No studies were found for the other anxiety disorders.
The reviewed studies reveal some cost patterns in France (for GAD) for patients with and without comorbidities and for Spain for panic disorder patients; but from a European-wide perspective, based on these scarce findings, the lack of available data makes it difficult, if not impossible, to use the identified data to extrapolate the costs in countries where no studies/data were found.
The only conclusion that can be made regarding this is the clear need for more research in this area, both in the Western European countries as well as in the Central and Eastern European countries.

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Economic evidence in brain tumour: a review

Introduction

The most striking feature of the literature on the cost of illness of brain tumours in Europe is the almost complete lack of comprehensive studies. There is, in fact, only one comprehensive study on the cost of brain tumours – a Swedish study published in the year 2000 [1]. The reasons for this are unclear. On the one hand, brain tumours are, thankfully, relatively rare. In comparison with prostate and breast tumours, the incidence is low. On the other hand, brain tumours often hit younger people and even small children, with the possible loss of many life years as the unfortunate consequence. After an overview of the epidemiology, classification and treatment of brain tumours, we will take a closer look at the Swedish study on the cost of brain tumours in Sweden in 1996, and briefly review some other studies with a more limited scope. For obvious reasons, the review section of this paper will be rather short. We will then go on to discuss the reasons for the lack of published studies and finally present some possible directions for further research in this area.

Brain tumours

Incidence and classification

Brain tumours represent about 2% of all newly diagnosed tumours. There were 1009 new cases in Sweden in the year 2000, which meant that the incidence was 11.3 per 100 000 inhabitants (Cancer Incidence in Sweden 2002). In Europe as a whole, there seems to be some variation in the incidence rates. In 1995, the incidence ranged from about 4 to about 11 per 100 000 inhabitants. Sweden is thus in the upper range among European countries. For Europe as a whole, the incidence was 7.9/100 000 for men and 5.4/100 000 for women. There were fewer than 50 000 cases of cancer of the brain and central nervous system in Europe in 1995. The age-standardized mortality rates were 5.9/100 000 for men and 3.9/100 000 for women [2].

Brain tumours, or intracranial neoplasms, are a diverse set of tumours that are primarily classified by site and malignancy [3]. Astrocytomas are the most common; they represent about 45% of all brain tumours. Second most common are benign meningiomas, which represent about 15-20% of all cases. Astrocytomas belong to the larger category of gliomas, which also includes oligodendroglioma. Roughly speaking, gliomas represent 70% of the cases, and menigiomas make up the remaining 30%.

Brain tumours are classified in primary and secondary. Primary brain tumours originate in the brain itself, while secondary brain tumours are metastases originating in another part of the body. Secondary tumours are always malignant, while primary tumours occur in both benign and malignant forms. Although primary brain tumours are not as common as breast or lung carcinoma, brain tumours affect children and young people to a significant degree and cause a high portion of cancer mortality in these age groups. Primary brain tumours occur in all age groups, but are significantly more frequent in children and adolescents under 15 years old and in the elderly. For every person diagnosed with a brain tumour, an average of 22 years of life expectancy is lost according to Turini and Redaelli [4], which is high compared to most other tu-

mour types. The most common primary childhood tumours are cerebellar astrocytomas and medulloblastomas, ependymomas and gliomas of the brain stem, while adults are affected by primary tumours such as meningiomas, schwannomas, primary lymphomas and gliomas of the cerebral hemispheres [3].

Symptoms, diagnosis and treatment

The symptoms of brain tumours usually progress gradually, although some sites may cause sudden and dramatic symptoms. Typical symptoms include headache (as a result of intracranial pressure), nausea and vomiting, drowsiness, behavioural and emotional changes (often an early sign in tumours affecting the frontal lobes), memory loss, motor dysfunction (e.g. partial paralysis) and impaired speech and writing. Depending on the site of the tumour, the symptoms may differ considerably. Since the neurological symptoms associated with brain tumours are similar to other conditions, a complete neurological examination, including magnetic resonance imaging (MRI) or computerized tomography (CT), is helpful for investigating the possible existence of a tumour. MRI and CT can show the tumours size and location with high precision. In addition, a biopsy is usually needed to identify the type of tumour [3].

The treatment of brain tumours depends on the type and stage of the disease, and the patient's age and overall state of health. Surgery is the first treatment option for most primary brain tumours. Benign tumours can often be completely removed and, in general, as much of the tumour as is neurologically safe should be removed [3]. A course of radiotherapy or chemotherapy may follow. Radiation therapy is required for infiltrating gliomas, though the use of radiation is limited by the risk of irradiation damage to healthy brain tissue. Chemotherapy may benefit some patients, but is less effective for brain tumours than for many other tumour types.

Prognosis

Despite more effective therapies, the prognosis for brain tumours has improved only slightly over the years. For malignant gliomas, the prognosis is poor. The median survival is only 1 year, and only 25% of the patients survive 2 years. Low-grade gliomas, medulloblastoma and ependymoma have better prognosis. For example, at least 50% of the medulloblastoma patients survive 5 years, and 40% 10 years. However, even a benign tumour may be fatal if it is located in a site where it is anatomically difficult to remove surgically or by radiation [3].

Methods

Literature search

An electronic search for literature on the cost of brain tumours was performed by using the Medline database. The following keywords were used: brain or intracranial in combination with cancer, tumo(u)r, malignancy, or neoplasm. These terms were, in turn, combined with cost(s), economics, cost analysis and cost of illness. The keyword brain tumour was also combined with cost(s) and the names of individual EU or EFTA countries included as part of the EBC project on estimating the cost of brain diseases in Europe. Additional studies were sought among the references in papers retrieved as a result of the electronic search.

Criteria for study selection were: estimates of direct and/or indirect costs of brain tumours; possible-to-discern main data sources and individual cost components; country of origin belonging to a list of 28 European countries (all European member states as well as Norway, Switzerland and Iceland). No restriction was made a priori as to the language or the date of publication.

Diagnosis definition

The goal was to establish the average cost per patient for brain tumours in various countries in Europe. The diagnoses included were defined according to the International Classification of diseases (ICD-10). However, the ICD-10 framework was not followed rigorously. A study which did not indicate the diagnoses included in terms of ICD codes was not discarded as long as the definition of brain tumours used in the study was sufficiently precise even in the absence of strict diagnostic criteria. A pragmatic approach is needed, since it is seldom possible to classify all costs in a cost-of-illness study along ICD-10 lines.

The following diagnoses were included:

- C70: Malignant neoplasm of meninges
- C71: Malignant neoplasm of brain
- C72: Malignant neoplasm of spinal cord, cranial nerves, and other parts of CNS
- B32: Benign neoplasm of meninges
- B33: Benign neoplasm of brain and other parts of CNS
- D42: Neoplasm of uncertain or unknown behaviour of meninges
- D43: Neoplasm of uncertain or unknown behaviour of brain and other parts of CNS

Cost-of-illness methodology

There are two main approaches to cost estimation in cost-of-illness studies: top-down and bottom-up [5, 6]. The top-down approach to cost estimation means that the total national costs for illnesses are divided between different diseases according to the frequencies of different diagnoses. In the bottom-up approach data are collected directly from a sample of patients during or after medical visits, and then the figures from the sample may be extrapolated to represent the whole population by using national prevalence figures.

The advantage of using the top-down approach is that no extrapolation is needed and that it avoids the risk of double counting. The disadvantages compared to the bottom-up approach are that diagnoses may be under-reported or misreported, and that there are important cost items that are missing from the national illness registers. For example, costs for social services or unpaid home help are unaccounted for if a pure top-down approach is used. The value of household production lost as a consequence of disease is also missing from a top-down approach to cost-of-illness studies.

Cost perspective

A societal perspective implies that all costs, whether incurred by individuals, employers or government, should be tak-

en into account. Direct costs are costs for goods and services used in the prevention, diagnosis and treatment of the disease in question as well as rehabilitation and other medical consequences of the disease, e.g. costs for medical visits, hospitalisation and pharmaceuticals. Private costs incurred by the patient and family and other public resources (e.g. transportation) are also included under this heading. Indirect costs are defined as the value of the output that is lost because people are impaired or too ill to work [7]. Typical cost items in this category are costs for short-term absence from work, early retirement pensions caused by disability and premature mortality. The approach of valuing life as the value of lost production is known as the human capital approach. For example, the loss of productivity associated with disability is valued using gross earnings lost or some proportion of the gross earnings if an individual is unable to work at full capacity [5, 7].

There are also intangible costs, which include pain, psychosocial suffering and changes in social functioning and activities of daily living. These costs are hard to quantify, and would turn up on the benefit side rather than the cost side in a cost-benefit analysis. Intangible costs are, in general, not included in currently available cost-of-illness studies. However, the intangible costs are probably far from insignificant for many diseases, and may often be dominating.

Prevalence- and incidence-based estimates

Cost-of-illness studies can be performed by using either prevalence- or incidence-based methods [5]. Prevalence-based studies examine costs incurred during a given time period, usually 1 year, regardless of the date of the onset of disease. Incidence-based studies examine costs for cases of the disease that develop for the first time in that year. Future costs and production losses are then estimated for the entire lifetime of these patients and calculated in terms of present values. Since incidence-based studies can be used for calculating the economic benefits of reducing the number of new cases, they are suitable for evaluating preventive measures [6].

For brain tumours, an incidence-based perspective would probably be the most relevant, since primary brain tumours are not chronic. The patients diagnosed with brain tumour either die within a few years or are cured, or at least symptom-free. There may, of course, be recurrences, but for practical purposes someone who has been symptom-free for 5 years may be regarded as cured. It would therefore be natural to base the cost estimation on the incidence and calculate the costs of the expected lifetime of the patients diagnosed with brain tumour during a certain year. As we shall see, however, a purely incidence-based study may not always be feasible, as the necessary data may be lacking or hard to find.

Results

Available literature

As a result of the electronic search, 310 abstracts were identified and reviewed. Most were directly discarded as they did not include any prevalence- or incidence-based data on costs. Judging from the abstracts, nine studies seemed to fulfil the inclusion criteria, and were retrieved in full text for further evaluation. On closer inspection, only one of these studies was considered to fulfil all of the inclusion criteria. The reasons for excluding studies were mainly that they did not include relevant diagnoses or costs. Many cost studies were based either on small case series, or were part of a comparative clinical investigation of particular treatments with little relevance for the population of brain tumour patients as a whole.

Review of the Swedish study

The Swedish study by Blomqvist et al. [1] had the objective of calculating both direct and indirect costs of brain tumours in Sweden in 1996. They begin by stating that, to their knowledge, studies on health-care utilisation and costs for brain tumours have been performed only for selected subgroups of patients, mainly in conjunction with new treatments. Many studies were based on a single case series from a local hospital.

They then go on to describe methodology and data sources in their study. A prevalence and top-down approach was used, which means that as far as possible national annual data for a specific year (1996) were used for the cost estimations.

Direct costs:

- Inpatient costs were obtained by combining data from the Swedish Cancer Registry, National Inpatient Register, and the Swedish Death Register with per diem unit costs for inpatient stay at different departments.
- Long-term care and home care were estimated from the National Inpatient Register and literature sources.
- Outpatient visits in primary care were obtained from a local primary care database, and then combined with a unit cost per primary care visit. For outpatient care at hospital clinics, no reliable statistics were found. The authors relied instead on a plausible chain of outpatient visits for patients with suspected and later confirmed brain tumour.
- The pharmaceutical costs were based on clinical guidelines and official Swedish price lists for drugs.

Indirect costs:

- Data on sickness leave were obtained from a survey performed by the National Social Insurance Board. The lost working time was valued by using age- and sex-specific average salaries in Sweden in 1996, including payroll taxes.
- Data on early retirement were also obtained from the National Social Insurance Board, and valued in the same way as sickness leave.
- The cost of productive life-years lost as a result of premature mortality was estimated by using data from the Swedish Death Register and average Swedish salaries.

The results showed that indirect costs represented 75% of the total cost, or 150 million USD (in € 2003: 167 million). Costs for early mortality constituted a majority of the costs. The direct costs were 52 million USD (in € 2003: 57 million), and hospital care was the largest cost item in this category. Taking the prevalence of brain tumours into account, the cost per pati-

Table 1

Cost of brain tumours in Sweden in 1996 [1]

	USD (millions)	€ (millions)	%
Direct costs			
• Ambulatory care	1.7	1.9	0.8
• Hospital care	36.8	40.8	18.2
• Long term and home care	9.9	11.0	4.9
• Drugs	3.3	3.7	1.6
Indirect costs			
• Sickness leave	11.6	371.9	5.7
• Early retirement	28.8	32.0	14.3
• Mortality	109.7	121.8	54.4
Total costs	201.8	224.0	100.0

ent amounted to 52 400 USD in 1996 (or € 58 000 in 2003 prices). Among tumour subtypes, astrocytomas III-IV accounted for 42% of the direct costs and meningiomas accounted for 30% (**Table 1**).

A sample of other studies

Latif et al. [8] studied the direct hospital costs of treating patients with biopsy proven malignant glioma (glioblastoma and anaplastic astrocytoma). The study was carried out at a neuro-oncology clinic at a British university teaching hospital and included 236 patients treated between 1989 and 1995. Unit costs were taken from the National Costing Project of the National Health Services (NHS). The mean costs in 1995 prices for 157 patients having surgery followed by radiotherapy were £ 442 for neuroradiological investigations, £ 2407 for neurosurgical bed days, £ 2068 for neurosurgery, £ 434 for neuropathology, £ 8832 for radiotherapy, £ 1078 for outpatients and £ 440 for chemotherapy. The mean total costs were £ 15 701 per patient, which corresponds to € 27 755 per patient in 2003 prices. The total treatment costs per patient ranged from £ 1978 to £ 26 980 (€ 3 497 to € 47 693). Not surprisingly, the median costs of care decreased sequentially with worsening brain tumour prognostic group. No indirect costs or costs for community-based care were included in the study.

A Swiss study by Wellis et al. [9] analysed the direct costs of microsurgical treatment of brain tumours and other brain pathologies in 1998 and 1999. The treatment costs of 127 microsurgically treated patients with arteriovenous malformation, acoustic neuroma, meningioma or brain metastasis potentially treatable with radiosurgery were studied. Costs for the surgical procedure, ICU care, medical and nursing care, interclinical bills for services provided by other departments and the overhead for basic hotel service were included. The mean total direct cost per patient amounted to € 15 242 (€ 15 812 in 2003 prices). However, treatment with radiosurgery had a lower cost than microsurgery. The mean direct cost per patient for treatment with Gamma Knife was € 7920 in 1999 (€ 8237 in 2003 prices). Indirect costs were not included in the analysis.

Dinnes et al. [10] reviewed the effectiveness and cost-effectiveness of temozolomide (TMZ) in the treatment of primary malignant brain tumours (astrocytoma and glioblastoma). They conducted a literature search in several databases, e.g. Medline and the Cochrane Library. The primary inclusion criteria were that the study should evaluate TMZ in malignant glioma patients, be a randomised controlled trial (RCT) or include more than 45 patients, and include effectiveness, QoL outcome measures, or both. Nine full reports of seven effectiveness studies were identified for inclusion: one RCT and six uncontrolled studies.

However, the RCT was, for the purposes of the study, deficient in several ways, and the uncontrolled studies were even less valid as evidence. As a complement to the inadequate clinical evidence, a simple model was developed to investigate the cost-effectiveness of TMZ in comparison with best alternative care. If a moderate impact on QoL alongside a moderate increase in progression-free survival was assumed, the cost per quality-adjusted life-year (QALY) gained for patients with either glioblastoma or astrocytoma was around £ 40 000 (for a QALY gain of 0.09 and 0.20, respectively). Only the direct costs of treatment at recurrence were considered.

There are also some American studies available in the literature, e.g. Hall et al. [11], Mendez et al. [12] and Silverstein et al. [13], but these almost exclusively concern economic evaluations of new treatments based on limited case series.

Discussion

Incidence- or prevalence-based mortality costs?

The authors of the Swedish study on the costs of brain tumours claimed that the prevalence approach was used, but the calculation of the indirect costs did not seem to be entirely prevalence-based. The costs for premature mortality were estimated in an ambiguous way from methodological perspective. A strict application of the prevalence approach would include costs for lost working time for: (1) patients who died from brain cancer before 1996 and before the age of 65 and who would otherwise have been alive and working in 1996; (2) patients who died from brain cancer in 1996, were below 65 years of age and who would otherwise have been alive and working. Patients (2), (3) and (4) in **Fig. 1** fulfil these criteria. Only costs for lost working time in 1996, represented by the dashed lines, should be included in the prevalence-based mortality costs.

A strict application of the incidence method would include patients who were diagnosed in 1996 but later died from brain cancer before their normal retirement age. It does not matter whether they died in 1996 or later as long as they died before retirement age as a result of their brain cancer diagnosed in 1996. This, of course, poses a problem for the analysis, because some follow-up time after the year of incidence may be needed to assess the survival prospects of the patients. The follow-up time may not be long enough to observe if patient

(5) in **Fig. 1** dies from the disease, but if a sufficient number of patients are followed for some time the survival prospects may be investigated by using survival analysis techniques. Alternatively, some survival assumption can be made based on historical survival data.

The methodology that seems to have been used in the study by Blomqvist et al. [1] coincides with neither a pure prevalence nor a pure incidence approach. Instead, they calculate the costs of lost working time based on the patients who died in 1996. In Fig. 1, this would apply to patients (3) and (4). This has the advantage that we know when they died, which makes it fairly straightforward to calculate the mortality costs, at least if we assume, as Blomqvist et al. [1] did, that the patients would otherwise have lived until the age of 65. However, the resulting measure of the mortality costs is neither a prevalence-based nor an incidence-based one, but something in between. Given that both the prevalence and the incidence approaches to estimating the mortality costs are somewhat tricky to handle, it is hardly surprising that they are not pursued consistently. The prevalence approach requires that patients who died from brain cancer before the year of interest are also included if they had still been alive and working in the absence of fatal disease. Since brain tumours affect children and adolescents, this would, in turn, require that the cancer registry would have to be scanned many years back in time for such patients. In practice, it may not be feasible to perform a strictly prevalence-based approach to the mortality costs.

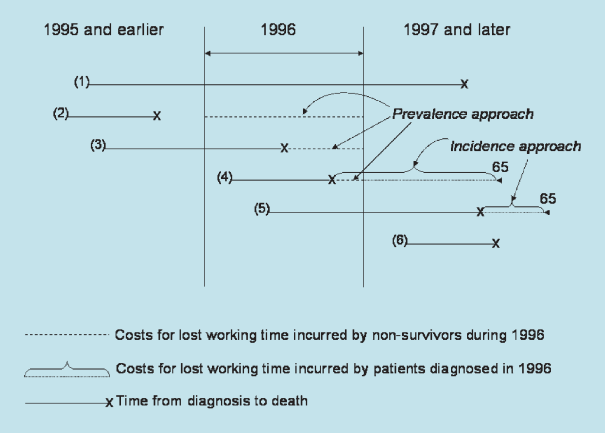

Fig. 1 ▶ **Prevalence and incidence approaches to mortality costs**

Why so few studies?

It is, of course, impossible to give a definitive answer to this question. If one may speculate, there are perhaps two good reasons for the almost complete lack of studies in this area. The first is that brain tumours are relatively rare, at least compared to prostate and breast tumours. The second is that it is hardly controversial that these patients should get a thorough treatment beginning immediately upon diagnosis. There is thus no need to catch the attention of health-care decision-makers by pointing out the high costs of the disease for society.

Directions for further research

Since there is an almost complete lack of comprehensive studies on the cost of brain cancer in almost all European countries, there is apparently much room for additional research in this area. As the evidence in the literature is very limited, however, it is hard to point out the most important problems for research. The best approach is probably to look first at the epidemiological evidence to identify the amount of available data about brain tumours. Since inpatient costs for hospital care and indirect costs for premature mortality represented about 73% of the total costs in Sweden, it is likely that it would be sufficient to gather information about these two items in other European countries in order to get a fair estimate of the total costs. Such data may be available in national registers in some countries.

Conclusions

Brain cancer is not among the most common cancer types overall, but it is the most common cause of cancer mortality among those under 35 years of age. Since it affects younger people, the costs of premature mortality are high.

There is only one comprehensive published study on the cost of brain tumours, a mainly prevalence-based Swedish study by Blomqvist et al. [1].

In the Swedish study, the indirect cost of early mortality was the largest single cost item, constituting 54% of the total costs. The direct cost of hospital care was the second largest cost item, representing 18% of the costs.

The cost of premature mortality in the Swedish study was calculated with a methodology that was neither purely prevalence- nor purely incidence-based. However, a purely prevalence-based approach would require long-term data that may be difficult to find.

Other studies available in the literature were limited in scope from a cost-of-illness perspective. Usually only direct costs based on a case series from a single hospital are included. The purpose of these studies is not to estimate the cost of illness, however, but rather to compare different treatment methods.

Since there are very few cost-of-illness studies available for brain tumours, there is apparently room for more research in this area.

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Economic evidence in dementia: a review

Introduction

Dementia is a syndrome characterised by a progressive loss of memory and other cognitive functions, leading to impairment of physical functions and ultimately to complete dependency. Alzheimer's disease (AD) is the most common cause of dementia, followed by vascular dementia, mixed dementia, Lewy body dementia and the fronto-temporal dementias [1]. Approximately 60% of demented patients have AD [2, 3].

Dementia is very costly to society. As an example, the total cost for dementia disorders in Sweden was estimated at 38.4 billion SEK in the year 2000 [4]. For comparison, the total health-care budget for Sweden in the same year was 160 billion SEK and the costs for elderly care within the communities about 60 billion SEK. The total cost of care for the elderly has been estimated at 110 billion SEK about 6% of the GDP.

The costs of care for patients with dementia can be measured by collection of empirical data. The costs due to dementia, however, cannot be measured directly. One way is to assume that certain resource use is attributable to dementia, and to estimate the cost of these resources. Alternatively, costs for patients with dementia can be compared with costs for matched non-demented controls, calculating the "net cost" of AD as the difference between the two. Yet another option is to compare costs for patients in early stages of dementia with the costs in progressed dementia.

This literature review summarises the existing evidence regarding costs of dementia in Europe.

Methods

Search strategy

The following search strategy was adopted:

- PubMed search on the terms dementia or Alzheimer's disease AND cost or economic, including English-language publications or local-language publications with abstract in English
- Ad hoc search in reports, databases and other sources known to the author.

The initial PubMed search identified 1848 publications. These were reviewed manually to identify studies relating to cost of illness of dementia in European countries. In total, 14 relevant original studies were identified, including references found in the ad-hoc search.

Diagnosis

The identified studies have included either subjects with Alzheimer's disease, or subjects with dementia (unspecified). Currently, there are no data in support of important differences in costs of care for patients with Alzheimer's disease compared with patients with other causes of dementia (e.g. vascular dementia). This review therefore does not distinguish between the different dementia disorders in the calculation of cost per patient.

Cost concepts

Costs are usually divided into direct costs and indirect costs, although this distinction is of little consequence. Direct costs include the costs of medical