Governments or other payers for health care, such as insurance agencies or employers, often think that spending on drugs is an area where savings can be made without detriment to patients [1]. They therefore make many attempts to contain these costs, by price negotiations, by restricting access to drugs though limited formularies, or by patient co-payments. These approaches are often integrated, e.g., selection of a drug for a formulary based on the negotiated price, and differential co-payments for patients based on the severity of the illness underlying the prescription, and perhaps whether the drug is prescribed as a generic or not.

A flaw with these approaches is that they focus on simple drug costs, when what should be of greater concern is the value of drug therapy, which is a function of its benefits as well as its costs [2, 3]. Health services after all do not exist to save money, but to use their limited resources to achieve the greatest health gain for the population. By these criteria, spending on drugs, which may for instance reduce the need for hospitalisation, may be a very efficient use of scarce resources. Drug costs should therefore not be considered in isolation without considering their benefits. Pharmacoeconomics assesses both the costs and benefits of any intervention; not to save money, but to make the costs and benefits explicit. This will inform health care providers to allow them to make better decisions about allocation of scarce resources. But pharmacoeconomics does not actually make these decisions, which may ultimately be based on availability of resources, local or national priorities and compassion as well as economic evaluation.
Pharmacoeconomics is simply health economics applied to drug therapy. Pharmaceutical companies increasingly include economics as part of their product evaluation at various stages, informing go/no go decisions on further development internally, but also at a later stage for external use, to support reimbursement applications or marketing [4]. Increasingly countries require such evaluations before a drug is approved for reimbursement – the so-called fourth hurdle for a new drug to leap after establishing safety, efficacy and tolerability [2].

This is well illustrated in considering drug treatments for migraine. Before the triptans, therapies for migraine were generally inexpensive, and migraine cost the health services very little – many patients did not even visit their doctors, knowing that there were only limited therapies available. In contrast, migraine cost patients (in the widest sense of the word – see below) a lot. Employers were also affected through lost productivity. The triptans increased health service costs substantially, but their benefits were also substantial. How were these drugs to justify this increase in costs for a non-life threatening condition, either in publicly funded health services dominated by attempts to reduce or contain costs, as often in Europe, or in employer funded systems as in the United States? As we will see, these perspectives can be quite different. Economic evaluations have provided evidence to support the use of these drugs in some settings, and encouraged reimbursement.

The concepts and language of health economics may be new to most researchers and practitioners in migraine and headache, but will be increasingly important in the future. This article is intended as an introduction to the basic concepts, methods and terminology of pharmacoeconomics. To illustrate the points in relation to migraine, I undertook a simple Medline search using terms “migraine” and “economics”. Many studies identified by this search and published since 2000 are used as examples here.

### Basic concepts and terminology

**Comparators**

Health economics is about making choices between options, and is fundamentally comparative. It weighs the costs and benefits of one intervention against those of another. So when we hear that “triptan x is cost effective”, our immediate response should be “compared to what”? We must then apply our clinical judgement as to whether the comparison is reasonable, or whether the study has been biased by deliberately choosing an unfavourable comparator. There is debate about what the ideal comparator should be – should it be the drug and dose most widely used for migraine (which may vary from country to country), or a “gold standard” comparator as defined in clinical trials? For instance in studies of a new triptan, is paracetamol a reasonable comparator? Or only another triptan? And might the results be biased by using unfavourable doses of a comparator?

This raises further questions about the sources of medical evidence used in economic studies. The economics can only be as good as the clinical evidence will allow. Studies should obviously be based on strong medical evidence, but more importantly on what actually happens in real world medical practice rather than in a clinical trial. But there is often little evidence available about what really happens in practice – how often do patients really return with a problem, as opposed to how often they are seen as a result of the protocol of a clinical trial. Furthermore, clinical trials may not describe subgroups of patients in whom the therapy may be especially effective or ineffective. In their evaluations, health economists are forced to make assumptions to fill these gaps in our knowledge. These assumptions can alter the results of a study completely, and so they should be reasonable and transparent, so that they can be challenged.

Any good economic study will challenge these assumptions itself, by varying them in a sensitivity analysis. A sensitivity analysis explores the extent to which a conclusion is dependent on factors which have been assumed or about which there is controversy, e.g., resource use or clinical benefits. For instance if a study shows costs that assumed a rate of relapse of migraine within 24 hours after a triptan was 30%, what happens if the relapse rate is actually 50%? A sensitivity analysis is essential in any good economic evaluation to confirm to the reader that the results of the evaluation are robust, and to clarify what the critical assumptions are.

There is another possible, more abstract, comparator: if the result of an economic evaluation across a range of different clinical areas can be presented in a uniform manner, e.g., cost per quality adjusted life years (QALY, see below), then we can set a crude threshold for how much we are willing to pay for a QALY. The English National Institute of Clinical Excellence (NICE) seems to operate to a loosely applied threshold of around £30 000 (€45 000) per QALY [5].

**Other concepts**

A number of other concepts are crucial in pharmacoeconomic evaluations and can be defined here.
**Efficiency:** This means deriving maximum benefit (i.e., health gain) from limited resources.

**Opportunity cost:** This is defined as the “benefit foregone when selecting one therapy alternative over the next best alternative”. What is of concern to us is not how much a health care intervention costs, but what we are giving up to use that intervention. For instance, if we spend €1 000 000 on triptans for migraine, then we have that much less to spend on any other treatment or condition. The opportunity cost of spending on triptans is our inability to provide other medical services. So we need to be able to justify our spending on triptans.

**Incremental analysis:** There is usually a current treatment for most conditions, with associated costs and benefits. Economic evaluations focus on the costs and the benefits of a new intervention over and above those of the current therapy. For instance, in migraine we already had treatments of limited effectiveness before triptans. The question therefore was not what were the benefits and costs of sumatriptan, but what were the added costs of sumatriptan over the costs of, say, paracetamol, and what extra benefits were obtained from using sumatriptan over those from using paracetamol [6]. In economic studies, the result is described as a ratio, the incremental cost effectiveness ratio (ICER).

\[
\text{ICER = Cost of intervention 1 (e.g., cost of sumatriptan+medical attendance costs+lost productivity)} - \text{cost of intervention 2 (cost of paracetamol+lost productivity, no medical costs)}
\]

\[
\text{Benefits of intervention 1 – benefits of intervention 2}
\]

**Methods of economic evaluation**

The various types of economic evaluations have a common structure in that they involve an explicit measurement of inputs (“costs”) and outcomes (“benefits”) around medical interventions.

Costs here means not just acquisition cost of a drug, nor even all monetary costs, but may include costs in the widest sense, including time lost from work, and distress. These costs might be:

**Direct**
Paid directly by the health service, including staff costs, capital costs, drug acquisition costs. These should be relatively easy to measure, at least in insurance based health care systems (like US health maintenance organisations or the German system) where there is an explicit charge for each service. It is much harder to estimate in capitation based systems like the Italian or UK health services.

**Indirect**
Costs experienced by the patient (or family or friends) or society; for example, these might include loss of earnings, loss of productivity, loss of leisure time, cost of travel to hospital etc. Many of these are difficult to measure, but should be of concern to society as a whole. They are certainly of concern to employers in relation to migraine.

**Intangible**
These are the pain, worry or other distress that a patient or their family might suffer. These may be impossible to measure in monetary terms, or even at all, and so are rarely considered in economic evaluations. Nevertheless, they are a concern for both doctors and patients.

The benefits we expect from an intervention might be measured in:

**“Natural” or “clinical” units**
E.g., reduction in numbers of episodes of migraine, or relief of headache at a defined end point. The issue of what is a valuable clinical measure of success in the treatment of migraine is very important here. For instance, many studies of triptans use outcomes such as improvement in migraine symptoms at two hours. This might be adequate for a licensing application, but may not represent the real concerns of migraine sufferers. Migraine sufferers might be more interested in more extensive outcomes, e.g., a composite outcome of improvement at one hour, pain free at two hours, with no recurrence at 24 hours after first dosing, and no need to use other rescue analgesics. The difference is that between efficacy and real clinical effectiveness. For example, a study reported success in 64–67% for eletriptan vs. 50–53% sumatriptan for the first “efficacy” outcome described above, but only 16–17% vs. 14–16% for the second more rigorous “effectiveness” outcome [7]. For a health economic study, the really useful clinical outcome is what is required. Unfortunately, many studies do not report these more useful outcomes.

**“Utility” units**
Utility is an economist’s word for satisfaction or sense of well being, and is an attempt to evaluate the quality of a state of health, and not just its quantity. Such utility measurements are therefore based on some measurement of quality of life, i.e., the physical, social and emotional aspects of the patient’s well-being, which are not readily measured in physical terms. This is the converse of the
intangible costs discussed above. The methods of measurement of quality of life are controversial, but are usually based on standardised self-completed questionnaires. Specific tools are available for measuring quality of life in migraine sufferers [8, 9], but so far have been seldom used in economic evaluations [10].

The QALY is a widely used utility measure which attempts to summarise quality and quantity of life. It multiplies years of life by quality of life. For instance, if one’s quality of life with angina is measured or judged to be 80% of that of a similar patient without angina, then a year of life for that angina patient would be 0.8 QALY. The patient’s life expectancy is 4 years. Imagine a treatment that could restore that patient to full quality of life at a cost of €50,000. The health gain is 0.2 QALY x 4 = 0.8 QALY, and the cost per QALY would be €50,000 / 0.8 = €62,500. Suppose as well as relieving the angina, the treatment also extended the patient’s life expectancy to 6 years: now the health gain is (0.2 x 4 = 0.8) + (2 x 1.2 = 2.4) or 3.2 QALY, and the cost per QALY is €50,000 / 3.2 = €15,625.

Note that most of the health gain in the second part of this example comes from the extension of life rather than improving its quality, and this may be part of the reason why this is little used in migraine studies. The QALY is relatively seldom used in migraine studies: the emphasis on most economic evaluations in migraine has been on acute treatment, like triptans. The QALY is more likely to be used in relation to chronic treatments in migraine, even without any extension of life.

**Associated economic benefit**

This is usually measured in money, which is a useful common denominator allowing comparisons across different disciplines. This measure includes, for instance, the economic benefits of returning someone to work by early termination of a migraine attack. It is a widely used measure in migraine studies in systems such as the US where employers are responsible for paying in part for health services and may choose to include or not include triptans in the formulary they fund. In contrast, publicly funded health services avoid this as a measure of benefit because it undervalues treatment for the elderly or for the unemployed.

**Basic methods: common types of study**

These costs and benefits give rise to the four commonly encountered types of economic evaluation: (a) cost minimisation analysis (CMA); (b) cost effectiveness analysis (CEA); (c) cost utility analysis (CUA); and (d) cost benefit analysis (CBA).

**Cost minimisation analysis**

This involves measuring only costs, usually only to the health service, and is applicable only where the health benefits are identical and need not be considered separately. An example would be a decision to prescribe generically instead of by brand name which should achieve the same effect at less cost, or two triptans with identical effects but different costs. For example, one recent study from an American point of view described how by being aware of simple cost-saving treatment strategies, as well as price variations among medications, doctors could be more efficient without compromising quality of care [11]. CMA cannot be used to consider different programmes or therapies with different outcomes.

**Cost effectiveness analysis**

The term cost effectiveness is often used loosely to refer to any economic evaluation, but should properly refer to a particular type, in which the health benefit can be defined and measured in natural units and the costs are measured in money. For example, one study looked at eletriptan vs. sumatriptan using the more complex outcome measure described above [7]. Another used another composite endpoint of sustained freedom from pain and no adverse effects to compare almotriptan and sumatriptan [12]. The same authors published an almost identical comparison of almotriptan and rizatriptan [13]: both studies were funded by the manufacturers of almotriptan and both concluded that almotriptan was the more cost effective. Three more studies used meta-analyses of studies to compare indirectly a range of different triptans, but used the less rigorous two hour outcome [14–16]. This method therefore compares therapies with similar outcomes (although perhaps different success rates). CEA is the most common form of economic analysis in the migraine literature; it is popular with pharmaceutical companies who want to persuade decision makers to include one triptan rather than another in their formulary. CEA does not allow comparisons to be made between two totally different areas of medicine, or even within the same area of health care where different outcomes measures have been used.

**Cost utility analysis**

This is a variety of cost effectiveness study that uses a utility based outcome, usually the QALY. One of its virtues is
that in theory its endpoint (the QALY) can be compared across different interventions – e.g., what is the cost per QALY of a treatment for migraine as opposed to a treatment for angina? If the cost per QALY for the angina therapy is lower, then it would be a better use of resources for the health service to invest in this than a migraine therapy. CUA can therefore in theory look at more than one area of medicine, but in practice this is not so easy as the QALY is not a well defined fixed unit, transferable from study to study. This is nevertheless the preferred approach used by the NICE, which uses a threshold as described above.

There are few studies in headache or migraine of this type, perhaps because it is better suited to chronic illness and treatments rather than immediate treatments like triptans, and therefore attracts less industry sponsorship [10]. One study evaluated the cost effectiveness (actually cost utility) of acupuncture in treating chronic headache, based on a clinical trial where patients were randomised to receive acupuncture and usual care, or usual care alone [17]. The costs for the acupuncture group over the whole year were greater – €600 vs. €325, mostly due to the acupuncturists’ fees, but the benefits were greater also – an additional 0.021 QALY. The ICER therefore was €275/0.021 QALY, or €13,095 per QALY gained, well below the NICE threshold.

Cost benefit analysis

Here, the benefit is measured as the associated economic benefit of an intervention, and hence both costs and benefits are expressed in money. CBA may ignore many intangible but very important benefits, which are difficult to measure in money terms, e.g., relief of anxiety. CBA may also seem to discriminate against those in whom a return to productive employment is unlikely, e.g., the elderly or the unemployed.

However this analysis is that it may allow comparisons to be made between very different areas, and not just medical, e.g., cost benefits of expanding university education (benefits of improved education and hence productivity) compared to establishing a migraine service (enhancing productivity by returning patients to work). This approach is not widely accepted for use in health economics in Europe, although it is used regularly in US studies of the benefits of anti-migraine therapies not just for patients but particularly for employers, by reducing lost productivity [6, 18, 19].

Further points

There are two further points that require definition: perspective and discounting.

Perspective

This asks from whose point of view is the study conducted – from that of the health service, where only direct costs are considered, or societal where indirect costs are studied as well. An employer’s perspective in the US might include (as direct costs) the added cost of including a triptan in the drugs reimbursed as part of an employee’s health care benefits paid in part by the employer, and (as an indirect cost) lost productivity, but not lost leisure time, which is of no interest to an employer. Some costs of illness studies suggest that lost productivity accounts for two-thirds of the overall costs of migraine [22, 25]. For publicly funded
health services, the societal perspective is generally considered the most appropriate, but a health care manager with a limited budget might be tempted to ignore the societal view and consider only the costs that fall on his own budget. A study of triptans in migraine that took the health service perspective only, might suggest that sumatriptan in migraine (a very high cost drug in an area which previously cost the health service very little) was highly undesirable as reductions in non-drug medical costs are unlikely to fully offset the high drug cost [10], but a study taking a societal or employers’ perspective might come to the opposite conclusion [26].

Discounting

There is often a difference in timing between the investment of health service resources and gaining the benefits (e.g., antihypertensives now to prevent a stroke in ten years time). Therefore we must discount future spending etc. to try to equalise the effects of inflation and health and financial preferences over a long period. In migraine studies looking at triptans, the benefits and the costs are quite immediate, and so discounting does not usually arise.

Limits of pharmacoeconomic evaluation

Many problems limit our ability to use health economics. The whole process may be thought open to bias [27] from choice of comparator drug, the assumptions made where accurate data is lacking and in the selective reporting of results. In migraine, most studies are funded by the manufacturers of these drugs, who may clearly have biases: in general they only fund studies of expensive acute treatments, particularly the triptans, and there is very little consideration of less expensive long-term prophylactic therapies or non-pharmacological interventions. No industry funded study reported that the sponsor’s drug was less cost effective than a comparator. It is clear that companies view these studies as part of their marketing. These issues are not unique to migraine – in the past such publication biases of only favourable results were standard [28]. One further danger is that the conduct of studies may encourage more money into the evaluated areas (e.g., expensive triptans), and away from other important but under-evaluated areas (e.g., long-term prophylactic therapies): this has certainly happened with the UK NICE [1, 2]. Only recently has a large body of such studies funded by public sources and less prone to bias become available.

In contrast to clinical studies, where the results are usually universally applicable, health economic studies are usually applicable only to the health service in which they are undertaken. This is because patterns of usual care, drug costs and rates of reimbursement differ between countries, and because of what is the most appropriate perspective [16]. For instance, it may be worthwhile for an employer to fund an expensive drug that avoids a worker taking time off work and visiting a doctor (both costs to an employer) in the US, but not for an Italian health service which has to pay extra for the drug but not for the doctor’s visit, which is covered already by existing capitation payments, nor for the lost productivity or other indirect costs [10]. So far, the large majority of economic evaluations concerning migraine have come from the US.

Conclusions

This has been a brief introduction to the basics of pharmacoeconomics. The interested reader is referred to textbooks such as that listed in further reading. The whole area remains controversial, but as long as medical practice remains limited by scarce resources, we will need a means to help us judge what is the most efficient and best use of these resources. Pharmacoeconomics has the potential to be a useful tool in this.

Funding This work had no specific funding. The author undertakes economic and other evaluations on behalf of the UK NICE but has no other competing interests to declare.

Further reading Walley T, Haycox A, Boland A (eds) (2004) Pharmacoeconomics. Churchill Livingstone, Edinburgh

References

1. Mossialos E, Mrazek M, Walley T (eds) (2004) Regulating pharmaceuticals in Europe: striving to improving efficiency, quality and equity while containing costs. Open University Press, London
2. Walley T, Haycox A, Boland A (eds) Pharmacoeconomics. Churchill Livingstone, Edinburgh
3. Walley T (1995) Drugs, money and society. Br J Clin Pharmacol 39:343–345
4. Langley P (2004) Focusing pharmacoeconomic activities: reimbursement or the drug life cycle? Curr Med Res Opin 20:181–188
5. Raftery J (2001) NICE: faster access to modern treatments? Analysis of guidance on health technologies. BMJ 323:1300–1303
6. Lofland JH, Kim SS, Batenhorst AS, Johnson NE, Chatterton ML, Cady RK, Kaniecki R, Nash DB (2001) Cost-effectiveness and cost-benefit of sumatriptan in patients with migraine. Mayo Clin Proc 76:1093–1101
7. Wells N, Hettiarachchi J, Drummond M, Carter D, Prapia T, Pang F (2003) A cost-effectiveness analysis of eletriptan 40 and 80 mg versus sumatriptan 50 and 100 mg in the acute treatment of migraine. Value Health 6:438–447
8. Terwindt GM, Ferrari MD, Tijhuis M et al (2000) The impact of migraine on quality of life in the general population; the GEM study. Neurology 55:624–629
9. Turner-Bowker DM, Bayliss MS, Ware JE Jr, Kosinski M (2003) Usefulness of the SF-8 Health Survey for comparing the impact of migraine and other conditions. Qual Life Res 12:1003–1012
10. Caro JJ, Getsios D (2002) Pharmacoeconomic evidence and considerations for triptan treatment of migraine. Expert Opin Pharmacother 3:237–248
11. Adelman JU, Adelman LC, Freeman MC, Von Seggern RL, Drake J (2004) Cost considerations of acute migraine treatment. Headache 44:271–285
12. Williams P, Reeder CE (2004) A comparison of the cost-effectiveness of almotriptan and sumatriptan in the treatment of acute migraine using a composite efficacy/tolerability end point. J Manag Care Pharm 10:259–265
13. Williams P, Reeder CE (2003) Cost-effectiveness of almotriptan and rizatriptan in the treatment of acute migraine. Clin Ther 25(11):2903–2919
14. Adelman JU, Belsey J (2003) 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 9:45–52
15. Reeder CE, Steadman S, Goldfarb SD (2002) Economic comparison of oral triptans for management of acute migraine: implications for managed care. Am J Manag Care 8[Suppl]:S80–S84
16. Belsey JD (2004) Cost effectiveness of oral triptan therapy: a trans-national comparison based on a meta-analysis of randomised controlled trials. Curr Med Res Opin 20:659–669
17. Wonderling D, Vickers AJ, Grieve R, McCarney R (2004) Cost effectiveness analysis of a randomised trial of acupuncture for chronic headache in primary care. BMJ 328:747
18. Gerth WC, Sarma S, Hu XH, Silberstein SD (2004) Productivity cost benefit to employers of treating migraine with rizatriptan: a specific worksite analysis and model. J Occup Environ Med 46:48–54
19. Biddle AK, Shih YC, Kwong WJ (2000) Cost-benefit analysis of sumatriptan tablets versus usual therapy for treatment of migraine. Pharmacotherapy 20:1356–1364
20. Lipton RB, Stewart WF, Scher AI (2001) Epidemiology and economic impact of migraine. Curr Med Res Opin 17[Suppl 1]:s4–s12
21. Burton W, Conti D, Chen C, Schultz A, Edington D (2002) The economic burden of lost productivity due to migraine: a specific worksite analysis. J Occup Environ Med 44:523–529
22. Edmeads J, Mackell JA (2002) The economic impact of migraine: an analysis of direct and indirect costs. Headache 42:501–509
23. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML (1999) Burden of migraine in the United States: disability and economic costs. Arch Intern Med 159:813–818
24. Pesa J, Lage MJ (2004) The medical costs of migraine and comorbid anxiety and depression. Headache 44:562–570
25. Smith DG (2003) Cost-effectiveness of migraine treatment: a commentary. Value Health 6:438–447
26. Cull R, Wells N, Miocevick M (1992) Economic costs of migraine. Br J Med Econ 5:103–115
27. Drummond MF (1992) Economic evaluation of pharmaceuticals: marketing or science? Pharmacoeconomics 1:8–13
28. Sacristan JA, Bolanos E, Hernandez JM, Soto J, Galende I (1997) Publication bias in health economic studies. Pharmacoeconomics 11:289–292