Triptans for Migraine Therapy: A Comparison Based on Number Needed to Treat and Doses Needed to Treat

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ABSTRACT

OBJECTIVE: Managed care and other decision makers need sound comparative information to support the formulary selection process and reimbursement decisions for the treatment of migraine. The objective of this study was to compare currently marketed triptan therapies using number-needed-to-treat (NNT) and doses-needed-to-treat (DNT) measures. DNT was further used to derive triptan treatment cost to achieve 100 successfully treated patients such that the cost-effectiveness of each treatment regime could be compared from the payer perspective.

METHODS: Using published meta-analysis data to categorize patients as treatment success or failure, an NNT and a DNT were derived for each triptan. Treatment success was defined as achieving a 2-hour pain response, sustained through 24 hours postdose. Costs were derived by multiplying DNT by the average wholesale price (AWP) minus 15% for each triptan.

RESULTS: Eletriptan 40 mg had the lowest NNT, with 361 patients needing to be treated in order to have 100 patients achieve clinical benefit; rizatriptan 5 mg had the highest NNT (597 patients). Eletriptan 40 mg required 388 doses to successfully treat 100 patients—the lowest number of doses of the triptans considered; rizatriptan 5 mg required the highest number (662 doses). Eletriptan 40 mg had the lowest total triptan cost of $5,630 to successfully treat 100 patients. The highest total triptan cost of treatment was $11,136 for naratriptan 2.5 mg.

CONCLUSIONS: Eletriptan 40 mg provides the best value in terms of the lowest DNT, assuming an approximately equal AWP discount for each triptan. Eletriptan 40 mg also was found to have the lowest total triptan cost to successfully treat 100 patients. Future research should further explore the utility of DNT in managed care decision making.

KEYWORDS: Migraine, 5-HT receptor agonists (triptans), Number needed to treat (NNT), Doses needed to treat (DNT), Placebo effect

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Managed care and other decision makers need sound comparative information to support their formulary selection process and reimbursement decisions. While some migraine clinical trials provide comparative results, these data are typically focused on traditional clinical end points (e.g., headache response within 2 hours posttreatment). Clinical end points provide limited information for formulary, pricing, and reimbursement decisions and must be supported with data related to quality of life, other patient-reported outcomes, and economic measures. These types of end points generally have not been included in most existing studies. Thus, there is a need to make clinical end points more intuitively interpretable, practical, and useful for the formulary decision maker.

Recent comparative reviews of 5-HT receptor agonists (triptans) in migraine therapy advocate the use of the end point "number needed to treat" (NNT) as a calculated measure of therapeutic effectiveness.[1-5] The primary advantage of NNT over other measures of efficacy is that NNT takes into account placebo effects, the underlying efficacy seen in patients randomized to placebo in clinical trials. Identifying and adjusting for placebo effects are important steps toward understanding the true efficacy of a treatment, especially in subjectively assessed disorders such as migraine, where the placebo effect has been well documented.

Migraine is a condition particularly susceptible to placebo effects because migraineurs experience remitting and relapsing symptoms that occur in an unpredictable manner. Migraine symptoms can wax and wane, spontaneously remitting and relapsing during a migrainous period. Some patients will experience relief of their migraine symptoms and attribute that to a medication when, in fact, the natural history of their migraine was to resolve, independent of taking their medication. The placebo effect may be exacerbated by these cycles, and the magnitude of placebo effects can differ between studies.[6] For example, it has been noted that the placebo effect is generally greater for injected treatments than for oral treatments for migraine.[7] Consequently, it is considered especially important to not only include a placebo arm in any trial of a migraine therapy but also to account for the effect due to placebo when considering efficacy of migraine treatments.[6]

Therapeutic gain is another end point that can be used to account for the placebo effect. It is a measure of the absolute effect of the treatment and is calculated by subtracting the response to placebo from the response to active treatment.[2] The

NNT is calculated as the reciprocal of the absolute risk reduction, or the therapeutic gain, when expressed as a proportion. The NNT is interpreted as the number of patients who must be treated in order for one patient to derive a desired level of efficacy from the treatment; it may be reported as the number required to be treated to achieve one or more successfully treated patients. Although both therapeutic gain and NNT account for the placebo effect, NNT is considered more meaningful for clinical decision-making purposes, and the measure offers a simple approach for assessing the clinical significance of available treatment options.[8]

NNTs can be calculated from raw data, odds ratios, or relative risk reduction and expected prevalence. Smaller NNT values are desirable and represent higher efficacy.[2,3] For example, an NNT of 1 indicates that the treatment is effective in every patient. NNT values for effective treatments are usually in the range of 2 to 4, while those for prophylaxis are larger.[9] The principle involved in the calculation of NNT can be applied to different outcomes, including treatment efficacy, efficacy of prophylaxis, and adverse events. Using a therapeutic gain removes the variability associated with placebo response rates observed across multiple clinical trials.

While the NNT measure provides a clinically meaningful way to understand the true efficacy of treatment, it may not be the most useful measure to other decision makers, such as third-party payers, whose primary concern is the cost per outcome of treating a population of migraineurs. For these stakeholders, the number of doses needed to treat (DNT) may be a measure that can be more readily used in a comparative analysis of the cost of treatment alternatives. In this study, the DNT is presented as a practical alternative to NNT. A DNT value is interpreted as the number of doses needed to treat a population to result in one patient deriving the desired level of efficacy from the treatment. As with NNT, smaller DNT values are preferable because they represent high efficacy and can be utilized as an indication of cost-effectiveness or value. For example, a DNT of 1 indicates that, on average, a single dose of drug is effective for all patients. Multiplying the DNT value for a treatment by the cost of the treatment yields an estimate of the total prescribed drug treatment cost associated with achieving the efficacy end point of interest. In this analysis we used a hypothetical cohort of 100 patients instead of 1 patient in order to eliminate 2 decimal points associated with efficacy and recurrence rates.

Ideally, a straightforward comparison of triptans would involve a head-to-head, controlled clinical trial of all available agents (currently, 7 triptans are approved in the United States) in a single study. This is not feasible for both practical and economic reasons. However, clinical trials of migraine treatment use a fairly standard design, and most employ a placebo group. This consistency in trial design facilitates comparison of the relative efficacy of triptans through meta-analysis.[3] Data from a meta-analysis can be used to calculate both the NNT and the DNT and can be used to compare the effects of the various triptans, while adjusting for the variable placebo effects.

Several meta-analyses have been performed for migraine treatments using therapeutic gain and/or NNT as end points of comparison. However, most of these studies have not considered the entire range of marketed triptans. In Adelman and Belsey's recent study,[1] eletriptan was not included since data for the drug were not available at the time of the analysis. Comparisons by Goadsby were performed prior to the approval of several recent triptans.[2] Oldman et al. excluded almotriptan and frovatriptan, as these were the newest products introduced to the market at that time.[3]

Ferrari et al. performed a comprehensive comparison of triptans in the U.S. market, which included at least a minimal amount of data on all products now available in the United States.[10,11] While these authors had limited access to data on frovatriptan, they did report on 7 eletriptan studies and reported findings that adjust for placebo effects. Recently, Belsey[5] carried out a transnational comparison of oral triptan cost-effectiveness in 6 countries and found the hierarchy of cost-effectiveness of oral triptans to be highly consistent in each of these countries. Gracia-Naya et al.[12] examined the cost-effectiveness of 8 triptan doses in the Spanish market, using therapeutic gain as an end point.

Other research groups have evaluated the cost-effectiveness of various strategies to treat acute migraine from the payer perspective. Sculpher et al.[13] provide a cost-effectiveness analysis from the societal perspective, comparing stratified versus stepped care and noting that stratified care has the higher probability of being cost effective. Adelman et al. address cost of triptans and rescue medications and advocate pill splitting, early treatment administration of triptans, and use of opioids, sedatives, and phenothiazines to prevent emergency room visits.[14]

The objective of this study was to compare triptan therapies for migraine using traditionally reported clinical measures as well as NNT and DNT, both of which were derived using clinical efficacy end points from the Ferrari et al. meta-analysis of clinical trial data.[10,11] Although some have referred to the Ferrari meta-analysis as a pooled analysis, to be consistent with the Ferrari manuscript and hopefully to minimize confusion, it is referred to in this manuscript as the Ferrari meta-analysis. The DNT was used to derive drug treatment costs and was included as the cost to achieve 100 successfully treated patients.

■ Methods

Clinical Data Source

This study compares 6 triptans, several with multiple doses, in the treatment of migraine by calculating NNT and DNT. Data were abstracted from the robust meta-analysis performed by

TABLE 1 Relevant Definitions for Migraine End Points[11]

Response rate at 2 hours (R2h)	The proportion of patients whose moderate or severe headache at baseline improves to mild or no pain at 2 hours postdose (response at 2 hours is the traditional primary efficacy end point in triptan migraine trials).
Pain-free response at 2 hours (PF2)	The proportion of patients whose moderate or severe headache at baseline improves to no pain at 2 hours postdose (pain-free at 2 hours is now the recommended primary efficacy end point in acute migraine trials).
Sustained pain-free rate at 24 hours (24h-SPFR)	The proportion of patients who were pain-free at 2 hours postdose and who did not experience a recurrence of moderate or severe headache and did not use any analgesic or other headache medication over the subsequent 22 hours.
Recurrence rate (RR)	The proportion of patients with headache response at 2 hours postdose who experience a return (or relapse) of moderate or severe headache in the subsequent 22 hours.

FIGURE 1 Model for Calculation of Treatment Success Versus Failure Using Clinical Data From a Published Meta-Analysis
(See Appendix for Model Description)
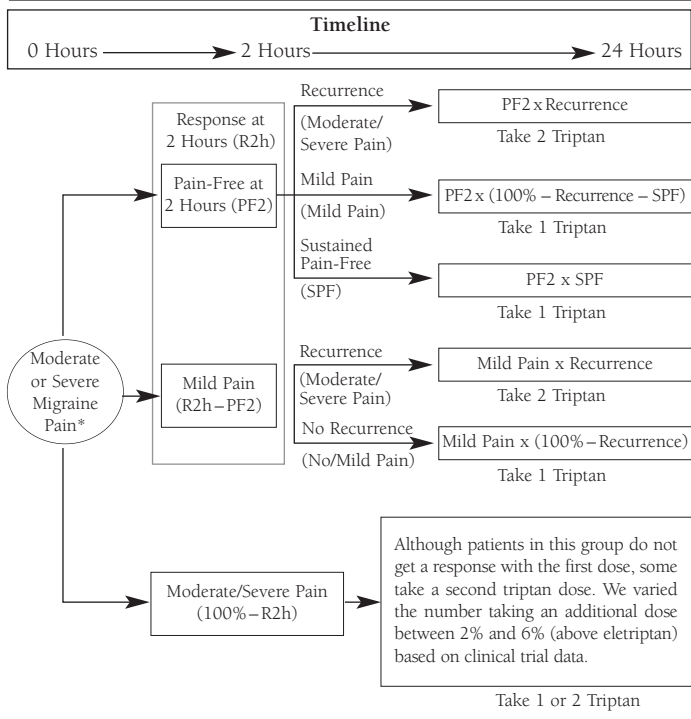
* Assumes complete data (no missing data) set.
PF=pain-free rate; PF2=pain-free response rate at 2 hours;
R2h=response rate at 2 hours; SPF=sustained pain-free rate.

Ferrari et al.[10,11] Frovatriptan (Frova) was not included in this study because only limited data on the drug were available in the meta-analysis. Eletriptan 80 mg also was included in the meta-analysis, but is not included here because it is not an approved dose in the United States. The Ferrari meta-analysis only captured the use of triptans; it did not capture the cost associated with other nontriptan treatment, over-the-counter drugs, doctor's office visits or ER visits, etc.

Ferrari et al.[10,11] reported both absolute and therapeutic-gain-adjusted figures for the 2-hour response rate (R2h and R2hTG, respectively) and the 2-hour pain-free rate and the 2-hour pain-free therapeutic-gain-adjusted rate (PF2 and PF2TG, respectively). Recurrence also was reported by Ferrari et al.[10,11] A 2-hour mild pain response therapeutic gain (MPRTG2) was derived from the meta-analysis data by subtracting the PF2TG from the R2hTG. (See Table 1 for descriptions of commonly used migraine therapy end points.)

Calculation of NNT

The NNT was calculated as the number of patients who need to be treated with a drug in order for 100 patients to achieve treatment success, defined as those patients achieving a 24-hour sustained response (24-h SR). Treatment failures were those patients who did not attain a response at 2 hours (nonresponders), plus those migraineurs who had an initial 2-hour response but subsequently experienced a migraine recurrence (i.e., response at 2 hours was not sustained for 22 additional hours). A model (Figure 1) was used to identify the number of patients who were treatment successes versus those who were treatment failures using the reported meta-analysis data. This model produced an estimate of the percentage of successfully treated patients (24-h SR). The NNT for 100 successful patients was estimated as (1/24-h SR) x 100. For a detailed description of the calculations and assumptions, see the Appendix.

Calculation of DNT and Costs

Calculated NNT values were used to estimate the DNT. The hypothetical population represented by each drug-specific NNT was split into 3 mutually exclusive groups that represented 3 potential outcomes for each patient. Those patients who achieved successful treatment (defined previously) comprised the first group. For all drugs, this represented 100 patients by definition, and it was assumed that all patients represented in this cohort had taken one dose of triptan therapy in the 24-hour period.

The second group (recurrence patients) comprised patients who initially achieved a response at 2 hours postdose, but then experienced a recurrence during the remainder of the 24-hour period. The number of patients in this group was calculated by multiplying the drug-specific NNT by the proportion of patients who achieved PF2TG, multiplied by the proportion of patients who experienced recurrence, plus the proportion of patients

TABLE 2 Migraine End Points Used to Calculate Number Needed to Treat

Triptan Drug	Ferrari et al.[11] End Points*				Derived End Points		
	2-Hour Response Therapeutic Gain (R2hTG) (%)	2-Hour Pain-Free Therapeutic Gain (PF2TG) (%)	24-Hour Sustained Pain-Free Rate (24-h SPFR) (%)	Recurrence Rate (RR) (%)	2-Hour Mild Pain Response Therapeutic Gain (MPRTG2) (%)†	24-Hour Sustained Response Rate (24-h SR)‡	Number Needed to Treat (NNT)§
Almotriptan 12.5 mg	25.0	21.0	25.9	26.2	4.0	18.5%	542
Eletriptan 40 mg	35.2	22.5	20.9	21.4	12.7	27.7%	361
Naratriptan 2.5 mg	22.2	14.1	15.9	21.4	8.1	17.4%	573
Rizatriptan 5 mg	27.6	22.0	18.9	39.3	5.6	16.7%	597
Rizatriptan 10 mg	34.6	30.4	25.3	36.9	4.2	21.8%	458
Sumatriptan 50 mg	30.9	18.0	19.8	27.8	12.9	22.3%	448
Sumatriptan 100 mg	29.1	19.5	20.0	29.9	9.6	20.8%	490
Zolmitriptan 2.5 mg	30.9	20.4	19.0	30.3	10.5	21.6%	464
Zolmitriptan 5 mg	33.8	25.2	21.9	34.2	8.6	22.2%	450

These end points are all taken from the Appendix of reference 11.

† MPRTG2 is the percentage of patients who received response to mild pain within 2 hours of taking a triptan, adjusted to take account of placebo effects, calculated as R2hTG−PF2TG.

‡ 24-h SR is the percentage of patients achieving a 24-hour sustained response, calculated as (R2hTG/100) x (100−RR).

§ NNT gives the number of patients who need to be treated to achieve 100 successfully treated patients, calculated as (1/24-h SR) x 100, where the 24-h SR is expressed as a proportion. For example, if 20 patients per 100 were successfully treated for 24 hours (24-h SR), 500 patients would need to be treated to achieve 100 successfully treated patients (1/0.2 x 100 = 500).

who achieved a MPRTG2, multiplied by the proportion of patients who experienced a recurrence, or NNT x (PF2TG x RR) + (MPRTG2 x RR). Because patients in this group achieved a pain response within 2 hours but then experienced a recurrence, it was assumed that one dose was taken for the original headache and a second dose was taken after the onset of the recurrence, for a total of 2 doses for all patients represented. The prescribing information for each triptan states that 2 doses should not be exceeded within a 24-hour period (with the exception of rizatriptan (Maxalt) 10 mg, where 3 doses are acceptable).

The final group (nonresponder patients) comprised nonresponders to treatment—those patients who did not achieve the initial 2-hour response status—and was calculated as NNT x (1 − R2hTG). The dosing assumptions for this third group were more complicated to operationalize. The base case assumption was that these patients took one triptan dose. By definition, none of these nonresponding patients achieved a 2-hour response, and, from the literature, it is unclear whether some non-responders took a second dose of triptan to achieve pain relief. A sensitivity analysis was conducted assuming that half of the 2-hour failures (nonresponders) took a second dose in an attempt to relieve their migraine.

The total number of doses was calculated by summing the total number of doses taken by each of the 3 mutually exclusive groups. Using the average wholesale price (AWP) minus 15% per dose for each triptan, the total triptan cost associated with achieving 100 successfully treated patients was calculated using the following formula: total DNT x (AWP per dose − 15%). A more precise cost per triptan dose would be the contracted price for each triptan dose for a given managed care organization (MCO). However, AWP − 15% is a reasonable estimate of MCO drug cost before manufacturer rebate since all of the triptans in this study are patent protected and do not have generic equivalent competitors. A given MCO with a lower net contractual price can substitute this price in our calculations of price per dose for each triptan.

■ Results

Table 2 presents the data abstracted from the meta-analysis, the derived end point, and the calculated NNT. The PF2TG ranged from a low of 14.1% (naratriptan 2.5 mg) to a high of 30.4% (rizatriptan 10 mg). Recurrence rates ranged from a low of 21.4% (eletriptan 40 mg and naratriptan 2.5 mg) to a high of 39.3% (rizatriptan 5 mg). Approximately one quarter of patients treated with any triptan were successful at the higher standard of success defined as attainment of sustained pain relief from taking one triptan dose for one migraine during a 24-hour period. The highest success rate was achieved with eletriptan 40 mg (24-h SR: 27.7%) and the lowest with naratriptan 2.5 mg (24-h SR: 17.4%). If the standard of success is redefined to a more easily attained goal, the rates of success for all the triptans will increase above one quarter. For example, this rate is much higher when one defines success as a 2-hour response; however, it does not capture the use of migraine medications because of recurrences during the remainder of the 24-hour period. The results of the NNT calculation show that eletriptan 40 mg had the lowest NNT, with 361 patients needing

TABLE 3 Doses Needed and Drug Cost to Successfully Treat 100 Patients With a Triptan Based Upon Number Needed to Treat

| | | Successfully Treated Patients | | Treatment-Failure Patients | | | | | Cost per Dose (AWP − 15%) ($)[17] | Cost to Successfully Treat 100 Patients ($) |
| | | | | Recurrence Patients* | | Nonresponder Patients† | | | | |
Triptan Drug	NNT	n	Doses	n	Doses	n	Doses	Total DNT		
Almotriptan 12.5 mg	542	100	100	36	72	407	407	579	15.67	9,073
Eletriptan 40 mg	361	100	100	27	54	234	234	388	14.51	5,630
Naratriptan 2.5 mg	573	100	100	27	54	446	446	600	18.56	11,136
Rizatriptan 5 mg	597	100	100	65	130	432	432	662	15.98	10,579
Rizatriptan 10 mg	458	100	100	58	116	300	300	516	15.98	8,246
Sumatriptan 50 mg	448	100	100	39	78	310	310	488	15.94	7,779
Sumatriptan 100 mg	490	100	100	43	86	348	348	534	16.01	8,549
Zolmitriptan 2.5 mg	464	100	100	43	86	321	321	507	14.89	7,549
Zolmitriptan 5 mg	450	100	100	52	104	298	298	502	16.93	8,499

* n = NNT x (PF2TG x RR) + (MPRTG2 x RR), Doses = 2n (see Methods section for details).

† n = NNT x (1 − R2hTG). Base case analysis where the nonresponders take only 1 dose of triptan.

AWP = average wholesale price; DNT = doses needed to treat; NNT = number needed to treat.

TABLE 4 Base Case and Sensitivity Analyses for Nonresponders in Doses Used to Calculate Doses Needed and Drug Cost to Successfully Treat 100 Patients

| | | Base Case (1 dose) | | Sensitivity Analysis (1.5 doses) | |
Triptan Drug	Cost per Dose (AWP − 15%) ($)[17]	Total DNT	Cost To Successfully Treat 100 Patients ($)	Total DNT*	Cost to Successfully Treat 100 Patients ($)
Almotriptan 12.5 mg	15.67	579	9,073	781	12,238
Eletriptan 40 mg	14.51	388	5,630	506	7,338
Naratriptan 2.5 mg	18.56	600	11,136	823	15,283
Rizatriptan 5 mg	15.98	662	10,579	878	14,025
Rizatriptan 10 mg	15.98	516	8,246	666	10,646
Sumatriptan 50 mg	15.94	488	7,779	642	10,228
Sumatriptan 100 mg	16.01	534	8,549	707	11,310
Zolmitriptan 2.5 mg	14.89	507	7,549	668	9,951
Zolmitriptan 5 mg	16.93	502	8,499	650	11,013

* Sensitivity analysis conducted assuming one half of the 2-hour nonresponders took a second dose. Calculated as Total DNT at base case + (0.5 x doses needed to treat nonresponders).

AWP = average wholesale price; DNT = doses needed to treat.

to be treated in order to have 100 patients receive clinical benefit. Rizatriptan 5 mg had the highest NNT (597 patients).

Table 3 details the results of the DNT calculations. The NNT from Table 2 is shown along with the number of patients in each of the 3 mutually exclusive groups (i.e., successfully treated, recurrence, and nonresponder). The number of doses taken by each group is listed and the total number of doses is calculated. Finally, the average wholesale price (AWP) subtracted by 15%

(AWP − 15%) is provided, and the total triptan cost to successfully treat 100 patients is listed.

Under the base assumption that one dose was taken by those patients deemed nonresponders, eletriptan 40 mg required 388 doses to successfully treat 100 patients—the lowest number of doses of all the triptans considered. Rizatriptan 5 mg required 662 doses to achieve the same outcome—the highest number of doses of the drugs considered. For the cost to successfully treat 100 patients, under the baseline assumption of one dose for patients characterized as 2-hour nonresponders, eletriptan 40 mg had the lowest cost of $5,630. The highest cost of treatment was for naratriptan 2.5 mg, at a cost of $11,136. The ranking of cost per 100 successfully treated patients for the other 7 triptans, from lowest to highest, was as follows: zolmitriptan 2.5 mg ($7,549), sumatriptan 50 mg ($7,779), rizatriptan 10 mg ($8,246), zolmitriptan 5 mg ($8,499), sumatriptan 100 mg ($8,549), almotriptan 12.5 mg ($9,073), and rizatriptan 5 mg ($10,579).

For the sensitivity analysis we increased the proportion of nonresponders at 2 hours who took an additional dose from the base assumption of 0% to 50%. The sensitivity analysis had no impact on the order of the drugs in terms of the cost to successfully treat 100 patients (Table 4).

■ Discussion

NNT is intuitively useful to the clinician, and the DNT is a potentially useful additional measure for MCO decision makers to consider when making product choices for drug formulary selection. The DNT describes the number of doses needed to achieve 100 successfully treated patients. Both the NNT and the DNT were calculated based on a 24-h SR as the measure of

treatment success. The present study demonstrates clear differences among the triptans, with large differences from both the lowest to highest NNT (361–597) and the lowest to highest DNT (388–662) among the triptans compared. The differences in the cost for successfully treating 100 patients reflect the differences seen in the calculated NNT and DNT measures ($5,630–$11,136).

The NNT reflects the demonstrated effectiveness of each triptan after accounting for placebo effects. Here, the effectiveness measure was constructed as a composite end point that combined the 2-hour pain response status with or without recurrence over the remainder of a 24-hour period. Thus, those products with both high efficacy (as evidenced by 2-hour pain response, adjusted for therapeutic gain) and low recurrence produced the best 24-hour composite measure, in this case 24-h SR. The calculated DNT incorporated the same concept of effectiveness as the NNT but converted the calculation so that the dose was the unit of measure. This value was used to compute the total triptan cost for successfully treating 100 migraine patients. The DNT may be a more useful measure for managed care decision makers, who seek to identify the most cost-effective products for their formularies.

Eletriptan 40 mg demonstrated the highest R2hTG at 35.2%, followed by rizatriptan 10 mg (34.6%) and zolmitriptan 5 mg (33.8%). Eletriptan 40 mg and naratriptan 2.5 mg demonstrated the lowest recurrence rates at 21.4%, while rizatriptan 5 mg and rizatriptan 10 mg had the highest recurrence rates (39.3% and 36.9%, respectively). Eletriptan 40 mg had the best combination of high efficacy and low recurrence rates. However, rizatriptan 5 mg, with its high recurrence rate, had the highest, and therefore the least desirable, NNT of 597 patients (Table 2).

The relative rank order of the triptans, based on NNT, remained virtually the same when the DNT measure was calculated (Figures 2 and 3). Under the initial assumption of one dose for those patients deemed treatment nonresponders at 2 hours, eletriptan 40 mg had the lowest DNT values. The combination of high efficacy and low recurrence reveals that eletriptan 40 mg appears to provide consistent overall clinical and economic value. In terms of the total cost of successfully treating 100 patients, eletriptan 40 mg was associated with the lowest cost of treatment ($5,630), while naratriptan 2.5 mg was associated with the highest cost ($11,136).

As a point of comparison, there are noteworthy results from previously published studies on NNT and therapeutic gain for triptans. These studies indicate that the rankings achieved by the triptans in this study are comparable to those noted elsewhere. For example, the Bandolier Library[15] compared 2-hour response for various triptans. Although not all of the same triptans were investigated in the current analysis and the Bandolier analysis, the hierarchy of triptan cost-effectiveness is similar (Table 5). Bandolier[15] and Oldman et al.[3] report that, of

FIGURE 2 Number Needed to Successfully Treat 100 Patients
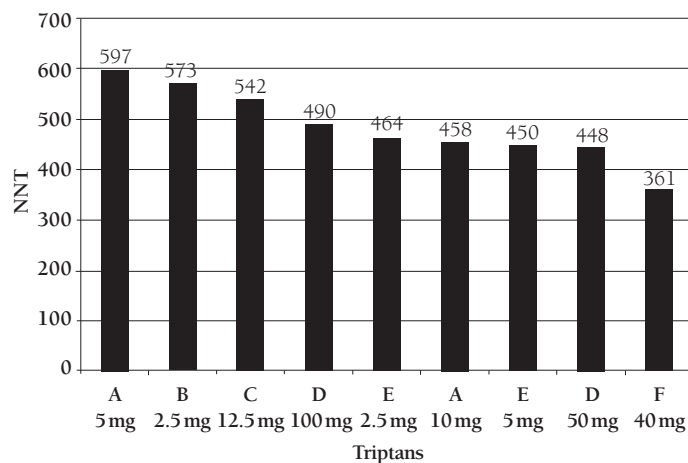
A=Rizatriptan; B=Naratriptan; C=Almotriptan; D=Sumatriptan; E=Zolmitriptan; F=Eletriptan

FIGURE 3 Doses Needed to Successfully Treat 100 Patients
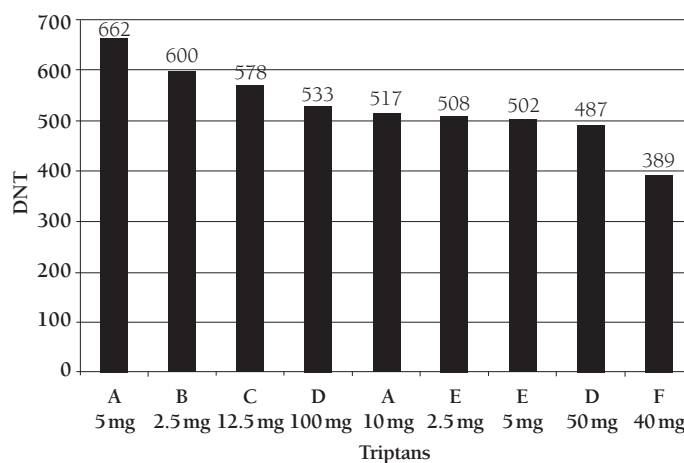
A=Rizatriptan; B=Naratriptan; C=Almotriptan; D=Sumatriptan; E=Zolmitriptan; F=Eletriptan

the oral triptans, eletriptan 80 mg and 40 mg and rizatriptan 10 mg had the lowest NNTs (ranging from 2.6 to 2.9 patients), whereas sumatriptan 50 mg and 100 mg and rizatriptan 5 mg had the highest NNTs (ranging from 6.0 to 8.3 patients). This is more than a 2-fold difference. Zolmitriptan, almotriptan, and naratriptan were not evaluated by Bandolier.

Tfelt-Hansen[16] reported a similar trend in a comparison of

TABLE 5 Published Meta-analytic Reports of Number Needed to Treat

Study	Bandolier[15] and Oldman et al.[3]	Adelman and Belsey[1]	Tfelt-Hansen[16]	Belsey[5]
Measure	NNT based on 24-h SR*	NNT based on PF2	NNT calculated from therapeutic gain based on response*	NNT based on PF2
Lowest ↑ ↓ Highest	Eletriptan 80 mg = 2.8 Eletriptan 40 mg = 3.6 Rizatriptan 10 mg = 5.6 Sumatriptan 50 mg = 6.0 Sumatriptan 100 mg = 6.7 Rizatriptan 5 mg = 8.3	Rizatriptan 10 mg = 3.2 Zolmitriptan 5 mg = 4.2 Almotriptan 12.5 mg = 4.7 Sumatriptan 100 mg = 4.7 Zolmitriptan 2.5 mg = 5.1 Sumatriptan 50 mg = 5.4 Naratriptan 2.5 mg = 8.2 Frovatriptan 2.5 mg = 11.3	Eletriptan 80 mg = 2.4 Eletriptan 40 mg = 2.6 Rizatriptan 10 mg = 2.6 Zolmitriptan 2.5 mg = 3.1 Sumatriptan 100 mg = 3.1 Sumatriptan 50 mg = 3.3 Rizatriptan 5 mg = 3.8 Almotriptan 12.5 mg = 3.8 Naratriptan 2.5 mg = 4.5 Frovatriptan 2.5 mg = 6.3	Rizatriptan 10 mg = 3.17 Eletriptan 80 mg = 3.51 Eletriptan 40 mg = 4.01 Sumatriptan 100 mg = 4.77 Almotriptan 12.5 mg = 4.79 Zolmitriptan 5 mg = 4.88 Zolmitriptan 2.5 mg = 5.72 Sumatriptan 50 mg = 5.86 Naratriptan 2.5 mg = 8.17 Eletriptan 20 mg = 9.26 Frovatriptan 2.5 mg = 11
Drugs not included/ not calculated	Almotriptan Frovatriptan Naratriptan Zolmitriptan Eletriptan 20 mg	Eletriptan Rizatriptan 5 mg	Zolmitriptan 5 mg Eletriptan 20 mg	Rizatriptan 5 mg

Response = patients met the criteria for responding to therapy but were not necessarily pain free.
NNT = number needed to treat; PF2 = pain-free response at 2 hours; 24-h SR = sustained pain-free rate at 24 hours.

therapeutic gain for response (not sustained) among oral therapies (Table 5), with eletriptan 80 mg and 40 mg and rizatriptan 10 mg having the highest therapeutic gain with the lowest NNTs. Naratriptan, sumatriptan 50 mg, and rizatriptan 5 mg again fell among the highest NNTs. Zolmitriptan 5 mg was not included in that study.[16] Adelman and Belsey[1] report NNTs for patients who were pain-free at 2 hours (not sustained) (Table 5). Rizatriptan 10 mg and zolmitriptan 5 mg had the lowest NNTs (3.2 and 4.2 patients, respectively). Sumatriptan 50 mg and naratriptan had the highest (5.4 and 8.2 patients, respectively). Eletriptan was not included in this study. Belsey similarly looked at NNTs for 2-hour pain-free rates, and included eletriptan in the analysis.[5] Rizatriptan 10 mg and eletriptan 80 mg and 40 mg were found to have the lowest NNTs (ranging from 3.17 to 4.01 patients), and the highest NNTs were calculated for frovatriptan 2.5 mg and eletriptan 20 mg (11.28 and 9.26, respectively).

Limitations

There are several limitations of the approach used in this study. The calculated DNT only includes the direct drug cost of the triptans, and it does not include the vast array of rescue medications used in clinical trials and routine patient care. These data were not available from the meta-analysis. It would be expected that products with higher nonresponse rates and recurrence rates would be expected to have higher total costs. For managed care decision makers, an ideal comparison would be head-to-head analysis of all health care resource utilization paired with clinical outcomes associated with actual use of the available triptans. In the absence of such outcomes, decision

makers often make decisions based on the available head-to-head efficacy trials and meta-analysis. Our analysis utilized the Ferarri meta-analysis, which relied upon efficacy data[10,11]; therefore, our analysis is technically a cost-efficacy analytical model.

The number of doses of triptans taken was based upon whether the patient was a success, had recurrence, or was a nonresponder to treatment. Actual utilization may differ; however, we used conservative estimates. Also, other drugs and health care resource utilization that may have been associated with the triptan doses were not accounted for in this analysis because these data were not available.

Clinical trials are conducted under controlled conditions in which patients are given specific directions on when and how to use the subject drug. This is not representative of real-world experience and what patients actually take during a migraine, including their use of other medications in addition to triptans. Our study tried to reflect the real-world experience using the available data and the recommended prescribing information. Our model assumed that patients would take one dose of triptan when their migraine pain was moderate to severe. If the patient attained a 2-hour response (migraine pain was mild or absent), then he or she did not take another triptan dose unless there was a recurrence of moderate-to-severe migraine pain. In the base case, patients who did not experience a 2-hour response were presumed not to have taken a second dose. However, recognizing that some patients will take a second dose even though they experienced a 2-hour response, we tried to reflect the real-world experience by modeling that 50% of them would take an extra dose.

APPENDIX Model Description (See Figure 1)

Ferrari et al.[9,10] used the 2-hour pain-free response rate (PF2) as the primary end point of their study (see definitions in Table 1). The therapeutic gain for each of these end points was reported in the meta-analysis (PF2TG). These data were used in this model. The model assumes no loss of data.

Patients with moderate or severe migraine pain who took 1 triptan dose for the initial treatment of their migraine pain experienced 1 of 2 possible outcomes: a response at 2 hours (to mild (MP2) or pain-free (PF2)) or no response at 2 hours (remained at moderate or severe pain). The R2h rate is the sum of the PF2 and MP2, with MP2 derived by subtracting the PF2 rate from the R2h rate.

There are 3 possible subgroup outcomes for those who attain a PF2 response: recurrence, mild pain, or pain-free during the remainder of the 24-hour period. The PF2 to recurrence subgroup was assumed to have taken a second triptan dose. The PF2 to mild pain subgroup was assumed to have taken only 1 triptan dose. The PF2 to SPF subgroup also did not take any additional triptan doses.

There are 2 possible subgroup outcomes for the mild pain at 2 hours group: recurrence or no recurrence (mild or no pain). The recurrence subgroup was assumed to have taken a second triptan dose. The no recurrence subgroup remained at the mild- or no-pain level throughout the remainder of the 24-hour period, and it was assumed that no additional triptan or rescue medications were taken.

Those patients experiencing recurrence were assumed to have taken a second triptan dose because they had success with a triptan at the 2-hour point. These patients constituted the "failures" in this model because they did not meet the requirement of 1 triptan dose for 1 migraine during a 24-hour period to obtain a sustained response to the mild- or no-pain level.

Real-world clinical experience also demonstrates that patients may take more than one triptan dose even if they have a 2-hour response sustained through the remainder of a 24-hour period to avert an anticipated recurrence. Some patients may take a second triptan dose even though they did not receive a 2-hour response. However, we modeled within the confines of the available data and recommended prescribing information, which states that the maximum dose for each of the triptans is 2 times the maximum dose available for all the triptans (except rizatriptan 10 mg, which recommends a daily maximum of 30 mg).[18–23] The ideal study would be a head-to-head observational study that captured all direct and indirect costs. Additional work is needed to clarify what patients actually take in the way of triptans, nontriptan treatments, and over-the-counter treatment during a migraine episode. A real-world analysis also would employ the actual cost of drugs incurred by the MCO, incorporating both drug manufacturer rebates and discounts. In the absence of the actual cost of the triptan doses to a payer, this study used an AWP − 15% calculation to estimate the cost of each triptan dose.

The original report by Ferrari[10] generated a significant amount of discussion in letters regarding the methodology used in the meta-analysis.[24-29] The issues raised included the use of active-to-placebo response-rate ratios versus placebo-subtracted rates, additive versus multiplicative models, homogeneity of data, encapsulation, the use of parameters from the number of patients for each outcome category rather than from the patients' records, meta-analytic pooling of data, and total adverse effect rates. Ferrari in his response noted, "the trials we included all had similar designs, populations of patients, and placebo responses. Furthermore, the profiles of the triptans and the differences among them were quite consistent in our analysis of the head-to-head comparative studies and using all four meta-analytic approaches. We are, therefore, confident in the validity of these results."[29] Meta-analytic techniques are a satisfactory alternative for aggregating and analyzing data. An update to the Ferrari et al. meta-analysis would affect the assumptions used in our model.

■ Conclusions

This analysis used data from a recent meta-analysis to find that eletriptan 40 mg provides the best value of all the triptans considered as measured by the lowest DNT, assuming an approximately equal price discount for each triptan. Eletriptan 40 mg also was found to have the lowest total triptan cost to successfully treat 100 patients. Future research should further explore the utility of DNT in managed care decision making.

REFERENCES

1. Adelman J, Belsey JD. Meta-analysis of oral triptan therapy for migraine: number needed to treat and relative cost to achieve relief within 2 hours. *J Manag Care Pharm.* 2003;9(1):45-52.

2. Goadsby PJ. A triptan too far? *J Neurol Neurosurg Psychiatry.* 1998;64:143-47.

3. Oldman AD, Smith LA, McQuay HJ, et al. Pharmacological treatments for acute migraine: quantitative systematic review. *Pain.* 2002;97:247-57.

4. Oldman AD, Smith LA, McQuay HJ, et al. Rizatriptan for acute migraine. *Cochrane Database Syst Rev.* 2002;CD003221.

5. Belsey, JD. Cost-effectiveness of oral triptan therapy: a trans-national comparison based on a meta-analysis of randomised controlled trials. *Curr Med Res Opin.* 2004;20:659-69.

6. Couch JR, Jr. Placebo effect and clinical trials in migraine therapy. *Neuroepidemiology.* 1987;6:178-85.

7. de Craen A. Placebo effect in acute treatment of migraine: subcutaneous placebos are better than oral placebos. *J Neurol.* 2000;247:183-88.

8. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Ann Intern Med.* 1997;126:712-20.

9. Bandolier Extra. Calculating and using NNTs. Available at: www.jr2.ox.ac.uk/bandolier/extraforbando/NNTextra.pdf. Accessed May 19, 2004.

10. Ferrari MD, Roon KI, Lipton RB, et al. Oral triptans (serotonin 5-HT1B/1D agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet.* 2001;358:1668-75.

11. Ferrari MD, Goadsby PJ, Roon KI, et al. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. *Cephalalgia.* 2002;22:633-58.

12. Gracia-Naya M, Rejas J, Latorre A, Gonzalez P. Economic evaluation of acute migraine attack treatment with triptans in Spain (in Spanish). *Neurologia.* 2005;20:121-32.

13. Sculpher M, Millson D, Meddis D, Poole L. Cost-effectiveness analysis of stratified versus stepped care strategies for acute treatment of migraine: the disability in strategies for care (disc) study. *Pharmacoeconomics.* 2002;20(2):91-100.

14. Adelman JU, Adelman LC, Freeman MC, Bon Seggern RL, Drake J. Cost considerations of acute migraine treatment. *Headache.* 2004;44:271-285.

15. Bandolier. Migraine league table: acute treatments and 24 hour sustained response. Available at: http://www.jr2.ox.ac.uk/bandolier/booth/Migraine/LeagueSR.html. Accessed April 20, 2005.

16. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. *Drugs.* 2000;60:1259-87.

17. AnalySource Online. 2004. Available at: http://www.analysource.com. Accessed August 19, 2004.

18. Amerge prescribing information. Available at: http://us.gsk.com/products/assets/us_amerge.pdf. Accessed April 20, 2005.

19. Axert product Web site. Available at: http://www.axert.com. Accessed April 20, 2005.

20. Imitrex prescribing information. Available at: http://us.gsk.com/products/assets/us_imitrex_tablets.pdf. Accessed April 20, 2005.

21. Maxalt product Web site. Available at: http://www.maxalt.com/rizatriptan_benzoate/maxalt/consumer/index.jsp. Accessed April 20, 2005.

22. Relpax product Web site. Available at: http://www.relpax.com. Accessed April 20, 2005.

23. Zomig product Web site. Available at: http://www.zomigconsumer.com. Accessed April 20, 2005.

24. Palmer BD, Salonen R. Triptan medications to treat acute migraine (letter). *Lancet.* 2002;359:1151.

25. Dowson A, Kilminister S. Triptan medications to treat acute migraine (letter). *Lancet.* 2002;359:1151-52.

26. Tfelt-Hansen P. Triptan medications to treat acute migraine (letter). *Lancet.* 2002;359:1152.

27. Kernick DP. Triptan medications to treat acute migraine (letter). *Lancet.* 2002;359:1152.

28. Cates C. Triptan medications to treat acute migraine (letter). *Lancet.* 2002; 359:1152.

29. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Triptan medications to treat acute migraine (letter). *Lancet.* 2002;359:1152-53.