

## Almotriptan Versus Sumatriptan in Migraine Treatment: Direct Medical Costs of Managing Adverse Chest Symptoms

Lisa K. Mannix, MD; James U. Adelman, MD;  
Scott D. Goldfarb, PharmD, MBA;  
Randal L. Von Seggern, PharmD, BCPS; and Chris M. Kozma, PhD

### Abstract

**Objective:** Triptans, a popular class of drugs for treatment of migraine headaches, can cause adverse events including chest symptoms. This study estimated the direct medical costs of managing chest symptoms in patients treated for acute migraine with almotriptan or sumatriptan using an economic model.

**Methods:** The economic model of this study combined data from a randomized clinical trial that compared almotriptan with sumatriptan and data from a practice pattern survey of physicians. The pertinent clinical evaluation period was the time immediately after administration of the first medication dose. The model was developed from the perspective of a managed care payer.

**Results:** The average direct medical cost of managing chest symptoms that appeared after the first dose of an oral triptan was \$0.22 for patients treated with almotriptan and \$1.64 for patients treated with sumatriptan, a difference of \$1.42 per patient.

**Conclusion:** Relative to sumatriptan, treatment with almotriptan is likely to reduce patient care costs associated with chest symptom adverse events.

(*Am J Manag Care* 2002;8:S94-S101)

Migraine, a chronic, intermittent, and debilitating condition, affects approximately 28 million Americans, 40% of whom use prescription medications to treat this condition.<sup>1,2</sup> The economic burden of migraine in the United States is substantial, exceeding \$14 billion annually for physician visits, diagnostic tests, drug therapy, and the indirect costs of missed workdays and impaired work function.<sup>3</sup>

Serotonin 5-HT<sub>1B/1D</sub> receptor agonists (triptans), which have been available for the treatment of acute migraine for more than a decade, are now considered the drugs of choice for acute episodes.<sup>4</sup> Despite the demonstrated benefits of triptans, Lipton and Stewart<sup>5</sup> found that an unmet need still exists for acute migraine treatments with both greater efficacy and an improved tolerability profile. In a survey, 71% of migraine patients reported less than complete satisfaction with their existing migraine therapy; 35% reported "too many side effects" as the reason for their dissatisfaction.<sup>5</sup>

Almotriptan, a new triptan, has undergone extensive clinical evaluation for the treatment of acute migraine.<sup>6-12</sup> Results from short- and long-term clinical trials have shown that treatment with oral almotriptan provides many benefits: rapid onset of action, effective pain relief, consistent response across multiple episodes, low recurrence rate, and a tolerability profile comparable to placebo.<sup>7-9,11,12</sup>

In a comparative study, patients with acute migraine were randomized to receive a single dose of almotriptan 12.5 mg (n = 591) or sumatriptan 50 mg (n = 582).<sup>12</sup> In both groups, 89% of the patients were women and the mean age was approximately 40 years (SD ± 10 years). Almotriptan and sumatriptan provided comparable headache pain relief within 2 hours to 58.0% and to 57.3% of the patients, respectively. Patients in the almotriptan group reported significantly fewer (P = .001) drug-related adverse events overall (9.1%) compared with those in the sumatriptan group (15.5%). Results from a patient satisfaction

questionnaire showed that patient satisfaction with pain relief was similar for the 2 treatment groups ( $P = .50$ ), but almotriptan-treated patients were significantly ( $P = .016$ ) less bothered by adverse events than sumatriptan-treated patients.<sup>13</sup>

One unusual group of adverse events related to triptan treatment is chest symptoms, which are described as tightness, heaviness, pressure, or pain.<sup>14</sup> Although the mechanism of these chest-related adverse symptoms is yet to be determined, they are not generally considered to be caused by cardiac ischemia. Possible mechanisms for triptan-related chest symptoms include pulmonary vasoconstriction, esophageal spasm, intercostal muscle spasm, bronchoconstriction or skeletal muscle mitochondrial impairment, and anxiogenic reaction from activation of 5-HT<sub>1A</sub> receptors.<sup>14</sup> These symptoms may cause some patients to seek medical attention. Healthcare providers may investigate these complaints in a variety of ways.

Across all controlled studies of almotriptan 6.25 and 12.5 mg, only 0.2% of patients reported chest symptoms,<sup>15</sup> a lower incidence than that reported for other oral triptans (Table 1).<sup>16-21</sup>

In this study we used data from a comparative trial of almotriptan and sumatriptan and data from a physician survey to compare healthcare resource use and associated costs of managing chest symptoms. Chest symptoms were selected for this analysis because the costs associated with this particular group of adverse events are measurable in the healthcare system. With the exception of those experiencing chest symptoms, most patients who experience routine adverse events, such as nausea or dizziness, from triptan therapy do not seek medical attention or incur additional healthcare costs. The objective of this study was to assess the economic value of using oral almotriptan versus oral sumatriptan with respect to reduced chest symptoms.

**Methods**

**Model Structure.** We developed a decision analysis model from the perspective of a managed care payer to estimate the

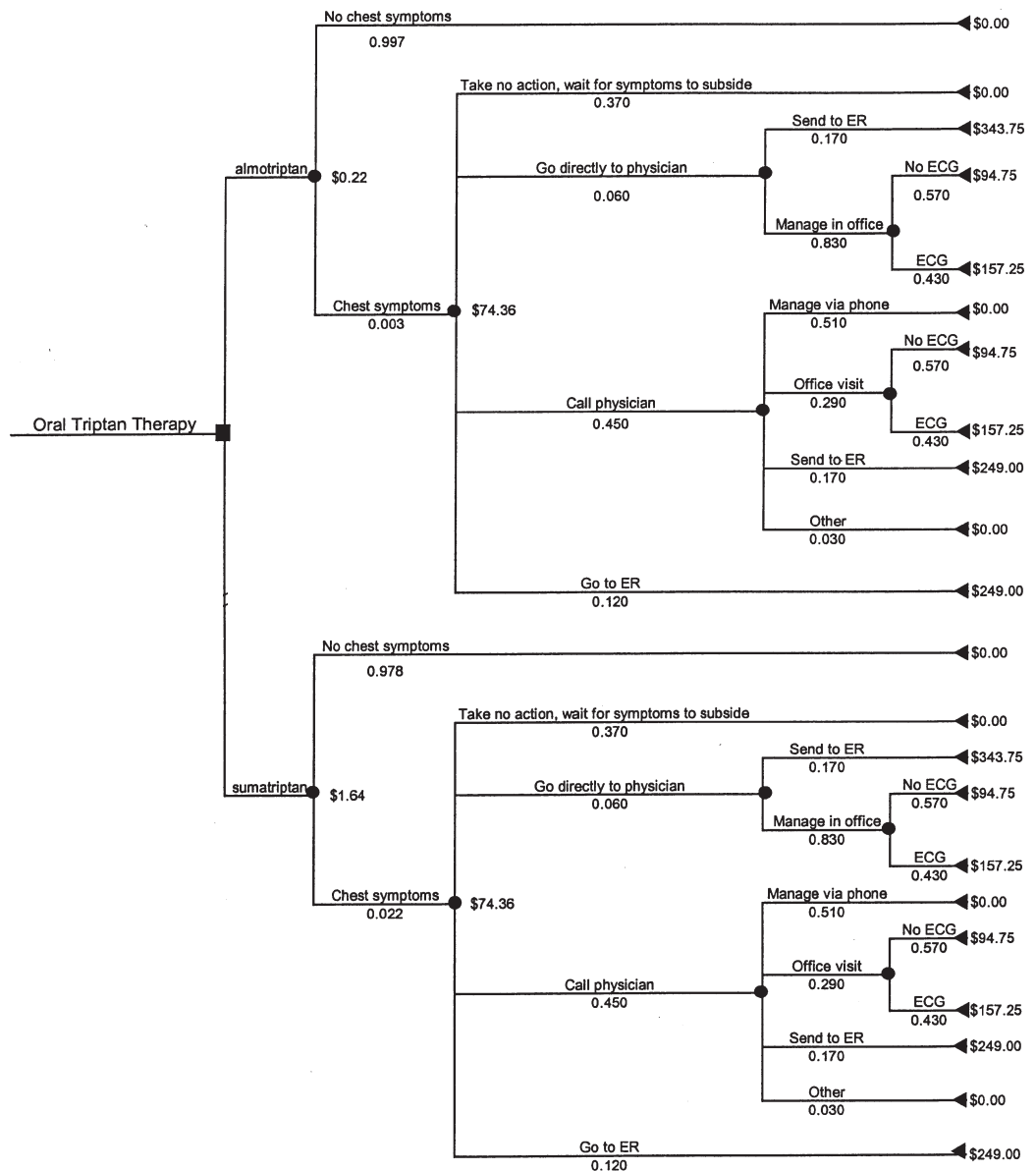
cost of managing chest symptoms in patients treated with oral almotriptan and in patients treated with oral sumatriptan (Figure 1). The clinical evaluation period was the time immediately after administration of the first medication dose. The model evaluated almotriptan and sumatriptan treatment with respect to resources used and costs incurred when patients experienced chest symptoms after initial treatment. For this trial, all chest symptoms were reported as chest pain. Patients who sought medical care for their chest symptoms either visited emergency departments or consulted their physicians

**Table 1.** Incidence of Pain and Pressure Sensation Adverse Events Associated With Oral Triptans (With the Subset of Chest Symptoms Only Listed)\*

	Percent			
	Placebo (n = 386)	6.25 mg (n = 527)	12.5 mg (n = 1313)	
<b>Almotriptan<sup>16</sup></b>				
Pain and pressure sensations	1.6	1.7	1.9	
Chest pain	0.3	0.2	0.2	
<b>Naratriptan</b>				
	Placebo (n = 498)	1 mg (n = 627)	2.5 mg (n = 627)	
Pain and pressure sensation <sup>17</sup>	2 (n = 107)	2	4 (n = 214)	
Chest pain <sup>18</sup>	0		2	
<b>Rizatriptan<sup>19</sup></b>				
	Placebo (n = 627)	5 mg (n = 977)	10 mg (n = 1167)	
Pain and other pressure sensations	3	6	9	
Chest pain/tightness/pressure and/or heaviness	1	< 2	3	
<b>Sumatriptan<sup>20</sup></b>				
	Placebo (n = 309)	25 mg (n = 417)	50 mg (n = 771)	100 mg (n = 437)
Pain and other pressure sensations	4	6	6	8
Chest pain/tightness/pressure and/or heaviness	1	1	2	2
<b>Zolmitriptan<sup>21</sup></b>				
	Placebo (n = 401)	1 mg (n = 163)	2.5 mg (n = 498)	5 mg (n = 1012)
Pain and pressure sensations	7	13	14	22
Chest pain/tightness/pressure and/or heaviness	1	2	3	4

\*Data are from separate studies and may not necessarily be comparable. Sources: References 16-21.

**Figure 1.** Decision Analysis Model for Physician Management of Triptan-Induced Chest Symptoms



The expected cost of managing triptan-induced chest symptoms is lower when almotriptan is prescribed for migraines (\$0.22) than when sumatriptan is prescribed (\$1.64). The difference is \$1.42. ER = emergency room/department; ECG = electrocardiogram.

by telephone or in person. Patients who responded to chest symptoms by going to emergency departments were assumed to have received a thorough medical evaluation to rule out cardiac pathology, such as a myocardial infarction. No costs were

attributed to chest symptoms when patients consulted their physicians by telephone. Patients who sought medical advice in their physicians' offices were assumed to have received a thorough physical examination. It was assumed

that, after the physical examination, some patients would be administered an electrocardiogram (ECG) to rule out myocardial infarction.

**Assumptions.** For the purpose of this study, adverse events other than chest symptoms were disregarded, either because they were assumed to be equivalent between treatments or because they were not associated with significant costs. The model assumed that medications were administered similarly across various populations. Drug efficacy was not included in the model, because pain relief was considered comparable between treatments.<sup>12</sup> Other assumptions used in this model were:

- Healthcare resource use not associated with chest symptoms was equivalent between groups.
- Physicians who managed patients for chest symptoms by telephone charged no consultation fees.
- The proportion of patients administered an ECG before being prescribed an oral triptan was equivalent for both groups.
- Physicians' reported recollections of their own practice patterns and their patients' behaviors were accurate.

**Probabilities.** The probability that chest symptoms would occur was estimated from the results of a randomized clinical trial comparing almotriptan 12.5 mg and sumatriptan 50 mg.<sup>12</sup> The 50-mg dose of sumatriptan is the optimal recommended dose.<sup>22</sup> Chest pain was reported by 0.3% of the almotriptan patients and 2.2% of the sumatriptan patients ( $P = .004$ ).<sup>12</sup> Other probabilities used in the model, such as the percentage of patients treated in the physician's office versus those treated in the emergency department or managed by telephone, were obtained from a physician survey.

The survey was administered to about 200 primary care physicians and neurologists attending a migraine medical conference in New Orleans, Louisiana in October 2000. Experience in prescribing

**Table 2.** Survey Questions

- What best describes your practice?
- How many years have you been practicing?
- In what city and state have you been practicing?
- What percentage of your patients are in managed care, private pay, Medicare, or other?
- What percentage of the total patients in your practice do you treat for migraine?
- What percentage of your migraine patients taking oral triptans experience chest symptoms?
- When do you discuss the possibility of chest symptoms following the use of oral triptans?
- What percentage of the time do you administer an ECG before prescribing the first dose of an oral triptan?
- What percentage of your migraine patients receive their first dose of an oral triptan while in your office?
- For migraine patients taking their first dose in your office, do you ask them to wait in the office a minimum length of time so that you can monitor for chest symptoms?
- What percentage of the time would you administer an ECG to migraine patients experiencing chest symptoms after taking the first dose of an oral triptan while in your office?
- What percentage of your migraine patients who develop chest symptoms following an oral triptan dose telephone your office, visit your office, go to the emergency department, or take no action?
- If migraine patients who experience chest symptoms after taking their first dose of an oral triptan subsequently contact your office, what percentage would you or a member of your staff manage the situation via the telephone, request that they come to the office, send to the emergency department, or other?
- What percentage of the time would you administer an ECG in your office to migraine patients who experience chest symptoms after their first dose of oral triptan at home?

ECG = electrocardiogram.

triptans was a criterion for invitation. The survey was administered at the beginning of the conference, before any educational sessions. It collected information on physician practice patterns and asked physicians to estimate the actions of their migraine patients who developed chest symptoms after an oral triptan dose (**Table 2**). Physicians were asked to estimate what percentage of their patients were managed by telephone and what percentage were advised to come to the office or go to the emergency department. Physicians also estimated how often they administered an ECG to those patients who visited their

offices because of chest symptoms after oral triptan therapy.

**Cost Information.** Cost information for ECGs and physician and emergency department visits was obtained from the 2000 *Physician Fee and Coding Guide*, which reports national averages.<sup>23</sup> The aim of the study was to estimate the added cost of treating chest symptom adverse events; therefore, medication costs were not included in the calculations.

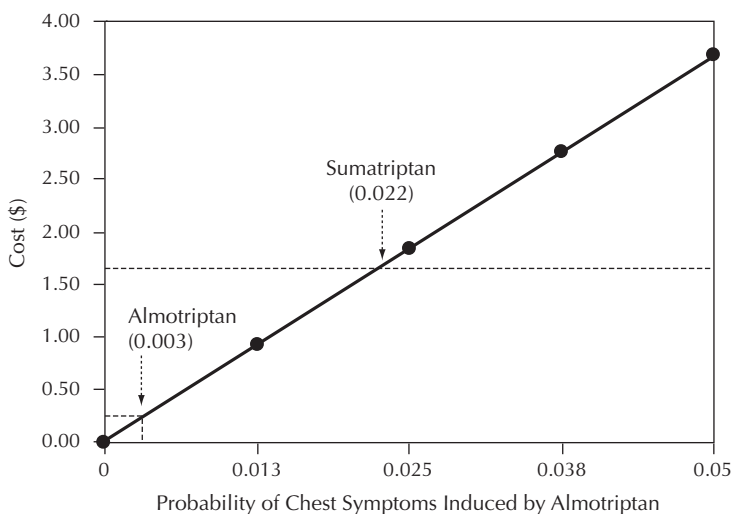
**Analysis.** Treatment alternatives were modeled using TreeAge DATA software (version 3.5, TreeAge Software, Inc., Williamstown, Massachusetts). The additional cost of managing chest symptoms was calculated for each arm of the model. To represent practice pattern variations, survey data were further analyzed by physician specialty. The outcomes and costs were modeled in the subgroup of patients treated by specialists to account for differences in treatment patterns and patient-management decisions.

The robustness of the decision analytic model was determined by one-way sensitivity analysis; the incidence of chest symptoms was varied (**Figure 2**). All other values were equivalent in both treatment groups, including the percentage of migraine patients whose chest symptoms were managed by telephone or in their physicians' offices; the proportion of patients administered ECGs in the physicians' offices; and the cost of ECGs, physician visits, and emergency department visits. Hence these factors were not included in the sensitivity analysis.

**Results**

**Survey Results.** A total of 176 surveys were returned in analyzable form. Approximately 38% of responders were family practice physicians, 32% were neurologists, and 18% were internists. Physicians reported that 45% of their patients had insurance coverage through a managed care plan, 25% were covered under Medicare or Medicaid programs, 23% were private payers, and 7% had other health insurance coverage. The responding physicians indicated that 31% of their patients had migraine attacks. The physicians estimated that 9% of these migraine patients experienced chest symptoms after their first dose of an oral triptan. Eighty-eight percent of physicians reported that they discussed the possibility of chest symptoms with patients at the time an oral triptan was prescribed. Also 16% of patients were administered an ECG before receiving the first dose of an oral triptan. **Table 3** shows physicians' estimates of the proportion of patients with chest symptoms after the initial oral triptan dose who called the office, visited the office without calling, went to the emergency department to seek care, or simply waited for symptoms to subside. **Table 3** also shows estimates on how telephone calls to physician offices were managed.

**Figure 2.** Sensitivity Analysis: A Hypothetical Increase in Probability of Chest Symptoms Induced by Almotriptan to Determine Robustness of Model



The break-even or threshold value occurs when the probability of chest symptoms on almotriptan increases to 0.022 (ie, equal to the probability of chest symptoms on sumatriptan). At this point, the cost of treating chest symptom adverse events is \$1.64 for both sumatriptan and almotriptan.

**Cost of Managing Chest Symptoms.**

The estimated direct medical cost of managing chest symptoms that occurred after the first dose of an oral triptan was \$0.22 per patient in the almotriptan-treated

group and \$1.64 per patient in the sumatriptan-treated group (Table 4; Figure 1).<sup>12</sup> The difference was \$1.42 per patient. A subgroup analysis showed that the cost of caring for chest symptoms was higher when patients were treated by general practitioners than when they were treated by specialists (Table 4).

**Sensitivity Analysis.** A one-way sensitivity analysis showed that the model was, in general, robust (Figure 2). Varying the probability that chest symptoms would occur after almotriptan administration demonstrated that the incidence of these adverse events would have to increase by a factor of 7 (from 0.003 to 0.022) for the cost of managing them to become equivalent for these drug treatment alternatives.

## Discussion

This decision model compared the direct costs of managing chest symptoms in patients whose acute migraines were treated with almotriptan versus patients treated with sumatriptan. Results indicated that the total healthcare costs associated with the use of triptans go beyond the acquisition costs of the drugs. The comparison of almotriptan and sumatriptan found that patients treated with sumatriptan, on average, cost the healthcare system \$1.42 more per patient for additional management of chest symptoms after the first dose. More than 9 million migraine patients were treated with sumatriptan through December 1998 in postmarketing clinical practice.<sup>24</sup> More than \$12.7 million in patient assessment costs could have been avoided had almotriptan been used instead. Also, subgroup analyses showed that chest symptom costs were higher when patients were treated by general practitioners than when they were treated by specialists, possibly because the specialists had more experience in using triptans.

This model was based solely on the healthcare costs attributable to chest symptoms, because these costs are readily measurable. Other adverse events from triptan therapy for acute migraine, such as nausea, paresthesia, and dizziness, rarely

**Table 3.** Practice Patterns Associated With Triptan-Induced Chest Symptoms\*

	General Practitioners <sup>†</sup> (%)	Specialists <sup>‡</sup> (%)	All Physicians (%)
<b>Patient patterns</b>			
Call physician	46	40	45
Go to physician's office directly	8	3	6
Go to ED directly	14	10	12
Take no action (wait for symptoms to subside)	32	47	37
<b>Physician patterns</b> (when patients contact their offices)			
Manage by telephone	42	65	51
Request office visit	43	10	29
Send to ED	14	20	17
Other care	1	5	3
Order electrocardiogram	57	25	43

\*Averages are from the practice patterns survey.

<sup>†</sup>General practitioners include family practice physicians and internists.

<sup>‡</sup>Specialists include neurologists, neurosurgeons, and headache and pain specialists. ED = emergency department.

cause patients to seek medical attention and therefore do not result in additional healthcare costs. Drug acquisition costs are not relevant in this model, because the costs associated with chest symptoms occur independently of acquisition costs.

Triptans have become a standard therapy for the treatment of acute migraine attacks because of their established profile of efficacy, tolerability, and safety.<sup>4</sup> Although their overall tolerability profile is acceptable, chest symptoms occur with each of the triptans and may require evaluation to rule out a cardiovascular etiology. Differences in the incidence of chest symptoms with triptans may be related to differences in their pharmacologic mechanisms.<sup>25</sup> In preclinical and clinical studies, almotriptan has been found to have little effect on peripheral arterial systems or the cardiovascular system.<sup>26-28</sup> In particular, almotriptan has minimal in vitro effect on pulmonary arteries.<sup>29</sup> This may explain its low incidence of chest symptom adverse events. And a lower incidence of chest symptoms leads to lower direct costs associated with managing them.

The physicians surveyed in the New Orleans migraine conference estimated

**Table 4.** Cost Analysis of Managing Triptan-Induced Chest Symptoms (by Medical Specialty)

	Incremental Cost of Treating Chest Symptoms (\$)		
	Almotriptan	Sumatriptan	Difference
General practitioners*	0.27	1.97	1.70
Specialists†	0.16	1.19	1.03
All physicians	0.22	1.64	1.42

\*General practitioners include family practice physicians and internists.

†Specialists include neurologists, neurosurgeons, and headache and pain specialists.

that 9% of their migraine patients experienced chest symptoms after their first dose of an oral triptan. This is consistent with other postmarketing epidemiologic data, which suggest that triptan-induced chest symptoms occur more frequently in clinical practice than in controlled clinical trials.<sup>30,31</sup> A postmarketing survey of 735 migraine patients at an outpatient university clinic revealed that of the patients who had used at least 1 dose of oral sumatriptan, 42% had experienced at least 1 episode of chest symptoms.<sup>31</sup> Of the patients who had used oral sumatriptan in at least 5 attacks, 24% experienced chest symptoms in almost all attacks. Of the patients who had used oral sumatriptan in at least 10 attacks, 30% reported that they had chest symptoms every time. Twenty percent of the patients with chest symptoms discontinued oral sumatriptan because of those adverse events.

The economic decision model has some limitations. Probabilities were based on data provided from a clinical trial and a survey of physician practice patterns. A prospective economic analysis of data collected from actual patients in clinical practice might produce a different result. The results of the current model may not apply to triptan-naive patients or to those patients with a contraindication for or hypersensitivity to triptans; all such patients were excluded from the clinical trial used here. Further, costs were derived from the *Physician Fee and Coding Guide* and may not be representa-

tive of costs at diverse practice sites. Also, because the analysis were done from a third-party payer's perspective, the costs of telephone consultation by the physicians' practices were not included. The costs associated with patients' reactions to subsequent doses after the first triptan dose were not evaluated, nor were the costs associated with physicians' decisions to change drug therapy after reports of chest pain. The model also ignores indirect costs, such as losses in work time and work productivity, which could be affected by medication continuation rates, a factor that may be influenced by chest symptoms. Another nuance is that the physicians surveyed were paid in various ways. It is possible that patient care patterns could differ by payer system.<sup>32</sup> Nevertheless, we believe that the diversity of payer types reported in the survey makes the model findings applicable to commercial managed care, government plans, and self-pay patients.

In summary, the results of this model suggest that managing chest symptoms measurably increases the direct medical costs of treating acute migraines. Treatment with almotriptan is less likely to cause chest symptoms that necessitate clinical evaluation than treatment with sumatriptan. Therefore, the use of almotriptan may reduce the direct costs of treating migraines. In addition, almotriptan's excellent tolerability profile may positively influence patient medication compliance and treatment satisfaction.

**Acknowledgments**

The authors thank Steven P. Burch, PhD, Medha R. Sasane, MS, Kevin W. Mayo, PhD, and Maureen Doyle Scharff, BA, for their contributions to this manuscript.

... REFERENCES ...

1. Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF. Migraine diagnosis and treatment: Results from the American Migraine Study II. *Headache* 2001;41:638-645.
2. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache* 2001;41:646-657.

3. **Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML.** Burden of migraine in the United States: Disability and economic costs. *Arch Intern Med* 1999;159:813-818.
4. **Silberstein SD.** Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754-762.
5. **Lipton RB, Stewart WF.** Acute migraine therapy: Do doctors understand what patients with migraine want from therapy? *Headache* 1999;39(suppl 2):S20-S26.
6. **Cabarrocas X.** Efficacy data on oral almotriptan, a novel 5HT<sub>1D</sub> agonist. *Cephalalgia* 1997;17:421.
7. **Dowson A.** Almotriptan is an effective and well-tolerated treatment for migraine pain: Results of a randomized, double-blind, placebo-controlled clinical trial. *Cephalalgia* 2002. In press.
8. **Pascual J, Falk R, Docekal R, et al.** Tolerability and efficacy of almotriptan in the long-term treatment of migraine. *Eur Neurol* 2001;45:206-213.
9. **Dahlöf C, Tfelt-Hansen P, Massiou H, Fazekas A, for the Almotriptan Study Group.** Dose finding, placebo-controlled study of oral almotriptan in the acute treatment of migraine. *Neurology* 2001;57:1811-1817.
10. **Mathew N.** A long-term open-label study of oral almotriptan 12.5 mg for the treatment of acute migraine attacks. *Headache* 2002. In press.
11. **Pascual J, Falk RM, Piessens F, et al.** Consistent efficacy and tolerability of almotriptan in the acute treatment of multiple migraine attacks: Results of a large, randomized, double-blind, placebo-controlled study. *Cephalalgia* 2000;20:588-596.
12. **Spierings EL, Gomez-Mancilla B, Grosz DE, Rowland CR, Whaley FS, Jirgens KJ.** Oral almotriptan versus oral sumatriptan in the abortive treatment of migraine: A double-blind, randomized, parallel-group, optimum-dose comparison. *Arch Neurol* 2001;58:944-950.
13. **Colman S, Brod M, Krishnamurthy A, et al.** Treatment satisfaction, functional status and health related quality of life of patients with migraine randomly assigned to almotriptan or sumatriptan. *Clin Ther* 2001;23:127-143.
14. **Dahlöf CG, Mathew N.** Cardiovascular safety of 5HT<sub>1B/1D</sub> agonists—is there a cause for concern? *Cephalalgia* 1998;18:539-545.
15. **Dodick DW.** Oral almotriptan in the treatment of migraine: Safety and tolerability. *Headache* 2001;41:449-455.
16. **US Food and Drug Administration.** *New Drug Approval—Almotriptan*. Bethesda, MD: Center for Drug Evaluation and Research; 2001. 21-001.
17. **Amerge [package insert].** Glaxo Wellcome; 1999.
18. **Bomhof M, Paz J, Legg N, Allen C, Vandormael K, Patel K.** Comparison of rizatriptan 10 mg versus naratriptan 2.5 mg in migraine. *Eur Neurol* 1999;42:173-179.
19. **Maxalt [package insert].** Merck; 2000.
20. **Imitrex [package insert].** Glaxo Wellcome; 2001.
21. **Zomig [package insert].** AstraZeneca; 2001.
22. **Pfaffenrath V, Cunin G, Sjonell G, Prendergast S.** Efficacy and safety of sumatriptan tablets (25 mg, 50 mg, and 100 mg) in the acute treatment of migraine: Defining the optimum doses of oral sumatriptan. *Headache* 1998;38:184-190.
23. **Physician Fee and Coding Guide.** Augusta, GA: Health Care Consultants of America; 2000.
24. **Welch KMA, Mathew NT, Stone P, Rosamond W, Saiers J, Guttermann D.** Tolerability of sumatriptan: Clinical trials and post-marketing experience. *Cephalalgia* 2000;20:687-695.
25. **Tfelt-Hansen P, De Vries P, Saxena PR.** Triptans in migraine: A comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs* 2000;60:1259-1287.
26. **Cabarrocas X, Robert M, Warrington S, Zayas JM, Ferrer P.** Cardiovascular safety of almotriptan in healthy volunteers. *Headache* 1999;39:346.
27. **Boyce M, Dunn K, Warrington S.** Hemodynamic and electrocardiographic effects of almotriptan in healthy volunteers. *J Cardiovasc Pharmacol* 2001;37:280-289.
28. **Gras J, Cardelus I, Llenas J, Palacios JM.** Cardiovascular safety profile of almotriptan, a new indolic derivative for the treatment of migraine. *Eur J Pharmacol* 2000;410:53-59.
29. **Gras J, Llupia J, Llenas J, Palacios JM.** Safety profile of almotriptan, a new antimigraine agent, on central nervous system, renal function, and respiratory dynamics. *Arzneimittelforschung* 2001;51:726-732.
30. **Dahlöf CG, Saiers J.** Sumatriptan injection and tablets in clinical practice: Results of a survey of 707 migraineurs. *Headache* 1998;38:756-763.
31. **Visser WH, Jaspers NM, de Vriend RH, Ferrari MD.** Chest symptoms after sumatriptan: A two-year clinical practice review in 735 consecutive migraine patients. *Cephalalgia* 1996;16:554-559.
32. **Erickson LC, Torchiana DF, Schneider EC, Newburger JW, Hannan EL.** The relationship between managed care insurance and use of lower-mortality hospitals for CABG surgery. *JAMA* 2000;283:1976-1982.