Jenny Berg · Stockholm Health Economics, Stockholm, Sweden

Economic evidence in migraine and other headaches: a review

Introduction

Headache encompasses a range of disorders, generally characterised by recurrent episodes of head pain and associated symptoms. While most people are affected by headache at some point in their lives, the varying types of headache are associated with differing epidemiological and economic data. The most common primary headaches are tension-type headache and migraine, for which a lifetime prevalence of 78 and 16% have been reported, respectively [1]. Other primary headaches, such as cluster headache, are quite rare, and usually affect less than 1% of the population. Secondary headaches include those related to systemic infections, fasting, head trauma, drug-induced headache, vascular disease and non-vascular intracranial disease. The different headaches can be classified according to the 1988 criteria of the International Headache Society (IHS), revised in 2004, which provide an established and tested framework for diagnosis.

Table 1

ICD-10 classifications for headache

Disease	ICD-10 classification
Migraine	G43
Other headache symptoms	G44
Headaches not included elsewhere	R51

Tension-type headache is the most common form of headache and is generally of mild to moderate intensity, non-throbbing and bilateral. Depending on the symptom severity, this type of headache may lead to reduced capacity for work and other activities. In contrast, migraine headaches are usually moderate to severe in intensity, of a throbbing quality and unilateral. Common symptoms of migraine include nausea, photophobia, phonophobia, vomiting and tiredness. Physical activity typically worsens the headache, and patients tend to be incapacitated until the migraine attack is over.

Tension-type headache and migraine both result in direct medical and indirect costs. Since these disorders particularly affect adults in their most productive ages of around 20-50 years [1], the related productivity loss leads to high costs to society. To date, most economic evaluations have been conducted for migraine only, which means that the data presented in this article will focus on this form of headache.

Despite the relatively high prevalence, a considerable proportion of headache sufferers have never consulted a physician about their symptoms and, upon presentation, may not necessarily receive a correct diagnosis or effective treatment [2]. Therefore, evaluations of the costs of migraine may underestimate the extent of its burden to society. Important future goals are thus to raise the awareness of migraine and improve relevant management strategies. In this context, a comprehensive assessment of the economic impact of migraine and other headaches in Europe can provide valuable information for prioritising research on a national and regional level.

There have been several studies looking at different cost aspects related to migraine, nearly all of which are based on the IHS classification criteria. However, only very few studies have covered all relevant cost types, and although more studies have been conducted on the productivity losses resulting from migraine than on the direct costs, many of these do not assign monetary values to their findings. While a number of reviews of existing studies have been performed, these were conducted some years ago and do not include the latest available data. Moreover, no study to date has taken a European perspective, which is becoming increasingly important with the closer collaboration between countries on a healthcare level. There is also a need for an assessment of the methodological issues in deriving cost-of-illness estimates for headache and to highlight important areas for future research.

In the light of currently available research, this paper aims to provide a comprehensive review of the economic data available on migraine, to allow an estimation of the cost of migraine to society in Europe as part of a separate paper. Furthermore, the study will highlight issues related to cost evaluations in migraine and needs for further research and analysis.

Table 2

Overview of published cost studies for migraine in Europe, 2003

Study	Michel et al. 1999 [11]	Michel et al. 1993 [10]	Neubauer and Ujlaky 2002 [14]	Göbel et al. 2003[a] [5]	van Roijen et al. 1995 [8]	Pop et al. 2002[a][6]
Country	France	France	Germany	Germany	Netherlands	Netherlands
Year of costing	1998	1990	2000	1995	1988	2002
Costs included	Indirect costs related to work absence	Direct medical costs	Direct medical and indirect costs	Direct inpatient costs	Direct medical and indirect costs, impact on unpaid productivity; Euro-QoL parameter	Indirect costs
Perspective	Society	Society	Society	Payer	Society	Specific employer
Methodology	Bottom-up, population-based (18years+) prospective study over 3 months	Bottom-up, population-based (14years+) retrospective study over 6 months	Top-down for direct costs (national registries and statistics), indirect cost estimates based on secondary data from statistics and literature	Top-down, using extract for chronic headaches (ICD-9) from health insurance fund in one federal state	Top-down for direct costs: national registries for inpatient care and large surveys for ambulatory care, estimates of outpatient visits based on hospital study and neurologist interviews Bottom-up for indirect costs: retrospective population-based (12years+) study using 2-week and 3-month recall	Bottom-up, retrospective study using 4-week recall with employees of manufacturing company Included both migraine and tension-type headache patients
Sample size	385 migraine patients, 313 controls	340 migraine patients	n/r[b]	n/r	436 migraine patients, 585 controls (for QoL and unpaid labour only)	1082 respondents
Stratification	None	None	None	None	Indirect costs by gender	None

[a] *Study excluded from analysis due to availability of better alternative estimates for relevant country*
[b] *n/r=not relevant*

Objectives

The overall objective of this study is to perform a cost-of-illness analysis for migraine and other headaches in Europe. The analysis is based on published data available for any of the 25 member of the EU as well as the three EFTA countries Norway, Iceland and Switzerland.

The primary objectives of the present study are to:

- Gather existing economic data on migraine and other headaches in Europe to assess data availability
- Increase awareness of the burden of migraine and other headaches
- Highlight the potential benefits of increased investments in research to reduce the burden of migraine and headaches

Secondary objectives of the present study are to:

- Identify shortcomings of presently available data sources and studies on the cost of migraine and other headaches in Europe
- Suggest improvements and identify needs for further studies in the area

Materials and methods

Definition of migraine

Headaches are classified according to the IHS criteria, which were established in 1988. Most economic evaluations are based on these criteria, although the available studies mainly focus on migraine. The definitions used in the International Classification of Diseases, 10th revision (ICD-10) are also structured according to these different headache types. The ICD-10 classifications related to headache are summarised in **Table 1**.

As mentioned above, most economic evaluations focus only on migraine and are generally based on the IHS classification criteria. Exceptions include the study by Blau and Drummond [3] , which used some data from national surveys conducted prior to the establishment of the IHS criteria to calculate direct costs for migraine in the UK. Similarly, the Swedish study by Björk and Roos [4] covered patients with migraine, cluster headache and those who had been diagnosed by a physician as having migraine, but did not fulfil the IHS criteria.

A study by Göbel et al. [5] assessed the financial impact of inpatient treatment of chronic headache disorders based on the ICD-9 classification in 1995. Furthermore, a company-based study on productivity loss conducted by Pop et al. [6] also covered tension-type headaches. However, due to the limited perspective of these two studies, they have not been included in the overall cost review.

No cost-of-illness study that met the set criteria for tension-type headache could

Table 3

Overview of published cost studies for migraine in Europe, 2003 (cont.)

Study	Lainez et al. 2003 [9]	Björk and Roos 1991 [4]	Cull et al. 1992 [16]	Blau and Drummond 1991 [3]	Clarke et al. 1995[a] [17]
Country	Spain	Sweden	UK	UK	UK
Year of costing	1995	1990	1992	1989	1995
Costs included	Direct and indirect costs	Direct medical and indirect costs	Indirect costs	Direct medical costs (and some top-line indirect cost estimates, which were not included in this study)	Indirect costs
Perspective	Workplace setting	Society	Society	Society	Specific employer
Methodology	Bottom-up for indirect costs: Retrospective study covering 12 months with employees from 11 companies representative of Spain's production sector Methodology for direct costs not available	Top-down for direct costs (national statistics and registries) and indirect costs (secondary data from statistics and literature). NB: migraine definition is wider than that used by IHS	Bottom-up, population-based (working adults) retrospective study based on 3-month and 12-month recall	Top-down approach using national registries and statistics. Some data generated prior to establishment of IHS criteria	Bottom-up, retrospective study with 3-month recall for productivity and work loss
Sample size	577	*n/r*[b]	347	*n/r*	158
Stratification	None	Some indirect costs by gender	Indirect costs by gender	None	None

[a] *Study excluded from analysis due to availability of better alternative estimates for relevant country*
[b] *n/r=not relevant*

be identified. A Danish study by Rasmussen et al. [7] analysed the impact of migraine and tension-type headache on medical resource use and sickness absence, but did not apply any cost estimates to the findings. Nevertheless, the study facilitates a ballpark comparison between the burden of migraine and tension-type headache and is referred to later.

Review methodology

To identify relevant cost studies, a comprehensive search of relevant electronic journal databases was conducted. The main sources for economic evaluations of migraine were PubMed (Medline) from 1966 to present and the OHE's Health Economic Evaluations Database (HEED), March 2003 version. A limited search was also conducted on the Internet and in hard-copy publications. The reference lists of obtained articles were searched further for potentially relevant publications, including papers published by national research institutes. Where necessary, authors were contacted to ask for underlying data, e.g. for quality of life (QoL) measurements; however, this produced only a very limited response.

Search terms used were migraine/headache, cost and cost of illness, in combination with Europe or single European countries. A selective search for QoL studies using generic instruments was also performed on PubMed to gain an overview of the intangible costs related to migraine. While the search language was English, where relevant, articles in French, German, Italian and Spanish were also included in the review.

Search results were screened by the author for relevance according to the title and abstract, after which the selected articles were reviewed in full. Initial inclusion criteria for the review were solely that the study should contain an evaluation of the direct or indirect costs of migraine. This yielded 11 cost studies for migraine in Europe. Upon closer review, three of these studies were excluded from the analysis, since they did not use a societal perspective, but considered costs only from an employer or a payer perspective. In all these cases, an alternative study using a broader approach was available for the country. For Spain, only one study analysed the costs of migraine in a workplace setting. However, since the study used a sample drawn from 11 companies which were to represent the Spanish production sectors, the results can be applied more widely than if the study had only been performed in one selected company.

For data on the QoL impact of migraine, five European studies were identified during the limited search that had used the Short-Form 36 (SF-36) questionnaire. In addition, the cost study by van Roijen et al. [8] included data based on the Euro-QoL instrument. For three of the SF-36 studies, the numerical data were not contained in the article. Although the authors were contacted for possible access to the underlying data, these were not available for this review.

Methodology for estimating the annual cost per patient

The eventual output of this research is an estimate of the yearly cost of migraine in Europe and the individual countries, based

Table 4

Annual direct medical costs (€) per migraine patient in six European countries, scaled to 2003 prices

Country	Total direct medical costs	Hospitalisation	Drugs	Outpatient care	Medical procedures and devices	Reference
France	66	18	13	20	14	Michel et al. 1993 [10]
Germany	28	4	13	11	n/a	Neubauer and Ujlaky 2002 [14]
The Netherlands	67	2	6	58	1	van Roijen et al. 1995 [8]
Spain[a]	32	n/a	n/a	n/a	n/a	Lainez et al. 2003 [9]
Sweden	30	3	2	25	n/a	Björk and Roos 1991 [4]
UK	12	1	8	3	n/a	Blau and Drummond 1991 [3]

[a]*Cost estimate for Spain refers to working population*

Table 5

Annual indirect costs (€) per migraine patient in 6 European countries, scaled to 2003 prices

Country	Total indirect costs	Short-term absence from work	Reduced productivity at work	Reference
France	n/a	334	n/a	Michel et al. [11]
Germany	847	490	356	Neubauer and Ujlaky [14]
The Netherlands	269	131	138	van Roijen et al. [8]
Spain	487	n/a	n/a	Lainez et al. [9]
Sweden	79	28	50	Björk and Roos [4]
UK	506	152	365	Cull et al. [16]

on existing published materials. The cost estimate is based on an annual cost per patient in combination with prevalence rates per country. For published studies, the prevalence rates in the relevant article were used in combination with population figures from national statistics offices for the year of costing to generate costs per patient from national estimates. As far as possible, the cost data included all relevant cost items for migraine, i.e. direct medical and indirect costs.

For countries where cost studies exist, the preferred methodology consists of prevalence-based cost estimates and a bottom-up approach to ensure full capture of all relevant cost items. The cost-of-illness estimates are generally based on opportunity costs, with indirect costs mostly drawing on the human capital approach. Where possible, the cost data is further disaggregated by gender; in the case of migraine, cost estimates for different age groups and disease severity were not available from the literature. All costs throughout this paper have been adjusted to a European standard using the Price Level Index for the EU from 2001.

Results

Review of available literature

A number of population-based studies have covered the resource use by migraine patients or the productivity loss associated with the condition, but without assigning a monetary value to these findings. Based on the research process described above, a total of 11 cost-of-illness studies for migraine in Europe were identified, including France, Germany, The Netherlands, Spain, Sweden and the UK. Of these studies, four did not use a societal perspective for their analysis; three of these, for which an alternative study was available, were excluded from further analysis. The study by Lainez et al. [9] was included despite its focus on costs in the workplace setting, since it was the only available data source for Spain. The studies and their key characteristics are summarised in **Tables 2 and 3**.

The studies use a mixture of methodologies and costs, with only four of the studies containing estimates for both direct medical and indirect costs. Except for the study by Michel et al. [10], all direct cost estimates were calculated using a top-down approach, which has the advantage of not double-counting any costs and of relating directly to total health-care expenditure; however, the potential drawback is that some costs may be excluded in this way. Most studies were conducted before 1995. This means that direct costs are likely to be underestimated when scaled up to current prices, since the triptans, a new and relatively expensive drug class used for migraine, had not yet been launched or only been on the market for a few years when these studies were conducted.

Seven of the studies used a bottom-up approach for deriving indirect costs, while only one study, [10], used this approach to estimate direct medical costs. With this approach, it is important to ensure a representative sample of the total patient population; therefore, those studies which sampled only from specific work settings were mostly excluded from further analysis. In general, the population-based studies used retrospective questionnaires to estimate the impact of migraine on work absence and productivi-

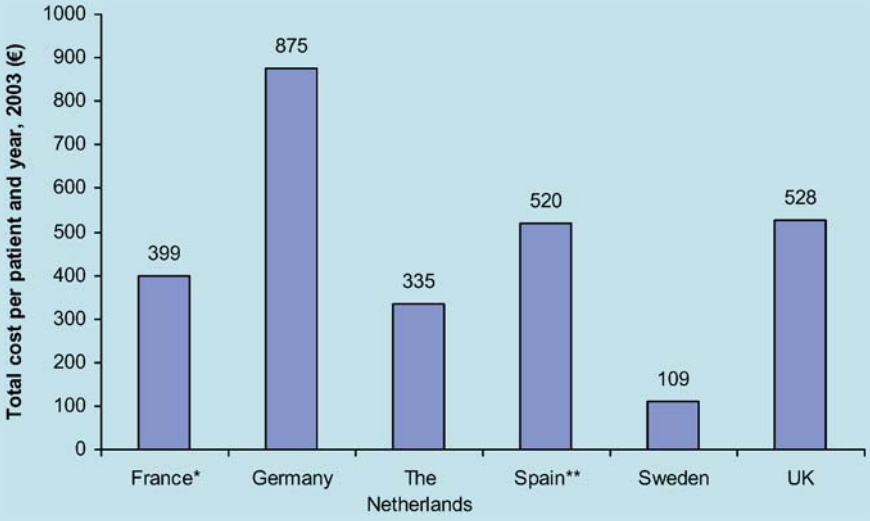

Fig. 1 ◀ **Total annual costs of migraine per patient in 6 European countries, scaled to 2003 prices**
NB: *Total estimate for France does not include costs of reduced productivity at work
****Cost estimate for Spain refers to working population**
Sources: Michel et al. [10, 11], Neubauer and Ujlaky [14], van Roijen et al. [8], Lainez et al. [9], Björk and Roos [4], Blau and Drummond [3] and Cull et al. [16]

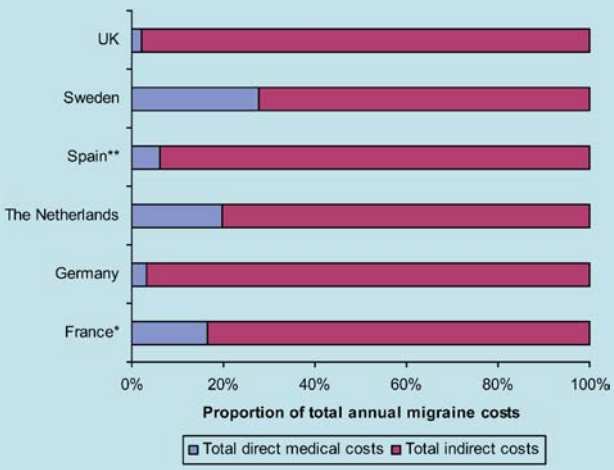

Fig. 2 ▲ **Direct and indirect costs as a proportion of total annual migraine burden**
NB: *Indirect cost estimate for France does not include costs of reduced productivity at work
****Cost estimate for Spain refers to working population**

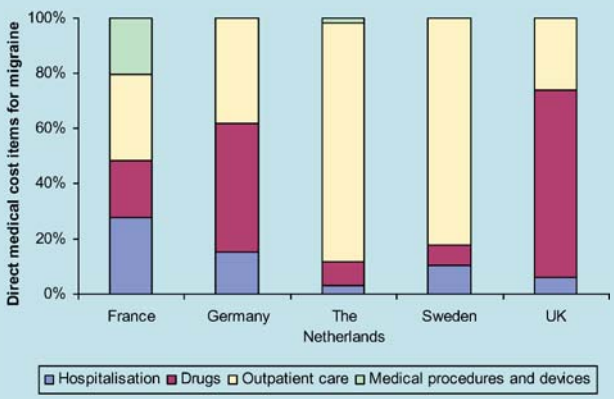

Fig. 3 ▲ **Components of direct medical costs for migraine across five European countries**

ty. The only exception to this is the 1999 study by Michel et al. [11], where a total of 698 patients were followed prospectively over a period of 3 months. The key advantage of the latter layout is that it avoids the introduction of recall bias, since it has been shown that respondents systematically tend to under-report their absenteeism because of self-presentation processes [12]. Finally, only two of the population-based studies used control groups to some extent, which allow more specific allocation of productivity losses to migraine compared to studies without controls, as these may attribute lost productivity to migraine even when other causes were present.

With regards to the data output, no study was identified which stratified costs by age or disease severity. A likely reason for the lack of studies looking at the cost by disease severity is the fact that there is no universally established method for defining different severity levels in migraine. While a number of scales exist, such as the MIDAS questionnaire, which assess the impact of migraine on patients' lives, there is no single aggregate measure of relevant clinical features that could be used to measure the severity of attacks [13]. Some QoL studies (e.g. Lipton et al. [20]) have classified severity according to the number of (work)days affected by migraine per month; however, this approach has not yet been applied to cost assessments. Thus, stratification by severity and age constitute potentially interesting areas for future research.

The cost-of-illness studies identified for migraine in Europe are summarised in **Tables 2 and 3**, together with key descriptive characteristics.

Existing cost estimates for migraine in selected European countries

On average, a migraine patient in Western Europe consumes health-care resources and leads to a production loss associated with their disorder worth € 461 per year. As can be seen in **Fig. 1**,

the estimated annual cost per migraine patient varies substantially across countries, from € 109 in Sweden to € 875 in Germany. A reason for this wide range lies in different methodological approaches and, importantly, in different years of costing. Another factor contributing to cross-country variations is differences in the national health-care systems, where, for example, cost constraints may lead to a focus on less expensive management strategies in some countries. However, due to the significant variations in methodology and years of reference, it is difficult to draw conclusions about the specific impact of health-care regulations on the costs of migraine.

The German study is the most recently conducted cost-of-illness analysis, as it uses data from 2000. In contrast, the Swedish estimate is based on cost data from 1990, and the authors themselves described the results as the "minimum costs for migraine". The Swedish study also used a wider definition of migraine than that used by the IHS, with "full migraine" constituting definitive migraine with or without aura and cluster headache, and "borderline migraine" with and without aura including cases diagnosed by physicians as having migraine but without meeting the IHS criteria. Since it is not clear which type of patients is covered by the cost data, only the prevalence rate of "full migraine" was used to derive the above cost per patient. Finally, both the German and the Swedish study used a top-down approach for indirect costs, which may have led to an underestimation of these costs. On the other hand, the German study used gross domestic income (GDI) rather than average salary levels as a basis for calculating indirect costs, which could lead to an overestimation of these costs.

The cost estimate for France is based on two separate studies on direct costs and indirect costs, where the indirect cost study only analysed the costs of work absence. Therefore, the actual cost per patient will be higher than € 399 per year. For the Spanish study, the cost estimates are based on a sample from the working population only, which means that, overall, the average cost per migraine patient is likely to be lower.

The studies by van Roijen et al. [8] and Cull et al. [16] used different recall periods as part of the patient interviews on productivity loss. van Roijen et al. used 2-week and 3-month recall periods, while Cull et al. used 3-month and 12-month periods. In the former study, the 2-week recall period, which was deemed to be more reliable by the authors, produced the more conservative estimates. In the UK study, by contrast, the longer recall period of 12 months led to the more cautious cost estimates. For the purposes of a cross-European comparison, the more conservative estimates were chosen for both countries.

Indirect costs account for the majority of migraine's burden to society. Across the six analysed countries, the average proportion of total costs accounted for by direct costs was 13%. The share accounted for by work absence and reduced productivity ranges from 72% in Sweden to 98% in the UK, as illustrated in **Fig. 2**. As noted above, the variation across countries can mostly be explained by differences in methodology, which are discussed in more detail in the relevant sections below.

Direct costs

Direct costs consist of medical and non-medical costs. In the case of migraine, direct non-medical costs, i.e. costs related to social services, informal care, transportation etc., are hardly relevant and have not been included in any of the European cost-of-illness studies. As discussed in the previous section, direct medical costs, which include hospitalisation, drug use, outpatient care and medical procedures and devices, account for a relatively small proportion of overall migraine costs across the studied countries.

There are large variations in the absolute amount and the distribution of direct medical costs across subcategories, which are illustrated in **Fig. 3** and **Table 4**. Total yearly direct costs range from € 12 per patient in the UK to € 67 per patient in The Netherlands, averaging at € 39 per patient. The reason for the low UK costs is the use of national surveys conducted in 1985 and 1986, which means that the costs do not take into account developments in the medical management of migraine, in particular new pharmacological treatments, over the past 15-20 years. Therefore, the direct costs of migraine in the UK are likely to be significantly higher today. A similar argument holds for several of the other older studies.

In The Netherlands, the vast majority (€ 53) of outpatient costs are due to the high use of alternative practitioners, such as homeopaths. The high estimate is probably a result of the mixed calculation method for outpatient costs. A pilot study with two hospitals and five neurologists was used to estimate the proportion of migraine patients visiting hospital outpatient departments as well as the average number of physician visits, while the number of visits to alternative practitioners was estimated based on a patient questionnaire.

In France, the reason for the comparatively high total estimate is likely to be the bottom-up methodology, whereby patients' recollection of medical resource use over the past 6 months was multiplied by the relevant tariffs to arrive at gross costs. The advantage of this approach is also that data could be gathered on the type of services used. Thus, among the migraine patients who had consulted a physician at least once in their lives, an average of 31% had visited a primary care physician 2.5 times during the past 6 months, compared to 36% who had visited another specialty. In the group of patients who had visited a doctor during the past 6 months, 2.6% had been hospitalised for an average duration of 7.2 days.

In general, drugs and outpatient care, including both primary care and secondary care visits, account for the highest costs. Pharmacological therapy for migraine includes analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), ergotamines and triptans. Interestingly, the German study also specified costs related to analgesic abuse, which was defined as regular medicine use for 20 days or more per month. The costs related to this, including inpatient treatment in the form of dialysis and withdrawal therapy, amount to € 37 per migraine patient per year, which is higher than the sum of the other direct costs in Germany.

Hospitalisation costs are generally low for migraine, as only the most severe cases will need inpatient treatment. Similarly, costs for medical procedures and devices are usually quite low, since diagnosis mostly can be made on the basis of a clinical assessment. However, only two studies had actually included medical procedures and devices in their analysis, meaning that further research in this area could add useful information.

To complement the above cost data, it is useful to consider the results of a Danish study [7], which investigated the extent and type of health service utilisation using a random sample of 25-64 year old individuals with migraine and tension-type headache. Among the 119 migraine sufferers, 56% had consulted a general practitioner at some time because of their headaches, compared to 16% for patients with tension-type headache. Specialists were frequented by 16% of migraine sufferers, followed by physiotherapists (8%) and chiropractors (7%). Consultation rates were generally higher for women than for men. Among the total of 697 headache patients, only 2% had ever been admitted to hospital. As indicated earlier in this section, supplementary diagnostic techniques, such as electroencephalograms, CT scans or X-rays, are not common, with only 2% of headache patients having received one of these.

Indirect costs

In the context of migraine, indirect costs constitute the major burden to society. The two basic measures relevant in this context are absenteeism and reduced productivity at work. While absenteeism is a relatively common measure in health economic evaluations, reduced work productivity is more difficult to assess and may go unnoticed in many cases. However, in the case of migraine, the highest costs often result from reduced productivity, with a higher total number of days lost due to lower efficiency than actual absence from work.

There are some inherent difficulties in measuring workplace productivity, including:

- Choosing an appropriate measurement method for absenteeism and productivity
- Assigning a monetary value to lost work days and productivity

One issue arises in the choice of measurement method, as the commonly used retrospective approach has the disadvantage of introducing the possibility of recall bias when asking patients about their work absence and level of productivity over a past time period. In this respect, prospective studies, where patients record work performance on a daily basis, can provide more objective estimates. Moreover, the ideal productivity measure would also include independent assessments, e.g. from supervisors, or use defined output parameters to generate a comprehensive assessment of impact on work performance. The substantial impact of the measurement method on cost outcomes can be seen in the study by van Roijen et al. [8], which used three different approaches to calculate costs of reduced productivity. These are discussed in more detail below.

Another issue lies in the valuation of lost work days and productivity. There are two possible approaches to this, the human capital approach and the friction cost method. The human capital approach, which is the more common method, values lost productivity using gross earnings. However, lost opportunity costs or income related to career advancement are not captured through this approach. The friction cost method, on the other hand, uses the time it takes a company to adapt to the productivity loss caused by a sick employee as a basis for valuation, which results in lower cost estimates than the human capital approach, but is related to some difficulties in estimation and introduces the potential for additional bias.

Due to the nature of migraine, work absence and reduced productivity at work play almost an equally important role for indirect costs. As can be seen in **Fig. 4**, reduced work productivity accounts for 42-71% of total indirect costs in the four European countries where these data were available. The specific costs are discussed in more detail in the following sections.

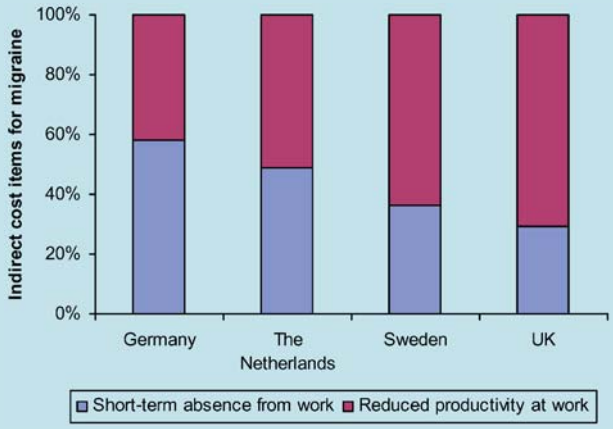

Fig. 4 ◀ **Components of indirect medical costs for migraine across four European countries**

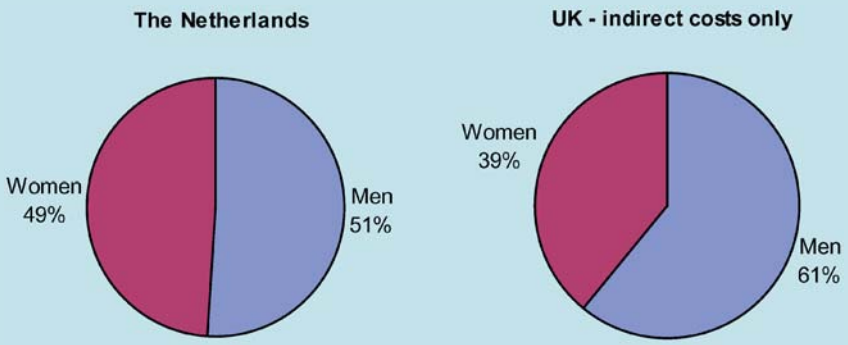

Fig. 5 ▲ **Proportion of migraine costs incurred per gender**
Sources: van Roijen et al. [8], Cull et al. [16]

Table 6

Impact of migraine on productivity

Country	Work absence (days/year)	Lost time due to reduced efficiency (days/year)	Efficiency level during migraine (%)	Reference
France	2.2	n/a	n/a	Michel et al. [11]
The Netherlands	3.2	2.7	72	van Roijen et al. [8]
Spain	Total of 8.5 workdays lost due to migraine		67	Lainez et al. [9]
Sweden	2.7	n/a	n/a	Björk and Roos [4]
UK	2.0	5.5	56	Clarke et al. [17]
Average	2.5	4.1	65	

NB: *German productivity metrics were not included in this table, as they were estimated on the basis of secondary data on productivity metrics from other countries*

Table 7

Impact of migraine on productivity by gender

Country	Work absence (days/year)		Lost time due to reduced efficiency (days/year)		Efficiency level during migraine (%)		Reference
	Men	Women	Men	Women	Men	Women	
The Netherlands	1.0	3.9	2.3	2.9	69	73	van Roijen et al. [8]
Spain	0.8	1.1	6.3	9.4	n/a	n/a	Lainez et al. [9]
Sweden	1.2	4.1	n/a	n/a	n/a	n/a	Björk and Roos [4]
UK	1.5	2.1	4.1	4.6	58	56	Cull et al. [16]
Average	1.1	2.8	4.2	5.6	64	65	

NB: *German and some Swedish productivity metrics were not included in this table, as they were estimated on the basis of secondary data on productivity metrics from other countries*

The level of indirect costs varies significantly across countries, depending on the calculation method used. The total indirect costs of migraine per year range from € 79 per patient in Sweden to € 847 per patient in Germany (see **Table 5**). The low Swedish data are probably a significant underestimation of the actual indirect costs incurred by migraine patients these days. The high estimate for Germany is probably due to the relatively high daily "production value" of € 252 per working person that was used for the calculations, which was based on the gross domestic income and economically active population in 2000. Other studies have generally used a mean income, sometimes including social charges, to calculate indirect costs. For example, if the average daily wage of € 110 is used [18], the indirect annual costs in Germany would amount to only € 370 per patient, constituting a significantly lower estimate. Considering the fact that the German study is based on 2000 data, which should include use of the more effective triptans, it could be expected that the indirect costs would be lower than in older studies, whereas the direct medical costs should be higher. However, this cannot be concluded from the published information, warranting further investigations.

It should be noted that the study by Michel et al. [11] is the only prospective study on the costs of absenteeism in migraine. It is also the only study that used a control group to calculate incremental costs compared to "average" employees. Interestingly, the study found that the higher absenteeism for migraine sufferers compared to that of the control group was not due to headache but related to other medical reasons, as migraine patients avoided taking sick leave during days with headache. The annual incremental cost per migraine patient was € 257, compared to the total cost of work absence of € 333.

The study by van Roijen et al. [8] employed three different methods for measuring reduced productivity at work, all of which yielded very different results. The first method, called the I&L approach, asked working respondents to indicate the number of additional hours they should have worked over the past 2 weeks to make up for productivity losses on days when they were at work despite suffering from migraine. The second approach, called Osterhaus 1, estimated reduced efficiency on the basis of the number of working days with symptoms of migraine multiplied by the estimated level of performance with migraine. The final method, referred to as Osterhaus 2, multiplies the number of attacks and the number of working hours affected by migraine by the estimated level of performance.

In the Dutch study, the I&L approach resulted in the lowest annual estimate for lost productivity at € 138 per migraine patient, shown in **Table 5**. By comparison, the Osterhaus 1 method yielded € 480 and the Osterhaus 2 method € 722 per patient. The three methods were tested for validity, but statistical tests yielded a low corre-

lation of their results. The authors pointed out that the Osterhaus methods estimate the number of hours or days lost due to reduced efficiency in a more indirect way than the I&L approach, which could increase the risk for inconsistencies and mistakes. Furthermore, the Osterhaus 2 method implies that all migraine attacks occur during working hours, which will lead to an overestimation of costs. Therefore, the I&L estimate was used for calculation of total costs, while highlighting the fact that actual costs could potentially be higher.

Another factor that could also have contributed to the comparatively lower indirect cost estimate for The Netherlands is the use of the friction cost method in this study. Furthermore, if the 3-month recall was used, the costs of work absence would be € 236 per patient, compared to the more conservative € 131 based on the 2-week recall. However, the authors considered the 2-week period to be a more reliable basis for patient recall and also to yield results in line with estimates for the number of workdays lost derived in other countries.

The indirect costs from the studies by Pop et al. [6] and Clarke et al. [17] are not included in **Table 5** because of their limited perspective focusing on a selected employer (a Dutch manufacturing company and a UK hospital, respectively). Nevertheless, for comparison purposes, the study by Pop et al. yielded an average cost of € 83 per migraineous employee for short-term absence and € 118 for lost productivity, which is considerably lower than for most of the above studies (costs were given in US$ and have not been adjusted by a price level index). The study by Clarke et al. arrived at an average cost per employee with migraine of € 153 for short-term absence and € 423 for lost productivity, which is more comparable to the other results.

Table 6 shows the number of work days lost due to absence and reduced efficiency where available. On average, 2.5 work days are lost due to work absence per year and migraine patient. An average efficiency level of 65% when working with migraine leads to a loss of further 4.1 days. Taking the average of the total work days lost due to migraine, 7.3 work days are lost per year per migraine patient, which results in the high indirect costs of this condition.

The study by Rasmussen et al. [7] showed that in the total population, the absence rate in patients with migraine was 5% during 1 year, compared to 9% for patients with tension-type headache. In terms of work days lost, the strong impact on tension-type headache on productivity is even more pronounced: per 1000 persons, 820 work days were lost due to tension-type headache during 1 year, compared to 270 work days for migraine. This means that tension-type headache leads to three times as many lost work days as migraine, suggesting that the overall burden of the two major primary headaches is considerably larger than for migraine alone.

In many diseases, the impact on unpaid labour plays an important role in the analysis of overall costs. For migraine, only the study by van Roijen et al. [8] has evaluated the role of unpaid labour in overall disease burden. As part of the patient questionnaire, respondents were asked about the impact of migraine on household work, shopping, care for children and miscellaneous household tasks. The numbers of hours spent on household activities were compared between the migraine and the control group; the hours lost due to migraine were then multiplied by the price that would be paid for a worker to perform the unpaid tasks. Based on this methodology, no significant differences in time spent on household activities was found between the migraine and the control groups. The authors noted, however, that the methodology is unlikely to pick up small differences in time spent, and that analysis of such changes would require a different approach, e.g. in the form of diary records.

Stratification of costs by gender

Only the Dutch and the UK study allowed stratification of costs by gender. In both cases, indirect costs were calculated separately for men and women by using different values for the number of work days lost and gender-specific salary levels. In the UK, a large difference in salaries led to higher indirect costs for men than for women, which is illustrated in **Fig. 5**. In The Netherlands, in contrast, the costs for male migraine sufferers are only marginally higher than for female ones. **Table 7** contains the number of work days lost and efficiency level by gender where available. This shows that, on average, women tend to lose more days of work due to migraine; however, because of lower salary levels and proportionally reduced labour force participation compared to men, the resulting indirect costs for women are similar to or even lower than for men (**Fig. 5**).

Quality-of-life measures

Health-related quality of life (HRQoL) in migraine and headache can be evaluated either with general or disease-specific QoL measures. As yet, a single optimal measure for HRQoL in migraine has not been established, meaning that a variety of different disease-specific tools are used, including the migraine-specific QoL instrument (MSQoLI), the migraine-specific QoL questionnaire (MSQoLQ) and the 24 h migraine QoL questionnaire (24-hMQoLQ). In addition to being useful endpoints in clinical trials for migraine therapies, such QoL measures provide valuable information on the burden of the disease from the patient's perspective. If specific utilities and values per quality-adjusted life year (QALY) lost are allocated to the QoL results, intangible costs of the disease can be calculated.

As part of the limited search on QoL for this review, relatively few studies with QoL assessments in migraine were identified in Europe, and no study allocating costs to QALYs were found. Studies that did not contain any control group or focused only on a subgroup of the migraine population, such as children, were not included. As mentioned earlier, five European studies were identified which had used the short-form 36 (SF-36) questionnaire. In addition, the cost study by van Roijen et al. [8] included data based on the Euro-QoL instrument. For three of the SF-36 studies, the numerical data were not contained in the article and were not provided by the authors upon request.

The study by van Roijen et al. [8] showed significant differences between migraine patients and controls for three of the five Euro-QoL dimensions: usual ac-

tivities, pain/discomfort and anxiety/depression. While scores for mobility and self-care were somewhat lower for migraine sufferers than for controls, differences were not statistically significant. When normalised to the control group, the average score of migraine patients was 0.96 on a scale from 0 = worst to 1 = best health status. Migraine patients' evaluation of their own health on a visual analogue scale from 0 = worst imaginable health state to 100 = best imaginable health state was 77, compared to 83 for controls.

In a study among employees of a French power company, called the GAZEL cohort, Michel et al. [19] compared the QoL of migraine patients with those suffering from tension-type headache, other headaches and no headaches. Migraine patients had lower scores on all of the eight SF-36 dimensions compared to controls. Migraineurs displayed scores similar to those suffering from headaches other than migraine or tension-type headache, except on the pain dimension, where migraine sufferers had a lower score than all other groups. When standardised to the control group, the average score of migraine patients was 0.85 on a scale from 0 = worst health status to 1 = best health status. The results for the different groups are illustrated in **Fig. 6**.

In a population-based study in England, Lipton et al. [20] investigated the QoL in migraine patients at different disability stages compared to controls using the SF-36 instrument. Work-related disability was defined by the sum of work days missed over the past year and the total number of days with work productivity reduced by at least a half. The migraine respondents could thus be classified as suffering from either low disability (0-15 days of work affected), moderate disability (16-38 days) or high disability (39-336 days). Overall, migraine sufferers had lower QoL scores than controls in the eight major SF-36 dimensions, with the greatest differences seen in the role-physical, pain, social functioning and role-emotional domains. In five of the eight dimensions, QoL scores for moderate and high migraine disability were significantly lower than for the mild group, while the difference between the moderate and the high disability groups was not found to be

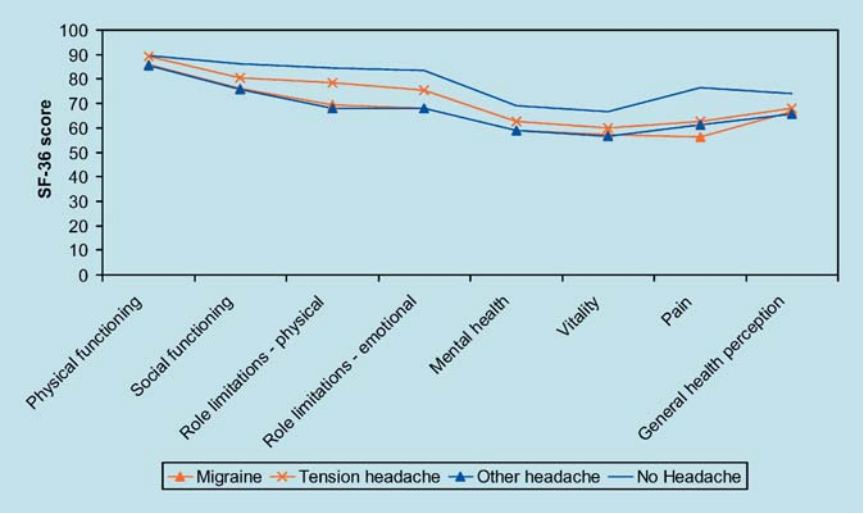

Fig. 6 ▲ **Quality of life reduction by headache type compared to control group. [19]**

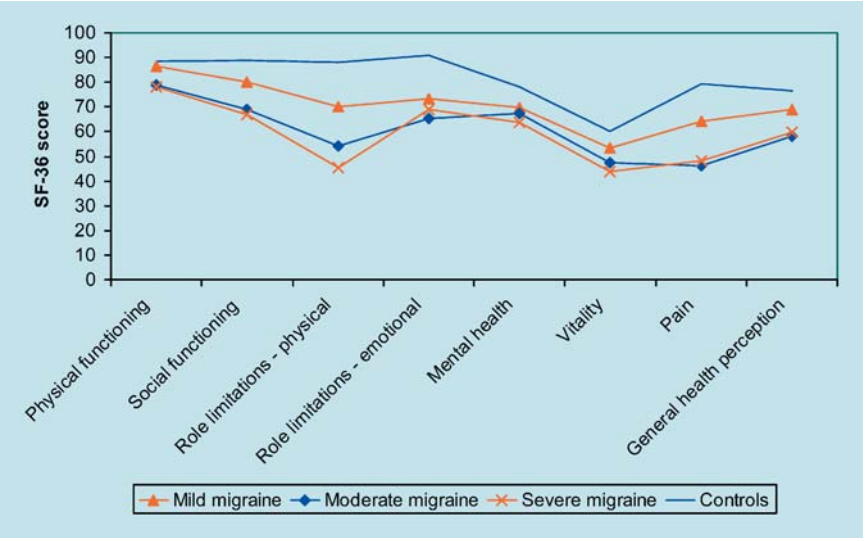

Fig. 7 ▲ **Quality-of-life reduction by migraine severity* compared to control group. [20]**
***NB: Severity was defined according to number of work days affected by migraine during previous year**

significant. Across the eight SF-36 dimensions, the standardised scores versus the control group were 0.87 for low, 0.75 for moderate and 0.73 for high disability. The specific results for each group are illustrated in **Fig. 7**.

Discussion

There are a number of issues that need to be considered when using the cost information for migraine in Europe. A key point is whether the data captures the whole population of migraine patients. Cost-of-illness studies may not always cover a sample representative of all patients; for example, more severely affected patients might be over-represented if a study is based on patients who seek care for their headache problems, rather than a random population sample. On the other hand, the fact that many headache sufferers never have consulted a physician about their symptoms or received a correct diagnosis suggests that the total costs could be even higher if all relevant patients actually consulted a physician and received treatment. Overall, it is likely that most cost estimates found for migraine in Europe are an underestimation of actual costs, due to a combination of factors:

- Most studies are based on cost data gathered up to 1995, which means

that particularly costs relating to triptan use are likely to be out of date.
- All except for one study used a top-down approach to estimate direct costs, which carries the risk of underestimating or leaving out cost items not fully captured in national statistics.
- For the indirect costs, the conservative estimates based on specific recall periods were used for the analysis in this article, which in some cases lead to a significant reduction in overall costs.

In relation to the first point, it is possible that the increased use of triptans over the past decade has led to a reduction in work absences and reduced work productivity due to better medical control of the condition. While economic evaluations of the triptans suggest that treatment of more severely affected patients is cost-saving for society, more research is needed in this area. On an overall level, it is important to note that the estimated costs per patient strongly depend on the respective prevalence rate used for the calculation. In this article, the prevalence rates were taken from the relevant cost studies, as most studies provided a total cost estimate for the given country.

On the whole, most studies reviewed in this article provided some interesting and useful information on the costs related to migraine in the general population. For France, the two studies by Michel et al. used somewhat different methodological approaches to the rest, with a prospective population-based study for indirect costs and a bottom-up approach for direct costs, which offer good data for comparisons with other countries. Although based on 1988 data, the study by van Roijen et al. is the most comprehensive European study on migraine, covering nearly all aspects of the disease and evaluating different methodologies for assessing productivity loss. The German study by Neubauer and Ujlaky has the benefit of offering the most up-to-date collection of cost data, gathered from secondary sources for both direct and indirect costs. However, this might have led to an overestimation of indirect costs. While the UK studies are relatively old, the estimates on indirect costs are still very much in line with other European data, suggesting a solid methodological approach.

Regarding the remaining cost-of-illness studies, although the data gathered for the Spanish analysis conducted in 1995 lies within the range of the majority of the other European studies, it is based on a selection of the working migraine population that is probably not representative of the total population. The Swedish study, on the other hand, is based on secondary data from 1990, and its very low cost estimates are not thought to be realistic by the author at this point in time.

Since all available cost studies have at least some limitations in terms of methodology or timeliness, any estimate of the average cost of migraine in Europe needs to be interpreted with some caution. Based on the above discussion, the most suitable country estimates for deriving a European estimate would be those from the UK, Germany (using wage rates instead of GDI for indirect costs) and France (using an average of the UK and adjusted German costs for reduced productivity at work). For consistency reasons, the Dutch results should not be included, since they are based on the friction cost method. Thus, the following total cost estimates would be suited for further evaluations: € 528 (UK), € 398 (adjusted German estimate) and € 659 (adjusted French estimate).

The average cost of migraine per patient is highly dependent on the total country costs and prevalence rates derived from the existing studies. Also, some studies offer several estimates based on different methodologies or recall periods, which means that the derived cost estimates per patient can vary according to the chosen data.

Finally, cost estimates are available only for migraine, which affects a smaller part of the general population than tension-type headache. However, existing evidence on the impact of tension-type headache on resource use and productivity suggest that migraine accounts for only 25% of work absences due to these two primary headache types [7]. Since the indirect costs account for the majority of the burden of headache, the total cost of headache is potentially about four times the cost of migraine. To understand the cost of non-migraine headache better, considerably more research is required in this area.

Conclusions

This review highlights the significant economic burden of migraine to society in Europe each year. The vast majority of the total costs, nearly 90%, are due to indirect costs in the form of absenteeism and reduced effectiveness when at work with migraine. This means that even though outcomes and direct costs may have been underestimated due to inclusion of older studies conducted prior to the establishment of the triptans, there remains substantial room for improving patient diagnosis and management. Such measures should ultimately lead to an improvement in work productivity for migraine sufferers. Subsequently, if the direct costs related to drug treatment are offset by the gains in productivity, this would lead to a reduction in the overall costs of migraine to society.

In the course of this review, several areas have emerged where a need for further research exists. On a data level, there is a need for more up-to-date population-based studies that capture all the costs resulting from migraine, particularly for direct medical costs. This also applies to the geographical scope of cost data, with more studies needed from countries outside the major pharmaceutical markets in Western Europe. Moreover, as new severity measures for migraine emerge, it would be of value to understand how costs are linked to disease severity, so that management strategies can be targeted more specifically towards each subpopulation. With regard to methodological approaches, further analysis of different productivity measures is needed to allow realistic evaluation of indirect costs, which constitute the key burden of migraine. In this context, it would also be of interest to understand the intangible costs of the condition by conducting research on the utility scores for different severity levels and the related costs of QALYs lost due to migraine.

Finally, on a wider disease level, this review confirm that while a certain amount of cost analysis exists for migraine, there is

hardly any information available for tension-type headache. This condition probably accounts for even higher total costs than migraine, since it affects a significantly larger proportion of the total population and is related to high work absence rates. As discussed earlier, migraine potentially accounts for only 25% of the total costs of these two primary headache types, highlighting the importance of a better understanding of the impact of non-migraine headaches on patients and society. Therefore, research in this area would provide valuable information for future decision-making and resource allocation in the field of headaches.

References

1. Lipton R, Scher A, Stewart W (2003) Overview of headache prevalence, burden, and management. In: Lipton R, Steiner T, Olesen J (eds) Reducing the burden of headache. Oxford, p 3-14
2. Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WF (2001) Migraine diagnosis and treatment: results from the American Migraine Study II. Headache 41:638-645
3. Blau J, Drummond M (1991) Migraine. Office of Health Economics, London
4. Björk S, Roos P (1991) Economic aspects of migraine in Sweden. In: Working paper no 8. Institute for Health Economics, Lund
5. Göbel H (2003) Healthcare utilisation for in-patient headache therapy. In: Olesen J, Steiner T, Lipton R (eds) Reducing the burden of headache. Oxford, p 185-188
6. Pop PH, Gierveld CM, Karis HA, Tiedink HG (2002) Epidemiological aspects of headache in a workplace setting and the impact on the economic loss. Eur J Neurol 9:171-174
7. Rasmussen BK, Jensen R, Olesen J (1992) Impact of headache on sickness absence and utilisation of medical services: a Danish population study. J Epidemiol Community Health 46:443-446
8. van Roijen L, Essink-Bot ML, Koopmanschap MA, Michel BC, Rutten FF (1995) Societal perspective on the burden of migraine in The Netherlands. Pharmacoeconomics 7:170-179
9. Lainez M (2003) The socioeconomic impact of migraine in Spain. In: Olesen J, Steiner T, Lipton R (eds) Reducing the burden of headache. Oxford, p 255-259
10. Michel P, Auray J, Chicoye A, Dartigues J, Lamure M, Duru G, Henry P, Salamon R (1993) Prise en charge des migraineux en France: coût et recours aux soins. J d'Econ Méd 11:71-80
11. Michel P, Dartigues JF, Duru G, Moreau J, Salamon R, Henry P (1999) Incremental absenteeism due to headaches in migraine: results from the Mig-Access French national cohort. Cephalalgia 19:503-510
12. Jones G (1994) How often were you absent? A review of the use of self-reported absence data. J Appl Psychol 79:574-591
13. El Hasnaoui A, Vray M, Richard A, Nachit-Ouinekh F, Boureau F (2003) Assessing the severity of migraine: development of the MIGSEV scale. Headache 43:628-635
14. Neubauer G, Ujlaky R (2002) Migraine-a disease and its costs. Pharm Unserer Zeit 31:494-497
15. Lanteri-Minet M, Auray JP, El Hasnaoui A, Dartigues JF, Duru G, Henry P, Lucas C, Pradalier A, Chazot G, Gaudin AF (2003) Prevalence and description of chronic daily headache in the general population in France. Pain 102:143-149
16. Cull R, Wells N, Moiechevich M (1992) The economic cost of migraine. Br J of Med Econ 2:103-115
17. Clarke CE, MacMillan L, Sondhi S, Wells NE (1996) Economic and social impact of migraine. Qjm 89:77-84
18. Statistisches-Bundesamt (2002) In: http://www.destatis.de/allg/d/veroe/d_datend.htm. Berlin
19. Michel P, Dartigues F, Lindoulsi A, Henry P (1997) Loss of productivity and quality of life in migraine sufferers among French workers: results from the GAZEL cohort. Headache 37:71-78
20. Lipton RB, Liberman JN, Kolodner KB, Bigal ME, Dowson A, Stewart WF (2003) Migraine headache disability and health-related quality-of-life: a population-based case-control study from England. Cephalalgia 23:441-450

Corresponding author

Jenny Berg

Stockholm Health Economics, Stockholm, Sweden
e-mail: jenny.b@healtheconomics.se

Gisela Kobelt · European Health Economics, Spéracèdes, France

Economic evidence in multiple sclerosis: a review

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that is characterised by inflammation and destruction of the myelin coating of nerve fibres. This demyelination leads to symptoms such as sensory disturbances, limb weakness, gait problems and neurogenic bladder and bowel symptoms, all of which become increasingly disabling over time. Irreversible functional disability occurs early, making MS the second most common cause of neurological disability in young adults [1].

The prevalence of MS is estimated at 0.04-0.15% [2]. At diagnosis, the majority of MS patients present with relapsing-remitting disease (RRMS), usually afflicting patients between the ages of 15 and 40 years. This form of MS is characterised by disease exacerbations that, initially, improve spontaneously or in response to treatment over several days or weeks. Over time, in a majority of patients, underlying disease progression and neurological damage continues to occur between relapses, resulting in secondary progressive disease (SPMS). Approximately 10-20% of MS patients have primary-progressive disease (PPMS) with a slightly older onset of age.

In recent years, several new treatments for RRMS have been introduced, such as interferon β-1a and interferon β-1b and glatiramer acetate. All of these products have shown a statistically significant reduction in exacerbations in clinical trials [3-6], but only one trial has shown a