LETTER TO THE EDITOR

Triptan Use in the Real World

I am writing to comment on the article by Ho et al. in the January 2005 issue of P&T. The authors used drug acquisition costs and efficacy rates to perform cost-efficacy and incremental cost-efficacy analyses on the seven marketed triptans. Although the efficacy rates employed in the model were derived from the drug manufacturers’ prescribing information, there are a number of limitations to the proposed model, and the analyses are unlikely to provide reliable estimates of cost efficacy.

To begin, the model focuses primarily on a single efficacy endpoint: reduction in migraine from moderate or severe pain to mild or no pain in two hours. Although this endpoint has been valuable in establishing efficacy of triptans in placebo-controlled trials performed for registration purposes, this endpoint by itself is of questionable utility in predicting satisfactory patient outcomes in the general clinical setting.

The flaw in focusing solely on the two-hour efficacy time point reported in product labels stems from artificial clinical trial designs that do not mirror practice. In general, patients in the triptan clinical trial programs were required to wait until their headaches became moderate or severe before taking the first dose. In clinical practice, however, many patients treat their headaches before they become disabling, and recent studies with various triptans have documented the benefit of early intervention. Taking a triptan before pain begins or when pain is still mild leads to reduced migraine progression and disability, compared with treatment that is begun when pain is moderate or severe. Thus, the efficacy endpoint used for determining cost-effectiveness by Ho et al. bears little relationship to how these drugs are used or should be used in clinical practice.

A further limitation of the study is that patients who experience reduced headache pain within two hours, but who subsequently have a recurrence of moderate or severe headache within 24 hours, cannot be considered to have received efficacious or cost-effective therapy, because they will likely require additional therapy to experience satisfactory relief from migraine symptoms.

In this context, it is important to note that there is an approximate 10-fold range in triptan elimination half-life (of two to three hours at the low end for rizatriptan and sumatriptan versus 26 hours for frovatriptan). According to a meta-analysis, a triptan’s elimination half-life is inversely correlated with rates of recurrence, with mean headache recurrence rates ranging from 17% with frovatriptan 2.5 mg to 40% with rizatriptan 10 mg. Thus, a more clinically relevant cost-effectiveness analysis could have been made if Ho et al. had used rate of migraine recurrence (usually defined as return of pain within 24 hours of achieving relief after initial dosing) and had combined this term with either two-hour or four-hour efficacy in the denominator of their cost-efficacy formula (see Table 1).

In this analysis, the relative cost-efficacy ratio (CE) ranking can change considerably because the initial efficacy is corrected only by continuing to count as treatment successess the fraction of patients whose headache did not recur within 24 hours (1 – mean recurrence rate).

Whereas rizatriptan and zolmatriptan were ranked 1 and 2, respectively, for CE solely on the basis of two-hour response, their relative CE rankings fall to 6 and 5, respectively, when headache recurrence is considered.

In the case of frovatriptan and naratriptan, the CE rankings change from 7 and 5 to 1 and 3, respectively. This stems partly from their lower rates of recurrence.

In the case of frovatriptan, an additional change in relative ranking is caused by using four-hour rather than two-hour efficacy data. Although Ho et al. correctly used four-hour data for naratriptan, they were not consistent in using four-hour data for the longer-lived triptans. Because of pharmacokinetic differences, longer-lived triptans, such as

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Efficacy (%)</th>
<th>Mean Recurrence (%)</th>
<th>AWP</th>
<th>Cost-Efficacy Ratio</th>
<th>Original Analysis</th>
<th>Current Analysis</th>
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<tbody>
<tr>
<td>Almotriptan</td>
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<td>2</td>
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<td>6</td>
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<tr>
<td>Sumatriptan</td>
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<td>33</td>
<td>$19.56</td>
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<td>7</td>
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<td>Zolmitriptan</td>
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<tr>
<td>Frovatriptan</td>
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<tr>
<td>Naratriptan</td>
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<td>$18.84</td>
<td>$38.23</td>
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<td>3</td>
</tr>
</tbody>
</table>

AWP = 2004 average wholesale price ($ per unit dose). The cost-efficacy ratio is defined as AWP/[efficacy × (1 – mean recurrence rate)].


† 1 = greatest cost-efficacy; 7 = least cost-efficacy.
naratriptan and frovatriptan, appear to have a longer mean time to headache relief that is compensated by a lower rate of recurrence. For these drugs, the use of four-hour data is more meaningful, and many clinicians factor these differences into their treatment decisions when they are considering patients’ individual migraine characteristics.

This latter point also underscores that accurate pharmacoeconomic modeling of triptan use will likely require stratifying patient populations by migraine parameters (such as speed of onset, severity, duration, and recurrence) that likely affect cost as well as treatment choices. Thus, for patients with rapid-onset but shorter-duration migraine attacks, a fast-acting triptan may be the logical treatment choice.

When symptoms are rapidly accompanied by nausea and vomiting, a non-oral formulation would be appropriate. In contrast, patients with long-duration migraines (such as menstrually related migraines) will likely require and benefit from a longer-acting triptan. Therefore, segmenting patients by their individual migraine characteristics allows clinicians to tailor therapy to successfully suit patients’ individual needs and can provide a more accurate framework for modeling costs.

In summary, formulary decisions should not be based on pharmacoeconomic modeling derived from a single artificial efficacy endpoint that is of limited utility in the broader true clinical setting. When making decisions about triptans, formulary committees might consider recurrence rate and other endpoints, including the incidence of headache relief at four hours after dosing and sustained pain-free response—defined as freedom from pain from two hours (or four hours) through 24 hours after dosing, with no recurrence and no repeated dose of the triptan or use of rescue medication. These endpoints reflect the true duration of action associated with triptan therapy and are perhaps at least as important as early post-dose measures in assessing the impact of—and, ultimately, the cost of—migraine treatment.

P&T committees can make better decisions regarding triptan use by stratifying patients according to clinical need and by then identifying the therapeutic options that are most clinically efficacious and cost-effective for addressing the specific needs of each migraine patient.

References

Sincerely,

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Authors’ Response

We agree with Dr. White’s insights on the concerns of using solely two-hour efficacy time point for triptans when conducting a pharmacoeconomic (PE) analysis for a P&T committee. However, the purpose of this case study was to introduce a systematic methodology for evaluating the available triptans as possible migraine treatments and to assist P&T committee members in the recommendation process using PE principles. Ours was a methodology paper intended to aid the formulary process when clinical information cannot clearly dictate the most optimal therapy. We used two-hour efficacy as the case example to illustrate the use of this methodology and to elucidate some PE principles in decision-making.

Further, the focus of our article was to demonstrate to P&T committee members how to incorporate cost-efﬁcacy analysis into the formulary decision-making process when evaluating a new agent that has only efficacy data from phase 3 clinical trials. As is often the case when a new product comes to market, effectiveness data from real-world utilization is not available. If the product is entering an established category, other agents in the category may very well have effectiveness data, but the new entrant is at a disadvantage. Under these conditions, the only common endpoint among all competitors in a category may be the primary endpoint from phase 3 clinical trials. Indeed, if a new triptan came to market today, two-hour efficacy may be the only common endpoint. A review of package inserts for all the triptan products clearly illustrates that this is the case.

It is clear that Dr. White’s letter has successfully detailed the process of cost-efﬁcacy, as demonstrated by his cost-efﬁcacy analysis. Dr. White chose efficacy rates and treatment recurrence as his outcome of interest, as opposed to
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the two-hour efficacy. The calculations followed the methodology illustrated by our article, but Dr. White used a different clinical endpoint that is relevant to his institution, as suggested by his letter. As expected, the analysis resulted in a different ranking that is suitable for his institution. However, other institutions may find adverse effects or other patient-specific responses as their primary clinical outcomes to measure.

Our article did advise caution in using this method for formulary review, as clinical endpoints should always precede economic findings. The article addressed the differences within the class of medications, such as the half-life of the drug, the rate of recurrence, adverse drug effects, and patient preferences. Ideally, P&T committee members would have the resources and the expertise to conduct a head-to-head cost-effectiveness study in their population, including total outcome (i.e., recurrence, complete relief, and side effects). Realistically, however, only a few groups would have the capability to conduct such extensive research prior to product approval.

The endpoint used in the article was chosen solely for illustrative purposes to aid in the formulary process when head-to-head outcomes trials are not available.

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