Oregon Health Resources Commission

TRIPTAN
Update Report

Update #3, January 2006

This report is the third update of the initial Triptan Subcommittee Report of March 2003. All revisions are highlighted.

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Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-Managed Prescription Drug Plan. The statute specifically directs the Health Resources Commission to advise the Department of Human Services on this Plan.

Through spring and fall of 2002 the Health Resources Commission appointed a subcommittee to perform an evidence-based review of serotonin (5-hyhydroxytryptamine (5-HT) (1B/1D) agonists, often referred to as triptans. Members of the subcommittee consisted of physicians, pharmacists, nurse practitioners, other health care professionals, consumers and advocates. The subcommittee had 8 meetings. All meetings were held in public with appropriate notice provided.

Subcommittee members initially worked with Oregon Health and Science University's Evidence-based Practice Center (EPC) to formulate and finalize three key questions for drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities.

Using standardized methods, the Evidence-based Practice Center reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The OHSU's Evidence-Based Practice Center draft report titled "Drug Class Review on selective 5-HT agonists (Triptans)" was completed the week of October 22, 2002, circulated to subcommittee members for review and posted on the web. The OHSU Final Evidence-based Report on Triptans was completed the week of March 7, 2003. An Executive Summary on the Triptans was completed by Dr. Mark Helfand, Director, Oregon EPC the week of March 7, 2003. All available sources of information: the EPC reports, documents and testimony presented by pharmaceutical manufacturers and additional references brought to the attention of the subcommittee by subcommittee members, were considered by the Triptans subcommittee in drawing the conclusions which comprise the body of this report. Time was allotted for public comment, questions and testimony at each meeting.

The EPC used several methods to display comparison data from triptan head-to-head clinical trials. Parameters assessed were the ability of the different triptans to treat symptoms of most importance to migraineurs: efficacy, onset of action, and sustained response. Although of lesser concern to migraine sufferers, adverse

events were similarly evaluated. Evidence was specifically sought for subgroups of patients based on race, ethnicity, age, demographics, other medications and co-morbidities.

The Triptan Update Committee of the Health Resources Commission, working together with the Evidence-based Practice Center, OMAP, and the OSU College of Pharmacy will monitor medical evidence for new developments in this drug class. Every year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and FDA changes in indications and safety recommendations will be evaluated. The Standing Update Committee of the Health Resources Commission (HRC) who may choose to approve the report, or if substantive changes are considered, the HRC may reconvene the Triptan Subcommittee

The OHSU-EPC's updated final report # 2, "*Drug Class Review on Triptans"* was completed September 2004, circulated to Triptan Subcommittee members and posted on the OHPR website at http://egov.oregon.gov/DAS/OHPPR/HRC. The Triptan Subcommittee met three times to review the document and write this report. By consensus, the committee members agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. All available sources of information from the EPC's report that included information submitted by pharmaceutical manufacturers and public testimony, were considered. The Triptan Subcommittee presented its findings to the HRC and the revisions were approved at its meeting on February 18, 2005.

The OHSU-EPC's updated final report #3, "*Drug Class Review on Triptans"* was completed November 2005, circulated to Triptan Subcommittee members and posted at http://www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml the OHPR website. The Standing Update Committee met twice to review the document and write this report. By consensus, the committee members agreed to adopt the EPC report. Time was allotted for public comment, questions and testimony. All available sources of information from the EPC's report that included information submitted by pharmaceutical manufacturers and public testimony, were considered. The Standing Update Committee presented its findings to the HRC and the revisions were approved at its meeting on February 17, 2006.

This report is prepared to facilitate the HRC in providing recommendations to OMAP for the plan drug list (PDL). This update report does not recite or characterize all the evidence that was considered by the OHSU Evidenced-based Practice Center, the Triptan Subcommittee or the Health Resources Commission. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials.

The full OHSU Evidenced-based Practice Center's report, Drug Class Review on Triptans, is available on the Office for Oregon Health Policy & Research Practitioner-Managed Prescription Drug Plan web site; http://www.oregonrx.org. Additional information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml. You may also request copies of the report, and minutes or tapes of the subcommittee meetings from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from OHSU Center for Evidence-based Policy by contacting:

John Santa, MD
Assistant Director for Health Projects
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There will be a charge for copying and handling in providing documents both from OHPR and OHSU Center for Evidence-based Policy.

Drug Class Review for Triptans

Migraine headaches affect up to 18% of all women, and 6% of men. The headaches are debilitating and impact not only quality of life and daily functioning, but also absenteeism and productivity in the work place.

The triptans selectively target the pathophysiological processes that are felt to be responsible for the characteristic pain of migraine.[1] Although the exact mechanisms remain unknown, the triptans activate 5-hydroxytriptamine receptors which results in the following:

- Cranial vasoconstriction
- Decreased release of vasoactive neuropeptides, specifically calcitonin gene-related peptide (CGRP)
- Increased inhibition of central and peripheral trigeminal nociceptors.

[1] Hargreaves RJ, Shepheard SL. Pathophysiology of migraine – new insights. *Can J Neurol Sci.* 1999;26 (suppl 3):S12-s19.

Table 1

Generic Name	Trade Name	Manu-facturer	Dosage Form(s)	Available Strengths	Doses Studied	FDA Approval
almotriptan	Axert	Ortho-McNeil	oral tablet	6.25 mg		May 2001
almotriptan	Axert	Ortho-McNeil	oral tablet	12.5 mg	12.5 mg	May 2001
eletriptan	Relpax	Pfizer	oral tablet	20 mg	20 mg	Dec 20 2002
eletriptan	Relpax	Pfizer	oral tablet	40 mg	40 mg	Dec 20 2002
eletriptan	Relpax	Pfizer	oral tablet		80 mg	NA*
frovatriptan	Frova	Elan	oral tablet	2.5 mg	2.5 mg	Nov 2001
naratriptan	Amerge	GSK	oral tablet	1 mg		Feb 1998
naratriptan	Amerge	GSK	oral tablet	2.5 mg	2.5 mg	Feb 1998
rizatriptan	Maxalt	Merck	oral tablet	5 mg	5 mg	Jun 1998
rizatriptan	Maxalt	Merck	oral tablet	10 mg	10 mg	Jun 1998
rizatriptan	Maxalt-MLT	Merck	ODT	5 mg		Jun 1998
rizatriptan	Maxalt-MLT	Merck	ODT	10 mg		Jun 1998
sumatriptan	Imitrex	GSK	SC injection	6 mg	6 mg	Dec 1992
sumatriptan	Imitrex	GSK	intranasal	5 mg		Aug 1997
sumatriptan	Imitrex	GSK	intranasal	20 mg		Aug 1997
sumatriptan	Imitrex	GSK	oral tablet	25 mg	25 mg	Jun 1995
sumatriptan	Imitrex	GSK	oral tablet	50 mg	50 mg	Jun 1995
sumatriptan	Imitrex	GSK	oral tablet	100 mg	100 mg	Oct 2000
zolmitriptan	Zomig	MedPointe	oral tablet	2.5 mg	2.5 mg	Nov 1997
zolmitriptan	Zomig	MedPointe	oral tablet	5 mg	5 mg	Nov 1997
zolmitriptan	Zomig-ZMT	MedPointe	ODT	2.5 mg		Feb 2001
zolmitriptan	Zomig-ZMT	MedPointe	ODT	5 mg		Feb 2001
zolmitriptan	Zomig	MedPointe	intranasal	5 mg		Sept 2003

GSK = GlaxoSmithKline; ODT = orally disintegrating tablet; SC = subcutaneous

NA* = eletriptan 80 mg not available in the US

1. Oral triptans are primarily considered:
    a. All triptans are available in this dose form.
    b. Most commonly prescribed product in patients without severe nausea and vomiting.
2. Nasal and subcutaneous triptans are unique dosage forms useful for patients with migraine-induced severe nausea and vomiting.
3. Oral dissolutions (ODTs) are not primarily considered:
    a. Not unique.
    b. No randomized double blind head-to-head trial comparing efficacy of oral dissolutions to other triptan dose forms.
    c. Drug delivery not well characterized compared to oral preparations.
4. Eletriptan was FDA approved on 12/20/02.
5. Although frovotriptan is available in the US, little peer-reviewed published literature is identified. Evidence currently available is insufficient for it to be considered in this report.

Critical Policy:

- *Senate Bill 819:*
    - "The Department of Human Services shall adopt a Practitioner-Managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

- *Health Resources Commission:*
    - "Clinical outcomes the most important indicator of comparative effectiveness;
    - "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Inclusion criteria

1. Populations:

Adult patients with migraine

Definition of Migraine[2]

- Five or more episodes of moderate to severe headache with or without aura, each headache lasting 4 to 72 hours.
- Headache prohibits daily activity and is aggravated by routine physical activity.
- Headache has various combinations of the following characteristics:
    - Unilateral pulsing pain
    - Nausea and/or vomiting

[2] *International Headache Society Criteria for Headache and Facial Pain*

    - Photo or phonophobia
- History, physical and neurological examination does not suggest organic disorders.
- Other types of headache are excluded, e.g. tension headache, cluster headache

Disorders

2. Interventions

- A triptan compared with another triptan
- A triptan compared with placebo.
    - Explicitly stated timing of the intervention
        - As soon as symptoms begin
        - Waiting until headache becomes moderate to severe

3. Outcomes

- Reduction or resolution of symptoms (pain, nausea, vomiting, phonophobia, photophobia)
- Reduction of duration of symptoms
- Duration of improvement
- Consistency of effectiveness (proportion of headaches successfully treated per patient)
- Functional outcome (e.g. change in days of work lost)
- Quality of life
- Adverse effect (including drug interactions).

4. Outcome Measures

- Response
- Time to response
- Sustained response
- Pain free
- Sustained pain free
- Significant response
- Rescue (use of rescue medications)
- Relapse (reappearance of any degree of symptoms within 48 hours) after response or becoming pain free
- Time to relief
- Relief of associated symptoms

5. Safety and Adverse Effects:

- The study is a controlled clinical trial or observational study.
- Drug-drug interaction studies will be included.
- Withdrawals
- Withdrawals due to adverse effects
- Withdrawals due to specific adverse effects, eg. chest tightness.

6. **Exclusion Criteria**

- No original data: Study does not contain original data (e.g. non-systematic review, editorial, letter with no original data).
- Good quality systematic reviews will be used as appropriate to inform the current review.
- Studies of multiple migraine drugs, such as a triptan plus an analgesic as *initial* therapy (not medications used for rescue).

7. Weighing the Evidence:

In weighing the evidence, the subcommittee utilized the EPC's ratings of good, fair or poor for the validity of studies. We took into account the number of studies and the total number of patients in each study. Statistical significance was an important consideration and trending data was looked at secondarily.

Key Questions

1. What are the comparative effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?

2. What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different triptans in adult patients being treated for migraine?

3. Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?

New Findings:

1. Using the same search strategy as was used in the original Triptan report, the EPC found 60 new publications (43 new trials) that met eligibility criteria for the triptans review (6 head-to-head, 9 active-controlled, 39 placebo-controlled, and 6 observational studies were added.
2. As of January 2004 sumatriptan has been reformulated as a fast disintegrating rapid-release tablet. Significantly more patients taking reformulated sumatriptan were completely free of pain at 2 hours that those taking placebo,[3] suggesting that reformulated sumatriptan is likely at least equivalent to conventional oral sumatriptan.

[3] Sheftell FD. Two Replicate Randomized, Double-Blind, Placebo-Controlled Trials of the Time to Onset of Pain Relief in the Acute Treatment of Migraine with a Fast-Disintegrating/Rapid-Release Formulation of Sumatriptan Tablets. *Clin Ther* 2005;27(4):407-417.

Amended Summary of Results

Key Question 1. **What are the comparative effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms, improving functional outcomes, and improving quality of life in adult patients with migraine?**

Comparing Evidence from Head-to-Head Trials

The subcommittee agreed that although there is a large volume of placebo-controlled trials including systematic reviews of triptans, head-to head trials are a higher level of evidence when considering the comparative effectiveness of these drugs. Seventeen fair to good head-to-head studies were thus compared, although only 9 of these compared recommended doses. The majority of the head-to-head trials involved an oral sumatriptan comparator. The placebo-controlled trials supported the results from the head-to-head studies.

Encapsulation

In 5 double-blind head-to-head trials [4,5,6,7,8] sumatriptan or another comparator were put in a gelatin capsule to ensure that patients didn't know what medication they received, as it is difficult to find triptan naïve patients to conduct these studies. Because the data about the effects of encapsulation on pharmacokinetics was conflicting, the OHSU EPC conducted a metanalysis to examine how encapsulation affected the results of head-to-head trials. For all triptans encapsulation was consistently associated with decreased efficacy; except paradoxically, the efficacy of eletriptan was increased.[9]

Fast-disintegrating/rapid-release Sumatriptan

The new fast-disintegrating/rapid-release formulation of sumatriptan has only been studied in placebo-controlled trials of patients that were evaluated regardless

[4] Goadsby PJ, Ferrari MD, Olesen J, et al. Eletriptan in acute migraine: A double-blind, placebo-controlled comparison to sumatriptan. *Neurology.* 2000;54(1):156-163.
[5] Mathew NT, Schoenen J, Winner P, et al. Comparative efficacy of eletriptan 40 mg versus sumatriptan 100 mg. *Headache,* 2003;43(3):214-222.
[6] Sandrini G, Farkkila M, Burgess G, Forster E, Haughie S, Sterring C., Eletriptan vs. sumatriptan:a double-blind, placebo-controlled, multiple migraine attack study. *Neurology.*2002;59(8):1210-1217
[7] Steiner TJ, Diener HC, MacGregor EA, Schoenen J, et al. Comparative efficacy of eletriptan and zolmitriptan in the acute treatment of migraine. *Cephalalgia.* 2003:23(10):942-952
[8] Garcia-Ramos G, MacGregor EA, Hilliard B, et al. Comparative efficacy of eletriptan vs. naratriptan *Cephalalgia*. 2003;23(9):869-876.
[9] Helfand M, Peterson K Drug Class Review on Triptans, Updated Final Report #2, September 2004, p14

of their previous experience with triptans.[10, 11] Significantly more patients taking reformulated sumatriptan experienced pain relief at a more rapid rate than those taking placebo. These findings suggest that reformulated sumatriptan is likely at least equivalent to conventional sumatriptan and other similar triptans.

Nasal dosage forms

Sumatriptan and zolmitriptan are available in nasal dosage forms in the US and Canada. Nasal sumatriptan has not been directly compared to any oral triptans. One good-quality trial compared nasal (0.5-5 mg) and oral (2.5 mg) forms of zolmitriptan.[12] Nasal zolmitriptan 5 mg provided superior 2-hour pain relief when directly compared to oral zolmitriptan 2.5 mg. Head-to-head trials have not compared nasal and oral 5 mg zolmitriptan.

Improving Quality of Future Head-to-head Trials

The Triptan Update Committee discussed the need for improving the quality of future head-to-head trials. First, studies should compare currently recommended doses and compare the newer to the traditional delivery forms. Second, rather than defining a single primary endpoint and selectively reporting others, studies should pre-specify a range of endpoints that encompass several aspects of single-attack efficacy at 1-hour, 2-hours, and 24 hours as well as long term studies for quality of life. Third, more comparisons among triptans, other than sumatriptan as the comparator, is needed. Fourth, better evidence concerning the efficacy of triptans for early and mild migraine would improve the applicability of research to everyday practice.

Treatment Priorities of Patients with Migraine[13]

International Headache Society guidelines for migraine clinical trials recommend assessment of pain relief at 2 hours as a primary end point. Patients, however, express a clear preference for more rapid pain relief, with most patients defining rapid relief as occurring within 30 minutes after drug administration. Although rapidity is key, the most common measure reported in clinical trials is two-hour pain relief, with limited one-hour data available.

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[10] Carpay J, Schoenen J, Ahmad F, et al. Efficacy and tolerability of sumatriptan tablets in a fast-disintegrating, rapid-release formulation for the acute treatment of migraine: results of a multicenter, randomized, placebo-controlled study. *Clin Ther.* 2004;26(2)"214-223.

[11] Sheftell FD, Two Replicate Randomized, Double-Blind, Placebo-Controlled Trials of the Time to Onset of Pain Relief in the acute Treatment of Migraine with a Fast-Disintegrating/Rapid-Release Formulation of Sumatriptan Tablets. *Clin Ther* 2005;27(4):407-417.

[12] Charlesworth BR, Dowson AJ, Purdy A, et al. Speed of onset and efficacy of zolmitriptan nasal spray in the acute treatment of migraine: a randomized, double-blind, placebo-controlled, dose-ranging study versus zolmitriptan tablet. *CNS Drugs.* 2003;17(9):653-667.

[13] Ryan RE jr. Patient treatment preferences and the 5-HT(1B/1D) agonists. *Arch Intern Med* 2001;161:2545-53

Predictable efficacy

Most of the trials report results for one to three attacks of migraine. A single experience with a drug does not necessarily represent the experience of using the drug repeatedly over time.

- Data from observational studies for zolmitriptan, sumatriptan, almotriptan and naratriptan indicate that many patients get consistent relief using the same medication over time (6 months to 1 year)
- No head to head, long term controlled trials compare consistency of triptans over time and/or multiple attacks.

Triptans in Mild or Early Migraine Attacks

Triptans are approved for moderate to severe migraine headache.

- In most studies, if participants took a triptan for mild headache, it was considered a protocol violation. Evidence is insufficient to assess effectiveness in mild migraines.

Summary of the Evidence for Triptan Efficacy

Medications Compared	1 hr Pain Relief	1 hr Pain Free	Return to Normal 1 hr	2 hr Pain Relief	2 hr Pain Free	Return to Normal 2 hr	2 hr Nausea Free	2 hr Phonophobia Free	2 hr Photophobia Free	4 hr Pain Relief	24 hr Sustained Relief
Riza 10 vs. Suma 100[14]	Riza NNT[15]=12	[16]	Riza NNT=21		Riza NNT=15	Riza NNT=12	Riza NNT=13				
Riza 10 vs. Nara 2.5[17]	Riza NNT=10	Riza NNT=17		Riza NNT=6	Riza NNT=5			Riza NNT=9	Riza NNT=9		Riza NNT=9
Nara 2.5 vs. Suma100	Similar[18]			Similar						Suma NNT=7	
Zolmi 5 vs. Suma100	Similar			Similar							
Ele 40[19] **vs. Other Triptans**	At least =	At least =	At least =	At least =	At least =	At least =		At least =	At least =		At least =
Almo[20] **vs. Other Triptans**	At least =	At least =	At least =	At least =	At least =	At least =		At least =	At least =		At least =
Frova vs. Other Triptans											
Zolmi Nasal 5 vs. Oral 2.5[21]				5mg =70.3% vs 2.5mg =61.3% (p=0.0067) [14]							
Suma Nasal vs. Other Triptans											
Suma Inj. vs. Oral[22]											
Suma Disint vs. Oral[23]				At least =	At least =						

Key Question 1 Consensus

The Triptan Subcommittee agrees by consensus that:

- *In comparing the effectiveness and duration of response of oral triptans in reducing the severity and duration of symptoms in adult patients with moderate to severe migraine, almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmatriptan were similarly efficacious.*
- *Nasal sumatriptan and zolmitriptan are effective, but there are no head-to-head studies comparing them to oral forms of these drugs*
- *Injectable sumatriptan is effective, but there are no acceptable head-to-head studies comparing injectable to the oral form.*

Key Question 2. **What are the comparative incidence and nature of complications (serious or life-threatening or those that may adversely effect compliance) of different triptans in adult patients being treated for migraine?**

- No studies have had side effects as a primary endpoint, but most report them.
- There is good evidence from 17 head-to-head trials that there are no differences in chest pain/tightness and central nervous system effects for oral eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan.
- Subcutaneous sumatriptan 6 mg was associated with higher rates of mild-to-moderate chest pain than eletriptan 80 mg (a dosage form not approved in the USA) in one open trial.[24]
- For almotriptan, data from two head-to-head trials of poor quality were not analyzed in this review.
- For frovotriptan there were no published trials.
- There is limited information about the comparative duration and severity of adverse events or about their impact on quality of life.
- Most of the efficacy studies were not powered to find differences among drug adverse effects.
- Patient surveys indicate that migraineurs are willing to endure significant side effects to achieve pain relief.

Key Question 2 Consensus

The Triptan Subcommittee agrees by consensus that:

- *In comparing the incidence and nature of complications of different triptans in adult patients being treated for moderate to severe migraine, oral eletriptan, naratriptan, rizatripan, sumatriptan and zolmitriptan have similar side effect profiles.*
- *Injectable and nasal triptans have insufficient evidence to make conclusions about adverse events.*

Key Question 3. **Are there subgroups of patients based on demographics, other medications, or co-morbidities for which one medication or preparation is more effective or associated with fewer adverse effects?**

In Regard to Demographics:

- Triptans are as effective in migraine induced by menses as in other attacks
- No studies specifically compared triptans by sex or age.
- Two placebo-controlled trials of eletriptan and zolmitriptan in Japanese migraineurs reported no significant difference in pain relief, pain-free response at 2 and 24 hours, 24 hr recurrence rate, use of escape medications, relief of associated symptoms, and adverse events when compared to similar samples of predominantly white patients.[25,26]
- The high prevalence of migraine in women during their reproductive years means that triptans are likely to be widely used by women of childbearing potential. All triptans studied are Category C for pregnancy and should be used only if other measures are not effective. The risks for adverse pregnancy outcomes do not appear to be increased, but the number of patients followed in one study of sumatriptan is too underpowered for significance.[27]

In Regard to Medication Interactions:

- Compatibility with prophylactic beta-blockers:
  Propranolol increases plasma concentrations of rizatriptan by 70%; a dose of rizatriptan 5 mg is recommended in patients on propranolol prophylaxis. Administration of rizatriptan with other beta blockers does not require consideration of a dose adjustment. Other triptans do not require a dose adjustment.

Table 3
Triptan Pharmacokinetic Parameters

Triptan	Increase in Cmax by propranolol	Increase in AUC by propranolol	Dosage adjustment Recommended
rizatriptan	75%	67%	Yes (5 mg)
zolmitriptan	56%	37%	No
sumatriptan	---	---	No
almotriptan	---	---	No

- All seven oral triptans are contraindicated within 24 hours of administration of ergotamine-containing or ergot-type medication (e.g., methysergide, dihydroergotamine).
- Product labeling advises that since eletriptan is metabolized by CYP3A4 thus it should not be used within 72 hours with potent CYP3A4 inhibitors such as ketoconazole, nefazodone, troleandomycin, clarithromycin, ritonoavir, and nelfinavir.

In Regard to Co-morbidities:
Although there are no comparative clinical studies for triptans concerning co-morbidity, the following conditions contraindicate the use of any triptan:

- Basilar migraine
- Hemiplegic migraine
- Ischemic heart disease
  - Angina pectoris including the Prinzmetal's variant
  - Myocardial Infarction
  - Silent Myocardial Ischemia
- Cerebrovascular syndromes
  - TIA, CVA
- Uncontrolled hypertension
- Prinzmetal's angina
- Peripheral vascular disease
  - Ischemic bowel disease

Key Question 3 Consensus

The Triptan Subcommittee agrees by consensus that:

- *Two placebo-controlled trials have demonstrated that Japanese migraineurs have similar responses as the general population to eletriptan and zolmitriptan.*
- *There is no comparative evidence to assess differences in efficacy and safety between triptans based on comorbidities.*
- *Rizatriptan dose should be lowered to 5 mg with the concomitant use of propranolol.*
- *All seven oral triptans are contraindicated within 24 hours of the use of ergotamine medications.*
- *Eletriptan should not be used within 72 hours of potent CYP3A4 inhibitors due to its metabolism by CYP3A4 enzyme system.*
- *There are clear medical contraindications to the use of triptans. Careful practitioner evaluation of prospective patients is required before prescribing.*

Concluding Remarks:

It has been noted in clinical practice, but not clearly defined in the available evidence, that there is inter- and intra-patient variability in response to triptan therapy. Therefore, it is reasonable to have alternative triptans (both formulations and alternative medications) available for clinicians to prescribe if an initial regimen is unsuccessful. When a regimen is successful, no attempt should be made to switch therapy.

CONCLUSION

It is the decision of the Triptan Subcommittee that:

1. *In comparing the effectiveness and duration of response of different triptans in reducing the severity and duration of symptoms in adult patients with moderate to severe migraine oral almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmatriptan were similarly efficacious.*
2. *Nasal sumatriptan and zolmitriptan are effective, but there are no head-to-head studies comparing them to oral forms of these drugs.*
3. *Injectable sumatriptan is effective, but there are no acceptable head-to-head studies comparing injectable to the oral form.*
4. *In comparing the incidence and nature of complications of oral triptans in adult patients being treated for moderate to severe migraine, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan have similar side effect profiles.*
5. *Injectable and nasal triptans have insufficient evidence to make conclusions about adverse events.*
6. *Based on clinical practice, but not clearly defined by the evidence, there is patient variability in response to triptan therapy. Therefore the triptan subcommittee strongly recommends that alternative triptans be available for clinicians to prescribe, if an initial regimen is unsuccessful. When a regimen is successful, no attempt should be made to switch therapy.*
7. *Ready availability of alternate delivery forms is necessary for patients who are unable to tolerate the oral route.*

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