Meta-analysis of Oral Triptan Therapy for Migraine: Number Needed to Treat and Relative Cost to Achieve Relief Within 2 Hours

JAMES U. ADELMAN, MD, and JONATHAN BELSEY, MBBS

ABSTRACT

OBJECTIVE: To determine the cost-effectiveness of the 5-HT_{1B/1D} agonists, or triptans, in the acute treatment of migraine.

METHODS: To determine the cost-effectiveness of the triptans, a meta-analysis was conducted of the efficacy data from 27 oral triptan trials, using the endpoint of "pain-free" status within 2 hours after initial dosing as the indicator of efficacy. Efficacy data were used to determine the number needed to treat (NNT) to achieve pain-free status in 1 patient within 2 hours postdose and then applied the per-dose costs for each triptan to the NNT values.

RESULTS: Rizatriptan 10 mg and almotriptan 12.5 mg were the most cost-effective of the triptans, costing \$48.34 and \$48.57, respectively, to achieve pain-free status in 1 patient within 2 hours postdose. Frovatriptan 2.5 mg was the most costly, with a cost-effective ratio of \$162.49. All other triptans fell between these extremes: zolmitriptan 5 mg (\$65.18), sumatriptan 100 mg (\$70.83), sumatriptan 50 mg (\$75.67), zolmitriptan 2.5 mg (\$78.74), and naratriptan 2.5 mg (\$141.43), in decreasing order of cost-effectiveness.

CONCLUSION: Using an NNT analysis, the least-costly drugs to achieve migraine cure within 2 hours are rizatriptan 10 mg and almotriptan 12.5 mg. From a population health perspective, the lower acquisition cost of almotriptan 12.5 mg allows for effective treatment of more patients than rizatriptan 10 mg for no additional medication cost.

KEYWORDS: Cost-effectiveness, Efficacy, 5-HT_{1B/1D} agonist, Triptan, Migraine

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Migraine is a common condition in the United States, affecting approximately 18% of women and nearly 7% of men.¹ This chronic, episodic disorder is characterized by moderate to severe, usually unilateral head pain that is typically accompanied by other symptoms, including nausea, vomiting, photophobia, and phonophobia.² Without treatment, a migraine attack can persist for several days,² significantly compromising a person's ability to work or perform everyday tasks.

Migraine not only adversely affects the "migraineur's" quality of life but also, when an attack strikes, affects his or her ability to function in society. Because of the severity of the pain and the accompanying symptoms, migraineurs often must retire to quiet, dark rooms until the headache resolves. Consequently, the costs of migraine are measured not only in terms of direct medical costs but also in terms of indirect costs from missed work days or reduced productivity while on the job.

Direct costs for treating migraine include prescription drug costs and physician, hospital, and emergency room services.³ In 1999, Hu et al. estimated the direct medical costs of migraine at \$1 billion per year, with about \$100 spent per diagnosed patient.³ Physician office visits accounted for about 60% of these costs, and prescription drugs for about 30%. Emergency room visits accounted for less than 1% of the total direct costs.³ The indirect costs of migraine include lost work days, losses related to reduced productivity, lost productivity of caregivers attending to them, and families made dysfunctional by a member disabled by migraine. In his 1998 review of the economic burden of migraine to society, Ferrari, citing data from the American Migraine Study, noted that 50% of female and 30% of male migraineurs missed 3 or more days of work per year because of migraine, and 31% of female and 17% of male migraineurs missed 6 or more days per year.⁴ Even when migraineurs are able to remain at work during a migraine attack, they are much less productive when experiencing migraine symptoms.⁵ Published estimates of the indirect costs of migraine vary widely, but they lie somewhere between \$1.4 billion and \$17.2 billion per year.⁴

Given the social and economic impact of migraine, effective treatment of this disorder can have a profound effect. Until the early 1990s, migraineurs relied primarily on over-the-counter analgesics such as aspirin or nonsteroidal anti-inflammatory drugs to relieve their headache. Those who consulted a physician for migraine might have been prescribed stronger pain relievers or preparations containing ergotamine. Although ergotamine and its analog, dihydroergotamine, are

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TABLE 1 Comparison Profile of Oral Triptans

	Sumatriptan	Zolmitriptan	Naratriptan	Rizatriptan	Almotriptan	Frovatriptan
Brand name	Imitrex	Zomig	Amerge	Maxalt	Axert	Frova
Source	GlaxoSmithKline (formerly GlaxoWellcome)	AstraZeneca (formerly Zeneca Pharmaceutical)	GlaxoSmithKline (formerly GlaxoWellcome)	Merck & Co., Inc.	Almirall Prodespharma Pharmacia Corporation	Vernalis plc Elan Corporation UCB Pharma
T_{max} (time to peak plasma concentration)	2.5 hrs. (acute pain period); 2.0 hrs. (nonpain period)	2.5 hrs. (acute pain period); 2 hrs. (non-pain period); 2 to 3 hrs. overall	3 to 4 hrs. (acute pain period); 2 to 3 hrs. (nonpain period)	1.0 to 1.5 hrs. (standard tablets); 1.6 to 2.5 hrs. (orally disintegrating tablets); not affected by pain status	1 to 3 hrs.	2 to 4 hrs.; increased by 1 hr. in the presence of food
Mean	2.5 hrs.; MAO-A	3 hrs.; active N-	6 hrs.; moderate	2 to 3 hrs. (plasma half-life)	3 to 4 hrs. (plasma)	26 hrs.
Elimination half-life (drug and active metabolites)	Inhibitors cause unpredictable increases in oral sumatriptan bioavailability, increasing elimination half-life by 40%	Desmethyl metabolite has two-thirds potency of parent compound and contributes to half-life	Renal impairment increases elimination half-life to 11 hrs.; moderate hepatic impairment increases elimination half-life to 8 to 16 hrs.		Clearance 40% reduced in moderate renal impairment and 60% reduced in severe renal impairment	Unaffected by impaired renal or hepatic function
Dosage	25 mg, 50 mg, or 100 mg every 2 hrs. as needed; maximum dose not to exceed 200 mg in 24 hrs.	2.5 mg to 5 mg every 2 hrs. as needed; maximum dose not to exceed 10 mg in 24 hrs.	1 mg to 2.5 mg every 4 hrs. as needed; maximum dose not to exceed 5 mg in 24 hrs.	5 mg to 10 mg every 2 hrs. as needed; maximum dose not to exceed 30 mg in 24 hrs.	6.25 mg to 12.5 mg, repeated after 2 hrs. if necessary. Maximum dose not to exceed 25 mg in 24 hrs.	2.5 mg, repeated after 2 hrs. if necessary. Maximum dose not to exceed 7.5 mg in 24 hrs.
How supplied	Oral tablets of 25 mg, 50 mg, 100 mg	Oral tablets and orally disintegrating tablets (wafers) of 2.5 mg, 5 mg	Oral tablets of 1 mg, 2.5 mg	Oral tablets and orally disintegrating tablets (wafers) of 5 mg, 10 mg	Oral tablets of 6.25 mg, 12.5 mg	Oral tablets of 2.5 mg

Data from Amerge⁶; Drug Infoline⁷; Drug Infoline⁸; Goadsby et al.⁹; Imitrex¹⁰; Maxalt¹¹; Axert¹²; Frova¹³; Muir et al.¹⁴; Napier et al.¹⁵; Parsons et al.¹⁶; Pharmalicensing¹⁷; VanDenBrink et al.¹⁸; Zomig.¹⁹ Revised labeling information on sumatriptan from Winner et al.²⁰; Zoler.²¹

migraine-specific drugs, their use is associated with a range of adverse effects, including nausea, vomiting, and vasoconstriction of systemic and coronary arteries. The most recent advance in the acute treatment of moderate to severe migraine has been the introduction of the 5-HT_{1B/1D} agonists, a migraine-specific class of drugs known as triptans. The first triptan, sumatriptan, became available in the United States in 1993 as an injectable formulation. Later, it became available as an oral tablet and a nasal spray. Since then, 5 other triptans—zolmitriptan, naratriptan, rizatriptan, almotriptan, and frovatriptan—have been introduced, each in an oral tablet formulation; rizatriptan and zolmitriptan are also available as orally disintegrating tablets (Table 1).⁶⁻²¹ New-drug applications have been filed with the U.S. Food and Drug Administration for eletriptan.

For many patients with moderate to severe migraine, triptans effectively relieve the migraine and its associated symptoms. Although triptans cost more per dose than do other migraine drugs, for patients with disabling migraine, triptans are becoming the drugs of choice. To compare the cost-effectiveness of the

various triptans, we conducted a meta-analysis of efficacy data from oral triptan studies. We then extrapolated these data to determine the true cost-effectiveness of each triptan. Our goal was to generate data that would enable providers to make appropriate, effective prescribing decisions and assist health care insurers in making informed formulary inclusion decisions.

Methods

Randomized, double-blind, placebo-controlled trials of oral triptan treatment for migraine were identified through electronic searches of MEDLINE and EMBASE databases and a manual search of reference lists from primary or benchmark papers and review articles. The time period searched was from January 1990 through February 2002. Studies were included in the meta-analysis if they met the following criteria: (1) were a randomized, double-blind trial, with a placebo control arm; (2) had a single-dose triptan treatment, with no rescue medications or repeat doses of triptan allowed for 2 hours after initial dosing; (3) data was available from a standard 4-point assess-

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TABLE 2 Oral Triptan Efficacy Trials Comparison: Number of Patients Pain Free Within 2 Hours After Initial Dosing

	Total	Active*† Pain free (%)	Total	Placebo Pain free (%)	NNT‡	95% CI
Sumatriptan 50 mg						
Cutler et al., 1995 ²⁹	62	10 (16.1)	65	5 (7.7)		
Pfaffenrath et al., 1998 ³⁰	240	72 (30.0)	64	5 (7.8)		
Savani et al., 1999 ³¹	300	66 (22.0)	145	6 (4.1)		
Combined	602	148 (24.6)	274	16 (5.8)	5.4	4.3 – 9.4
Sumatriptan 100 mg						
Cutler et al., 1995 ²⁹	66	15 (22.7)	65	5 (7.7)		
Geraud et al., 2000 ³²	499	150 (30.1)	55	7 (12.7)		
Goadsby et al., 2000 ³³	125	29 (23.2)	139	8 (5.8)		
Myllyla et al., 1998 ³⁴	42	21 (50.0)	41	3 (7.9)		
Nappi et al., 1994 ³⁵	158	38 (24.1)	86	10 (11.6)		
Oral Sumatriptan Group, 1991 ³⁶	120	31 (25.8)	75	4 (5.3)		
Pfaffenrath et al., 1998 ³⁰	246	96 (39.0)	64	5 (7.8)		
Tfelt-Hansen et al., 1995 ³⁷	122	36 (29.5)	126	10 (7.9)		
Tfelt-Hansen et al., 1998 ³⁸	387	127 (32.8)	159	15 (9.4)		
Visser et al., 1996 ³⁹	72	16 (22.2)	85	3 (3.5)		
Combined	1,837	559 (30.4)	895	70 (7.8)	4.7	4.0 – 5.9
Rizatriptan 10 mg						
Ahrens et al., 1999 ⁴⁰	186	78 (42.2)	180	17 (9.5)		
Bomhof et al., 1999 ⁴¹	201	90 (44.8)	107	9 (8.4)		
Gijsman et al., 1997 ⁴²	145	40 (27.6)	67	2 (3.0)		
Kramer et al., 1998 ⁴³	320	142 (44.4)	82	6 (7.3)		
Pascual et al., 2000 ⁴⁴	292	126 (43.2)	146	14 (9.6)		
Teall et al., 1998 ⁴⁵	455	191 (42.0)	302	30 (9.9)		
Tfelt-Hansen et al., 1998 ³⁸	385	155 (40.3)	159	15 (9.4)		
Visser et al., 1996 ³⁹	89	23 (25.8)	85	3 (3.5)		
Combined	2,073	845 (40.8)	1,128	96 (8.5)	3.2	2.9 – 3.5
Zolmitriptan 2.5 mg						
Pascual et al., 2000 ⁴⁴	289	103 (35.6)	146	14 (9.6)		
Rapoport et al., 1997 ⁴⁶	260	70 (26.9)	121	8 (6.6)		
Solomon et al., 1997 ⁴⁷	178	39 (21.9)	92	9 (9.8)		
Combined	727	212 (29.2)	359	31 (8.6)	5.1	3.7 – 8.2
Zolmitriptan 5 mg						
Dahlof et al., 1998 ⁴⁸	179	69 (38.5)	88	1 (1.1)		
Geraud et al., 2000 ³¹	491	144 (29.3)	55	7 (12.7)		
Rapoport et al., 1997 ⁴⁶	245	81 (33.1)	121	8 (6.6)		
Visser et al., 1996 ³⁹	21	3 (14.3)	20	1 (5.0)		
Combined	936	297 (31.7)	284	17 (6.0)	4.2	2.9 – 7.5
Naratriptan 2.5 mg						
Bomhof et al., 1999 ⁴¹	213	44 (20.7)	107	9 (8.4)		
Combined	213	44 (20.7)	107	9 (8.4)	8.2	5.0 – 21.4
Almotriptan 12.5 mg						
Dahlof et al., 2001 ⁴⁹	164	62 (37.8)	80	9 (11.3)		
Dodick, 2002 (CL14) ⁵⁰	183	53 (29.0)	99	15 (15.2)		
Pascual et al., 2000 ³¹	373	144 (38.6)	176	27 (15.4)		
Combined	720	2,159 (36.0)	355	51 (14.4)	4.7	3.5 – 7.0
Frovatriptan 2.5 mg						
Rapoport et al., 2002 ²⁴	199	27 (13.6)	184	6 (3.3)		
Ryan et al., 2002 (study 1) ²³	204	29 (14.2)	104	2 (1.9)		
Ryan et al., 2002 (study 2) ²³	733	88 (12.0)	378	11 (2.9)		
Ryan et al., 2002 (study 3) ²³	475	43 (9.1)	242	5 (2.1)		
Combined	1,611	187 (11.6)	908	24 (2.6)	11.3	9.3 – 14.3

NNT = number needed to treat; CI = confidence interval.

Adapted from Belsey,²² with additional data from frovatriptan studies included (Ryan et al.²³; Rapoport et al.²⁴).

* All active treatments are significantly more effective than placebo ($P < 0.0001$ for all comparisons).

† When expressed as an NNT, rizatriptan 10 mg is found to be significantly more effective than sumatriptan 100 mg, zolmitriptan 2.5 mg ($P < 0.05$ for both), sumatriptan 50 mg, almotriptan 12.5 mg, ($P < 0.01$ for all), naratriptan 2.5 mg ($P < 0.001$), and frovatriptan 2.5 mg ($P < 0.0001$). There was no significant difference between the NNTs for rizatriptan 10 mg and zolmitriptan 5 mg.

‡ Combined data for NNT was derived using DerSimonian Laird random effects pooling mode.

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FIGURE 1 Summary of Absolute Triptan Efficacy Data

Note: Percentage of patients pain free at 2 hours. All active treatments were compared against placebo ($P < 0.0001$).

FIGURE 2 Summary of Relative Triptan Efficacy Data: Number Needed to Treat per Patient Pain Free at 2 Hours

Note: Comparisons versus rizatriptan 10 mg; sumatriptan 100 mg, zolmitriptan 2.5 mg ($P < 0.05$ for both), sumatriptan 50 mg, almotriptan 12.5 mg, ($P < 0.01$ for all), naratriptan 2.5 mg ($P < 0.001$), and frovatriptan 2.5 mg ($P < 0.0001$). There was no significant difference between the NNTs for rizatriptan 10 mg and zolmitriptan 5 mg.

ment scale, for baseline and posttreatment headache severity analysis; and (4) definitive data was available for determining the percentage of patients (in both the treatment arm and the control arm) who were "pain free" at 2 hours postdose.²² Studies were excluded from the meta-analysis for lack of relevance (not randomized, open label, endpoints solely pharmacologic, or endpoints other than pain free and pain relief used), for use of a drug not approved in the United States or use of a dose or for-

mulation not approved or available in the United States, and for protocol deficiencies.²² At the time we conducted our analysis, eletriptan had not yet been approved for use in the United States, and therefore data on this drug are not presented. Summary data relating to frovatriptan were published in April 2002^{23,24} and have been included in this analysis, although insufficient data were available to carry out a full critical appraisal of these studies.

Data from each study for each triptan were aggregated at commonly used doses. Data relating to dosages below the present recommended starting dose were excluded from the analysis. Thus sumatriptan 25 mg, naratriptan 1 mg, rizatriptan 5 mg, and almotriptan 6.25 mg were not included in the meta-analysis. Aggregate efficacy rates were calculated for the percentage of patients who were pain free within 2 hours after initial dosing, from which the number needed to treat (NNT) was calculated (Table 2).²² The NNT is the number of patients that must be treated to obtain one positive response. It is calculated as the reciprocal of the therapeutic gain, when the therapeutic gain is expressed as a proportion (the therapeutic gain is calculated by subtracting the response to placebo from the response to active drug).²⁵ Thus if 60% of patients respond to a drug and 25% respond to placebo, the therapeutic gain is 35%, and the NNT is 1 divided by 35% (1/0.35), or 2.86 patients.²⁵

The cost-effectiveness ratio (CER), the mean expense to achieve pain-free status in one patient within 2 hours of initial dosing, was then calculated for each triptan by multiplying the NNT by the cost per dose of each triptan. The cost per dose of each triptan was obtained from <http://www.drugstore.com> and is shown in Table 3. The costs of triptans as

listed by this online drug store are generally lower than those at community pharmacies but higher than the discounted prices, before member copayment, enjoyed by many managed care organizations.

Although direct comparative trials are the ideal means of comparing treatments, we found only a few studies that involved direct, head-to-head comparison of triptans.

Nonetheless, nearly all triptan trials use comparable protocols. We therefore assumed, for the sake of analysis, that all placebo-controlled studies not involving direct comparison of triptans were fundamentally comparable.²² We used the clinical endpoint of pain free at 2 hours as the indicator of efficacy as this is the currently recommended endpoint by the International Headache Society. In addition, this endpoint is the one that patients identify as being the “most important,”²⁶ and it also correlates well with return to full function. The endpoint of “24-hour sustained pain free” could also have been used in this meta-analysis and would have produced data similar to the “pain-free”²⁷ data presented here.

We used standard significance testing for paired comparisons of absolute efficacy rates, NNT, and CERs. For each triptan, we combined results for the placebo groups and for the treatment groups to determine clinical efficacy (defined as the percentage of patients who were pain free within 2 hours of initial dosing). The methodology of Cook and Sackett was adopted to calculate the 95% confidence intervals for the NNTs.²⁸

Results

Forty-five randomized, controlled trials of acute oral triptan therapy were identified in the primary search. An additional 4 studies were identified in the frovatriptan data summary.²³⁻²⁴ Twenty-seven of these studies, incorporating 36 active treatment arms, qualified for inclusion in the meta-analysis.²⁹⁻⁵¹ Reasons for exclusion were as follows:

- 6 studies related to a triptan not licensed in the United States (eletriptan),
- 4 studies related to doses not licensed in the United States,
- 3 studies used methods of ascertaining outcome incompatible with the standard 4-point scale,
- 8 studies did not record the proportion of patients pain free at 2 hours, and
- 1 study presented only aggregated data from multiple attacks.

In addition, data from 8 additional treatment arms from included studies were not incorporated in the meta-analysis because they related to doses below that recommended for most patients (sumatriptan 25 mg, naratriptan 1mg, rizatriptan 5 mg, and almotriptan 6.25 mg). No data for naratriptan 1 mg were included because this is only indicated in a prophylactic role.

Clinical Efficacy

When results from each of the studies meeting our inclusion criteria were combined, the percentage of patients who were pain free within 2 hours after drug administration ranged from 11.6% for frovatriptan 2.5 mg to 40.8% for rizatriptan 10 mg (Table 2 and Figure 1). The absolute percentage of patients who were pain free at 2 hours was significantly higher for all triptan doses than for placebo ($P<0.0001$). Placebo response rates ranged from 2.6% in frovatriptan 2.5 mg studies to 14.4% in almotriptan 12.5 mg studies (Table 2). Although this efficacy comparison is

TABLE 3 Cost per Dose of Oral Triptans

Agent	Package Price	Package Size	Cost for Single Dose
Almotriptan 12.5 mg	\$61.97	6	\$10.33
Zolmitriptan 2.5 mg	\$80.64	6	\$13.44
Frovatriptan 2.5 mg	\$129.69	9	\$14.41
Sumatriptan 50 mg	\$134.70	9	\$14.97
Sumatriptan 100 mg	\$134.70	9	\$14.97
Rizatriptan 10 mg	\$91.45	6	\$15.24
Zolmitriptan 5 mg	\$47.05	3	\$15.68
Naratriptan 2.5 mg	\$155.86	9	\$17.32

Source: <http://www.drugstore.com>. Single-pack prices quoted on July 2, 2002, for commonly used doses. Dosages below the present recommended starting dose were excluded from the analyses in this paper.

useful in that it gives a general idea as to the relative effectiveness of each of the triptans, it would be more meaningful if the variable placebo rates had been taken into consideration. A more meaningful way to compare clinical effectiveness of the triptans then would be to compute the NNT.

The NNT values ranged from 3.2 for rizatriptan 10 mg to 11.3 for frovatriptan 2.5 mg (Table 2 and Figure 2). Rizatriptan 10 mg was significantly more effective than all the other triptans except zolmitriptan 5 mg. Although the hierarchy of clinical effectiveness of the triptans was maintained as before (Figure 1), broader overlaps in the confidence intervals were obtained with the NNT calculation.

Cost-Effectiveness

The cost per dose of oral triptans varies considerably between \$10.33 for almotriptan 12.5 mg to \$17.32 for naratriptan 2.5 mg (Table 3). We applied the cost per single dose of each triptan to the NNT to calculate the best “real-world” assessment of the expenditure necessary to yield 1 patient pain free within 2 hours after initial dosing. As shown in Figure 3, the cost to achieve pain-free status in 1 patient within 2 hours postdose ranged from \$48.34 for rizatriptan 10 mg to \$162.49 for frovatriptan 2.5 mg. Here we report that the most cost-effective triptans in our analysis were rizatriptan 10 mg and almotriptan 12.5 mg.

Discussion

The 2 principal treatment goals for patients with migraine are to (a) decrease the frequency of migraine attacks and (b) decrease the duration and intensity of attacks when they do occur.⁵² With acute therapy, the ultimate objective is to eliminate the headache as quickly as possible, with no recurrence of the pain. The results of our meta-analysis indicate that there are differences in the ability of individual oral triptans to completely relieve migraine pain within 2 hours in spite of the fact that triptans are generally considered to be equally effective. Rizatriptan 10 mg and zolmitriptan 5 mg were the most clini-

FIGURE 3 Mean Cost to Achieve Pain-Free Status in One Patient at 2 Hours After Initial Dosing

Note: Comparisons versus rizatriptan 10 mg: sumatriptan 100 mg, sumatriptan 50 mg, ($P<0.01$ for both), naratriptan 2.5 mg ($P<0.001$), frovatriptan 2.5 mg ($P<0.0001$).

cally effective triptans on our measure of clinical effectiveness. When clinical effectiveness was computed with medication costs, rizatriptan 10 mg emerged as the most cost-effective triptan, together with almotriptan 12.5 mg.

A closer analysis of the cost-effectiveness data reveals that though both rizatriptan 10 mg and almotriptan 12.5 mg have a similar CER (\$48.34 versus \$48.57), this does not necessarily imply that the 2 agents are comparable. In the case of rizatriptan, this CER reflects high levels of clinical efficacy ($NNT=3.2$), coupled with an average pricing (\$15.24 per dose), while for almotriptan, average efficacy ($NNT=4.7$) is coupled with a low price per dose (\$10.33) to achieve the same result. At the other end of the scale, lower efficacy and average or above average pricing results in much higher CERs for naratriptan 2.5 mg (\$141.43) and frovatriptan 2.5 mg (\$162.49).

The 2 different components of the CER, observed above, may potentially influence the conversion of these theoretical financial benefits into actual budgetary savings. At first sight, the use of both rizatriptan 10 mg and almotriptan 12.5 mg might be expected to yield the most cost-effective outcomes in acute migraine management. The differences in clinical efficacy, however, may be expected to impact on actual drug usage. In a recently published study of triptan consumption,⁵³ it was shown that significantly more migraine attacks are controlled with a single tablet of rizatriptan 10 mg than with almotriptan 12.5 mg (79.4% versus 56.4; $P<0.005$). This means that aver-

age tablet usage per attack was 1.24 for rizatriptan 10 mg compared to 1.55 for almotriptan 12.5 mg ($P<0.005$). The potential cost consequences of this difference are clear.

It should be borne in mind that although drugs are the principal means of treating migraine attacks, drug costs are only a portion of the total costs of migraine management.⁵² Indeed, attempting to control costs by limiting the amount of triptan therapy available to a patient each month might not produce the desired results, as demonstrated in a longitudinal retrospective review by Goldfarb et al.⁵⁴ These authors studied health maintenance organization direct costs and health care resource use of patients with migraine who were taking sumatriptan and who were subject to a monthly limit on the drug.⁵⁴ They found that the limit on sumatriptan access decreased pharmacy costs but did not significantly lower other migraine-related direct medical costs and health care resource use.

Triptans are more effective than older migraine medications for moderate to severe migraine, and their use might decrease the overall direct costs associated with migraine by decreasing the need for physician office visits and emergency department services. Restricting access to these drugs by requiring patients to fill prescriptions with a generic drug, mandating higher copayments for brand-name or off-formulary drugs, or restricting the number of pills a patient can receive each month may decrease the costs of migraine drug therapy but might not decrease the overall costs of treating migraine, of which physician office visits account for the greatest expense.⁵⁵ A more rational approach may be to permit access to triptans but encourage prescribing of the more cost-effective drugs within this class.

Study Limitations

Our study is not without limitations. Firstly, we did not include all of the studies of triptans reported in the literature in our meta-analysis. Studies that did not meet our inclusion criteria were excluded.

Secondly, our study is a meta-analysis and, as such, is subject to the limitations of meta-analyses in general. Direct head-to-head comparisons in randomized clinical trials remain the gold standard for comparing the clinical efficacy of drugs. However, in the absence of such trials, meta-analyses provide first approximations of the general efficacy of one drug over the

other. Luckily, most clinical trials of triptans have followed standardized protocols in computing clinical efficacy, which makes comparisons among these trials reliable. However, it should be noted that patient populations may differ between trials, which could contribute to differences in responses.

Our calculations are based on the percentage of patients who achieved pain-free status within 2 hours of dosing using “standard” dosing schemes, in which patients are instructed to take the drug when the headache is moderate to severe. Investigators are now looking at the efficacy of triptans when given early in the headache phase, when the pain is mild. Data available to date indicate that early treatment will yield pain-free response rates higher than those obtained with later dosing.⁵⁶ Consequently, cost-effectiveness meta-analyses such as ours will need to be redone taking into account the pain-free response rates achieved with triptan dosing earlier in the headache episode.

Another limitation of our study is the generalizability of our results to a larger population. To provide clinically relevant data, we must differentiate between efficacy studies and effectiveness studies. Efficacy studies, such as those included in our meta-analysis, record the performance of a drug under ideal and controlled circumstances. However, data from efficacy studies might be applicable to the general population only to the extent to which the treatment protocol and patients are comparable to those in the community. Effectiveness studies track the performance of a drug and its treatment outcomes under “usual care conditions.”⁵⁷ Effectiveness studies typically have less restrictive criteria for entry than do efficacy studies and thus also have larger sample patient populations. Treatment regimens used in effectiveness studies are more likely to reflect usual community practice patterns and usual health care resource use.⁵⁷

Lastly, our study did not include the adverse effects associated with triptans in computing NNT and cost-effectiveness. The true efficacy of a drug is a balance between clinical efficacy and adverse effects. In addition, costs associated with treating adverse effects could contribute to the overall costs of a particular treatment and ideally should be computed in the cost-effective calculations. In general, triptans appear to be well tolerated and have similar adverse-effect profiles. The only exception is naratriptan, which has a lower adverse-effect profile consistent with its lower clinical efficacy.⁵⁸

Conclusion

The NNT method of drug comparison is important for managed care organizations in evaluating the relative value of similar drugs. Using an NNT analysis, the least-costly drugs to achieve migraine cure within 2 hours are rizatriptan 10 mg and almotriptan 12.5 mg. From a population health perspective, the lower acquisition cost of almotriptan 12.5 mg may allow for effective treatment of more patients than rizatriptan 10 mg for no additional medication cost. If, however, lesser treatment effi-

cacy results in increased medication usage, this apparent financial benefit may be partially or totally offset.

DISCLOSURES

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