost of migraine management in the United States is estimated to be $17.7 billion dollars every year; of this, $1.3 billion represents migraine medical care and $16.5 billion represents medical costs related to lost of productivity. To equate these costs to the percentage of migraineurs who suffer MRMs, it is estimated that between $1.7 and $8.85 billion is spent on MRM management. Of this, it is estimated that between 130 million and 650 million dollars is spent on direct medical care and between 1.65 and 8.25 billion dollars is spent on loss of productivity due to MRMs.

Three pharmacologic approaches exist for the treatment of MRMs. Short-term therapy is directed at decreasing both the length and severity of individual migraine attacks. Long-term preventative therapy taken daily without reference to menstruation is directed at decreasing attack frequency and severity. Short term preventative therapy is intended to take before the onset of monthly menstruation. Pharmacologic options for MRM prophylaxis include NSAIDS, ergotamine, dihydroergotamine (DHE), methysergide, magnesium, beta blockers and calcium channel blockers. Triptans are not only one of the most frequently used medications in the treatment of acute migraines, but also are the most effective treatment option. The indication of Triptans for the prevention of MRMs remains to be seen.

**Objective**

The objective of this selective EBM review is to determine whether or not Triptan drugs are safe and effective for use in the prevention of menstrually related migraines (MRMs).
Methods

Specific criteria was designated for the selection of the three trials used in this paper. Criteria for population included women migraineurs aged > 18 years old with MRM. Menstrually related migraines were defined as migraines that occur in at least two of three consecutive cycles on days -2 to +3 of menstruation. The intervention used was prophylactic oral Triptan drugs. The treatment group receiving a Triptan drug was compared to the control group receiving a visually matched placebo. Outcomes measured included the incidence of MRM based on self-report, number of relapses, patients’ subjective evaluations of effectiveness based on questionnaire, and adverse effects of Triptan treatment. The types of studies included two RCT (randomized controlled trials) and a pilot randomized controlled trial.

In Silberstein’s study, patients treated each of their three perimenstrual periods (PMP) with placebo, Frovatriptan 2.5 mg QD, or Frovatriptan 2.5 mg BID for six days, beginning two days before anticipated start of MRM. The primary outcome that was measured in this study was the incidence of HA during these six days.\(^1\) The results of this study were presented as two different subsets of populations. The “ITT” group represented those patients who took their medication for at least one PMP (perimenstrual period). The “ITT2” group represented those patients who took all three doses for all three PMPs.

Mannix’s study was comprised of two identically designed, randomized double-blind parallel group studies. Women received Naratriptan 1 mg BID or a placebo; they took the study medication three days before their predicted MRM for a total of six days and repeated this for four consecutive menstrual cycles.\(^2\) The primary outcome measured in this study endpoint was the mean percentage of treated PMPs without MRM, as per patient report.
Secondary outcomes measured were the percentage of patients who were free of MRM during all treated PMPs and patient satisfaction. To determine safety of Naratriptan, adverse events, laboratory tests and vital signs were recorded and analyzed.²

Facchinetti’s study evaluated patients over two menstrual cycles. The patients received Sumatriptan suppositories (25 mg) to treat attacks in the first cycle and oral Sumatriptan tablets (50 mg) to treat all attacks in the second cycle.³ The primary outcome measured was pain relief two hours post-administration. Secondary outcomes of interest in this study were the number of relapses as well as patients’ appraisal of the study medication after each treatment period, according to a verbal scale: “ineffective”, “moderately good”, “good”, “excellent.”³

**Data Sources**

Keywords used in literature search were “migraine”, “Triptan”, and “menstruation”. All articles were published in peer reviewed journals in the English language. Literature searches were conducted via Medline, Pubmed, and OVID. Articles were selected based on their relevance and on the importance of outcomes to the patient -- patient oriented evidence that matters (POEMS). Studies included in the search were randomized, placebo-controlled, double-blind studies. Studies that were excluded were those with a patient population under the age of 18 and with a patient population that included males. Statistics reported in these studies included RRR (relative risk reduction), ARR (absolute risk reduction), NNT (numbers needed to treat), and p-values.
Table 1- Demographics and Characteristics of included studies

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TYPE</th>
<th># PTS</th>
<th>AGE</th>
<th>INCLUSION CRITERIA</th>
<th>EXCLUSION CRITERIA</th>
<th>W/D</th>
<th>INTERVENTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silberstein¹, 2004</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>546</td>
<td>18-56</td>
<td>Mean age = 37.6</td>
<td>Women migraineurs aged &gt; 18 years with: migraine headaches according to IHS criteria</td>
<td>103</td>
<td>Frovatriptan 2.5 mg QD and Frovatriptan 2.5 mg BID (both for 6 days)</td>
</tr>
<tr>
<td>Mannix², 2007.</td>
<td>2 identical, randomized, double-blind, placebo-controlled, parallel-group studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Naratriptan 1 mg BID for 4 PMPs</td>
</tr>
<tr>
<td>Facchinetti³, 2010</td>
<td>pilot study</td>
<td>71</td>
<td>22-48 (avg 35.3 +/- 7.5)</td>
<td>2 groups of women suffering from migraine without aura, age range 18-50, diagnosed according to the criteria in IHS, <strong>First group:</strong> women suffering from MRM <strong>Second group:</strong> women suffering from OCMM (oral contraceptive menstrual migraine)</td>
<td>Patients on prophylactic medication to prevent migraine; patients taking oral contraceptive for &lt; 3 months</td>
<td>8</td>
<td>Sumatriptan suppositories (25 mg) for all migraine attacks in the first cycle &amp; Sumatriptan tablets (50mg) for all attacks in the second cycle.</td>
</tr>
</tbody>
</table>

Outcomes Measured

Outcomes measured were those of patient oriented evidence that matters (POEMs).

Incidence of MRMs was reported via self-report. Patient’s subjective evaluations of overall effectiveness were measured via questionnaires: “poor”, “fair”, “good”, or “excellent” (Silberstein); “very” to “somewhat” satisfied, “neutral”, “very” to “somewhat” dissatisfied (Mannix); “ineffective”, “moderately good”, “good”, “excellent” (Facchinetti).¹,²,³ Adverse events were measured based on patient report.
Results

In Silberstein’s ITT group, Frovatriptan 2.5 mg QD and 2.5 mg BID were both superior to placebo in reducing incidence of MRMs. The incidence of MRM with placebo was 67% (n=325).\(^1\) This percentage was reduced to 52% (n=251; p<0.0001) with use of Frovatriptan 2.4 mg QD and 41% (n=199; p<0.0001) with use of Frovatriptan 2.5 mg BID.\(^1\) In ITT2, the percentage of patients with an incidence of MRM was 69% (n=307), 52% (n=232; p<0.0001), and 43% (n=190; p<0.0001), respectively.\(^1\) For both ITT and ITT2, the QD dosed group represents the experimental event rate (EER) and the placebo dosed group represents the control event rate (CER).

Both the QD and BID doses reduced the incidence of migraines more effectively when compared to placebo (p<0.0001). However, the BID dose was rated as more effective than the QD dose (p<0.0001).\(^1\) In the placebo-dosed patients, 66% rated the effectiveness as either “fair”, “good”, or excellent. This percentage was increased to 80% in the QD-dosed patients and 86% in the BID-dosed patients.

It was determined that the incidence and type of adverse events in the intervention groups were similar to those seen in placebo patients. The incidence of adverse events was 4.1% (BID) and 2.7% (QD) higher than the placebo group. The most common adverse events were headache, nausea, dizziness, nasopharyngitis, dysmenorrhea. Overall, the study concluded that Frovatriptan, given prophylactically for 6 days, reduced the incidence of MRMs.\(^1\)

The results of the two Mannix studies demonstrated, as per patient report, that the mean percentage of PMPs without MRM was higher in the Naratriptan group compared to the placebo group in those patients who treated at least one PMP as well as in those patients
who treated all four PMPs (p<0.05). Of the patients who treated at least one PMP, the percentage of patients with no MRM in any of the four treated PMP was higher (p=0.006) in the Naratriptan group than in the placebo group in the second study only. The percentage of patients with no MRM in at least 50% of PMPs was higher in the Naratriptan group as compared to the placebo group in both studies (p<0.05). To summarize these results, the Mannix trial displayed that Naratriptan prevented MRMs better than placebo.²

At visit two, satisfaction ratings of the efficacy of the study drug were measured via a patient questionnaire. At this visit, satisfaction in the Naratriptan-treated group was similar in comparison to the placebo group. However, at visit 5, based on the Cochran Mantel-Haenszel test, significantly more Naratriptan-treated patients reported greater overall satisfaction with the medication compared to placebo-treated patients (p<0.05).²

There were no significant adverse events reported in Mannix’s studies. In study one, the adverse events of the placebo and Naratriptan groups were comparable. In study two, the incidence of adverse events was slightly higher with Naratriptan as compared to placebo-treated patients. The adverse events were paresthesia (drug related), acute pulmonary edema (not drug-related), and vertigo (drug related), migraines (not drug-related) and gastritis (drug-related). Overall, Mannix’s study concluded that Naratriptan 1 mg BID for 6 days is effective and generally well tolerated for short term prevention of MRMs.²

The results of Facchinetti’s study demonstrated that the oral formulation of Sumatriptan was 91% effective. A relapse occurred in 52% of MRM cases when being treated with Sumatriptan.³
Table 2. Efficacy of Triptan drugs on preventing MRMs

<table>
<thead>
<tr>
<th>Study</th>
<th>CER</th>
<th>EER</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silberstein</td>
<td>0.67</td>
<td>0.41</td>
<td>-0.39</td>
<td>-0.26</td>
<td>4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mannix</td>
<td>0.76</td>
<td>0.60</td>
<td>-0.21</td>
<td>-0.16</td>
<td>6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

RRR= Relative Risk Reduction; ARR= Absolute Risk Reduction; NNT= Numbers Needed to Treat; CER= control event rate; EER= experimental event rate

Table 2 displays the treatment effects of the studies. ARR shows the decrease in amount of MRMs in the Triptan group compared to the placebo group. RRR determines the effectiveness of Triptan therapy and also the likelihood of another MRM despite Triptan therapy. NNT determines the number of patients that needed to be treated with Triptan therapy to prevent a bad outcome (i.e. MRM) from occurring. In Facchinetti’s study, a p-value was unable to be calculated. Instead, a percent change from baseline was calculated to determine efficacy. Significant pain relief was reported in 78% of attacks (98/123) treated with oral Sumatriptan.3

Table 3. Safety of Triptan drugs in preventing MRMs

<table>
<thead>
<tr>
<th>Study</th>
<th>CER</th>
<th>EER</th>
<th>RRI</th>
<th>ARI</th>
<th>NNH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silberstein</td>
<td>0.402</td>
<td>0.443</td>
<td>0.102</td>
<td>0.041</td>
<td>24</td>
<td>p= 0.185</td>
</tr>
<tr>
<td>Mannix</td>
<td>0.29</td>
<td>0.33</td>
<td>0.14</td>
<td>0.04</td>
<td>25</td>
<td>NR</td>
</tr>
</tbody>
</table>

RRI= Relative Risk Increase; ARI=Absolute Risk Increase; NNH= numbers needed to harm; CER= control event rate; EER= experimental event rate
Table 3 displays the safety of Triptan drugs in the prophylaxis of MRMs. RRI determines the safety of Triptan therapy and also the likelihood of experiencing an adverse event during Triptan therapy. ARI shows the increase in amount of adverse events in the Triptan group compared to the placebo group. NNH was calculated to determine the number of patients that needed to be treated with Triptan therapy to cause an adverse event; 24-25 patients need to be treated to get one adverse event.

**Discussion**

The randomized controlled trials used for this study demonstrate that administration of Triptans during the PMP for the prevention of MRMs is effective in reducing the incidence of MRMs. The studies did not prove whether or not Triptan drugs were safe for MRM prophylaxis; the only p-value that was able to be calculated was shown to be insignificant. However, it can be argued that the benefit of short-term MRM prophylaxis versus long term chronic prophylaxis is that short-term prophylaxis is not only able to reduce the amount of time that the body is exposed to medication but also decrease the amount adverse events.

The three trials that were chosen for this paper studied three different types of Triptan drugs: Frovatriptan, Sumatriptan, and Naratriptan. Although each of these three drugs are in the same class, they vary in duration of action, side effect profile, effectiveness in relation to prevention of MRMs, etc.

Timing of the dosing of the study medication in relation to the anticipated onset of MRM was seen to be a area of potential imprecision. Since women have differing lengths of menstrual cycles, it is difficult to determine a fixed PMP that would accurately apply to every woman. In Mannix’s study, the percentage of patients who reported a post-treatment
migraine was higher in patients who received Naratriptan compared to the placebo group.\textsuperscript{2}

What remains to be seen is whether the post-treatment migraines were delayed MRMs, MRMs occurring during PMP due to treatment not covering the entire PMP, or if the post-treatment attacks were simply a non-MRM attack.\textsuperscript{2}

The Facchinetti study looked at Triptan drugs in the acute treatment of MRMs whereas the other two studies looked at prophylaxis of MRMs with Triptans. The Silberstein and Mannix studies were interested in the incidence of MRMs as their primary outcome. Since Facchinetti’s study looked at the treatment of MRMs instead of prophylaxis of MRMs, it was difficult to find a primary outcome that would parallel with the Silberstein and Mannix studies. However, prevention of MRM incidence was able to measured by using “number of relapses” as a marker for incidence of MRMs. The relapse rate used as a marker for incidence does not delineate between oral and per rectum routes of administration. Indeed, this represents an area of debate.

Only one patient reported a adverse event that caused a disruption in medication administration. Adverse events include sensation of chest tightness, a lump in the throat and tachycardia but the paper does not state which adverse events correlated with the oral-dosed group and which correlated with the suppository-dosed group. The paper also does not state which adverse event was due to the medication.\textsuperscript{3}

Additionally, in the Mannix study, “nearly 30% of patients in each study were receiving daily migraine prophylaxis.”\textsuperscript{2} Therefore, it is difficult to determine whether the results of the study were truly due to that treatment regimen itself or to the daily prophylactic treatment previously taken by the patient.
Triptans are in the class of 5-HT\textsubscript{1} agonists. Serious cardiac events have been seen with the use of Triptan drugs: coronary artery vasospasm, transient myocardial ischemia, atrial and ventricular arrhythmias, and myocardial infarction.\textsuperscript{5} These adverse effects are very rare. In general, side effects are minor: paresthesias, fatigue, flushing, chest tightness drowsiness, dizziness, nausea, and sweating.\textsuperscript{5}

Triptans are contraindicated in patients who have a history of CAD, CVA/TIA, PVD, hemiplegic or basilar migraines, and IBD. Triptans may cause an increase in blood pressure and thus are contraindicated in patients with hypertension that is uncontrolled. Specifically, Naratriptan is contraindicated in patients with renal or hepatic dysfunction and Sumatriptan is contraindicated in patients who have taken a MAO inhibitor two weeks before administration of Sumatriptan.\textsuperscript{5}

Sumatriptan taken during pregnancy does not appear to increase the risk of birth defects. There is not enough data to make the same case for other Triptan drugs. Breast feeding also does not appear to cause any adverse events in the infant. However, the data that supports this claim is limited.\textsuperscript{6}

**Conclusions**

Triptans were shown to be effective in the prophylaxis of MRMs. The results of the trials showed a significant decrease in incidence of MRMs when Triptans were administered during the PMP. The studies did not prove whether or not Triptan drugs were safe when used in the prevention of MRMs; only one p-value out of the three studies was calculated and it was found to be statistically insignificant.

Further studies need to be conducted that compare Triptan dosing schedules, dosages, duration of treatment, and routes of administration. Further trials are also warranted comparing drugs within the Triptan class and their efficacy in preventing MRMs.
References


