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HEADACHE: THERAPEUTIC CHOICES

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## Risk-benefit and cost-benefit ratio in headache treatment

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**Abstract** The cost–benefit and the risk–benefit ratios are two of the most relevant items in ongoing health organisation procedures. The choice of a new or an old therapeutic treatment depends on a number of factors and the evaluation of the cost, in terms of economics, but also in terms of quality of life and type of facilities necessary for one treatment are crucial criteria. Therefore, we have to consider in evaluating treatment strategies not only the activity of a drug in reaching the main end-

points, (i.e., pain free or headache relief) but also the safety and perception of safety by patients, and the cost effectiveness, including indirect costs compared with personal and social benefits. Because it is reasonable that a subgroup of migraine patients may have a clinically progressive disorder, studies should be necessary to assess strategies for migraine treatments.

**Key words** Cost benefit • Headache • Pharmacoeconomy • Impact • Risk factors

### Introduction

Headache disorders are ubiquitous, common, disabling and to a very large extent treatable in primary care. Migraine headaches affect 12% of the adult population worldwide and cause significant economic loss due to decreased workplace productivity. Although interactions between pharmacists and individuals with headache are common, few pharmacists receive adequate training regarding migraine therapy. There are several misconceptions that hinder effective care, such as that migraine is a vascular disease, triptans cause rampant cardiac-related morbidity and even mortality. The last decade's experience with triptans in more than half a billion people worldwide reveals a benign adverse-effect profile, particularly when taken early in an attack. Published reports and real-world experiences illustrate that these drugs do not

merit fears of triptan-induced cardiac consequences in appropriately selected individuals. Society's productivity loss due to migraine is measured in billions of dollars. Restoring a patient's ability to function normally is now recognised as the primary treatment goal, not merely relieving pain. Thus, the over-reliance on "pain killer" drugs such as butalbital-containing products and the continued underutilisation of migraine-specific drugs need to be addressed [1].

### Attack treatment

One of the main problems in treating migraine is how to treat attacks. In this situation it has been shown that stratified care is more efficacious and economic than step care strategies [2]. These results were confirmed later and a

stratified care strategy, which included zolmitriptan, was the dominant strategy and was unequivocally more cost effective from a societal perspective than either step care strategy. When the uncertainty around these means was considered, stratified care had the highest probability of being cost effective [3].

This approach was of high impact because of the common view to delay more potent (and often effective) drugs until verified failure of mild analgesics or less specific drugs.

A composite efficacy/tolerability end-point was used to compare the cost effectiveness, from the perspective of a US healthcare payer, of almotriptan and sumatriptan in the treatment of an acute migraine attack [4]. Almotriptan was economically superior to sumatriptan in the treatment of a migraine attack (US\$ 82 vs. 133 per attack, respectively).

Another study compared the direct medical costs of managing chest symptoms in patients treated for acute migraine with almotriptan or sumatriptan using an economic model [5]. The economic model of this study combined data from a randomised clinical trial that compared almotriptan with sumatriptan and data from a practice pattern survey of physicians. 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.

Adelman [6] compared the cost of packages of triptans and the number of pills for each package, and published a list of cost per pill as follows:

Current triptan retail prices (per unit) include: Amerge 1 and 2.5 mg, \$17.78; Axert 6.25 and 12.5 mg, \$16.31; Frova 2.5 mg, \$13.89; Imitrex 50 mg, \$14.96; Imitrex 100 mg, \$14.41; Imitrex Nasal Spray 20 mg, \$21.61; Imitrex SQ 6 mg, \$50.26; Maxalt 5 and 10 mg, \$15; Maxalt-MLT 5 and 10 mg, \$15; Relpax 40 mg, \$13.58; Zomig 2.5 mg, \$13.67; Zomig 5 mg, \$15.89; Zomig-ZMT 2.5 mg, \$13.67; and Zomig-ZMT 5 mg, \$15.89.

In conclusion, practitioners can optimise the use of healthcare dollars without compromising quality of care through awareness of cost-saving treatment strategies, as well as price variations among medications.

Also, the evaluation of cost-related side effects can be considered, and an economic model has been developed to estimate cost of chest-pain-related care in migraine patients receiving almotriptan 12.5 mg compared with those receiving sumatriptan 50 mg [7]. Among a cohort of 1390 patients, the incidence of chest-pain-related diagnoses increased significantly (43.6%) with sumatriptan, from 110 during the baseline period to 158 during the treatment period ( $p=0.003$ ). Aggregate costs for chest-pain-related diagnoses and procedures increased 33.1%, from \$22 713 to

\$30 234. Sumatriptan treatment was associated with a 3-fold increase in payments for services for painful respiration and other chest pain. The model predicted \$11 215 in direct medical cost savings annually per 1000 patients treated with almotriptan instead of sumatriptan.

In a recent article, the benefit of intranasal sumatriptan in adolescents was evaluated. The results of published papers are listed [8]:

1. The reference first-line drug therapy for migraine attacks in adolescents is a non-specific analgesic such as paracetamol or a non-steroidal anti-inflammatory drug like ibuprofen. Two specific analgesics are authorised for use in this setting in France, namely ergotamine and dihydroergotamine.
2. Nasal sumatriptan is the first triptan to be licensed for this age group in France.
3. Evaluation data includes three flawed placebo-controlled trials.
4. Effects were modest at best. Only one of the three trials showed that sumatriptan was more likely than placebo to give complete pain relief within two hours. The three trials fail to show that sumatriptan is effective against symptoms such as nausea and vomiting, photophobia and phonophobia.
5. The principal known adverse effects of sumatriptan are chest tightness, flushing and increased blood pressure.
6. In the only trial report containing relevant information, an unpleasant taste was the only adverse effect more commonly associated with sumatriptan than with placebo.
7. Postmarketing follow-up revealed a number of serious adverse effects, including stroke, myocardial infarction and loss of vision.
8. The packs containing 6 or 12 spray vials carry a risk of overuse and self-induced headache.
9. In practice, sumatriptan must not be used to treat migraine attacks in adolescents.

Dowson et al. [9] provide advice on what information should be taken into account by the physician before they consider switching from one triptan to another. Switching triptans can therefore only be recommended if the patient experiences problems such as lack of efficacy or intolerable side effects following repeated use of the initial triptan. The retrospective database study revealed that most patients who had their triptan switched were subsequently switched again during a 15-month review period, most usually back to their original triptan. Overall, switching a patient's triptan led to increased costs (analysed as costs of medication and the GP consultation) to the healthcare provider. These data indicate that patients should only be switched from one triptan to another for clinical reasons and not for perceived economic reasons, i.e., cost of the medication.

An economic evaluation of acute migraine attack treatment in Spain was evaluated recently [10], by a cost-effectiveness analysis, using 2003 prices, comparing almotriptan 12.5 mg, eletriptan 40 mg, naratriptan 2.5 mg, rizatriptan 10 mg, sumatriptan 50 mg, sumatriptan 100 mg, zolmitriptan 2.5 mg and zolmitriptan 5 mg. Rescue medication use and 24-h attack relapse rates were assessed. Thirty-eight clinical trials (19 872 patients) were used to assess triptan effectiveness.

At the end of the study eletriptan 40 mg and sumatriptan 50 mg showed the lowest costs per successfully treated attacks with 2 h anti-migraine response (€ 16.50 and € 17.44) and with 24 h sustained pain free (€ 31.47 and € 33.61), while the lowest costs per attack that was pain free at 2 h were observed with rizatriptan 10 mg (€ 21.36) and eletriptan 40 mg (€ 22.99). Considering the cost-effectiveness measurements assessed, eletriptan 40 mg was the most cost-effective triptan in the majority of economic analyses carried out.

The final impact of migraine cost and an analysis of this aspect was carried out by Stang in 2004 [11], who concluded that migraine families incur far higher direct and indirect healthcare costs than non-migraine families, with variation depending on which family member is the clinically detected migraineur.

### Prophylactic treatment

An increasing problem is the evaluation of the impact of prophylactic treatment on use and, therefore, the cost of this strategy in treating headaches. A retrospective administrative database study was conducted to measure the direct (pharmacy and medical) costs of migraine-related healthcare services in moderate-to-severe migraine patients treated with drug prophylaxis compared with migraine patients who are not treated with drug prophylaxis [12].

Thirty-nine percent of new triptan users received only 1 triptan claim during the 12-month follow-up period, accounting for 11.5% of the total triptan cost incurred by the health plan for this cohort. For new triptan users, triptan use in the first or second quarter was correlated with triptan use in the entire 12-month follow-up period ( $r=0.187$  and  $0.279$ , respectively). The mean migraine-related pharmacy cost per patient during the follow-up was \$871; however, continuous users had mean costs (\$1505) nearly 3 times the mean costs for new users (\$506,  $p<0.05$ ). The average treatment effect of drug prophylaxis in moderate-to-severe migraine patients was a decrease of \$560 (\$514–\$607) per patient per year in 1998–2001 dollars. High utilisers of migraine therapy can be identified early in treatment. Drug prophylaxis for

migraine is cost saving, and an intervention programme that increases the use of migraine prophylaxis in potential candidates could be cost beneficial.

Similar results were obtained by Adelman [13], who examined the prices of different medications. In spite of similar effectiveness, the costs of these treatments vary tremendously. Costs of migraine prophylactic medications vary within and between categories.

Certain strategies may be employed to reduce the cost of care:

1. choose generic options when possible;
2. maximise doses of medications so that single larger tablets are used instead of multiple smaller tablets;
3. employ pill splitting; and
4. choose medications that may also treat comorbid medical conditions such as hypertension or depression in order to reduce or eliminate secondary medications.

The anti-epileptic drugs (AEDs) are rapidly emerging as first-line agents for migraine prevention. The cost of these medications can be substantial. Only one AED (valproic acid) considered effective for migraine prevention is available as a generic in the USA. As a group, the costs for the AEDs are greater than the antihypertensives and antidepressants.

Generic beta-blockers and tricyclic antidepressants tend to be effective and inexpensive. The exceptions include long-acting propranolol, protriptyline and trimipramine, which are not available in generic form and are more expensive.

Among the newer antidepressant medications used for migraine prevention, bupropion, fluoxetine, fluvoxamine and paroxetine are available as generics. In cases where an extended-release form is only available as a non-generic and the short-acting formula is available as a generic (e.g., bupropion), the generics' lower cost per tablet must be balanced with the possible need for multiple dosing, increased adverse events, and decreased compliance.

Many other drugs are employed in headaches treatment, and some are used in chronic headaches (migraine derived or tension-type headaches), which have a high impact on quality of life.

Recently, to evaluate the efficacy of mirtazapine, 24 non-depressed patients with chronic tension-type headache were included in a randomised, double-blind, placebo-controlled, crossover trial. All patients had tried numerous other treatments [14].

A good example of a risk-benefit ration is the use of oral contraceptives (OCs) in migraine [15]. Is this intake associated with an increased risk of ischaemic stroke? Migraine *per se* is not a contraindication for OCs use; but all OCs, even those with low oestrogen content, are a major risk for venous thrombosis, particularly in women with hereditary thrombophilia.

Cardiovascular risk-assessment algorithms discussed elsewhere in this supplement suggest that patients at low risk (1 or no risk factors) of coronary heart disease can be prescribed triptans without the need for a more intensive cardiovascular evaluation. Conversely, patients with established coronary heart disease or coronary heart disease risk equivalents should not be prescribed triptans according to the current prescribing recommendations. Patients at intermediate risk (2 or more risk factors) of coronary heart disease require cardiovascular evaluation before triptans can be prescribed. Cardiovascular risk-assessment guidelines should be evaluated in the context of this limitation [16].

## Conclusions

Usually suggestions are set out for their optimal management, although many of these are necessarily based more

on expert opinion than on formal evidence, because clinical trials have covered only narrow areas of headache treatment [17]. Most people whose lives are adversely affected by headache disorders benefit from drug interventions, either acute or preventative, but other forms of treatment are always important and should never be overlooked. An important disorder is entirely iatrogenic: its recognition is crucial to its effective management, which requires medication withdrawal. Future research is needed not only into the mechanisms of headache causation, as a prerequisite for the development of better treatments, but also into public health aspects seeking an explanation of (and remedy for) the low priority given worldwide to headache-related healthcare despite the severe human and socioeconomic consequences.

Future epidemiological studies should focus on identifying patients who are at higher risk for progression and on assessing the impact of intervention strategies on disease progression [18].

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