Pharmacological Research 107 (2016) 79–84

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Perspective

Addressing the burden of epilepsy: Many unmet needs

Ettore Beghi

Laboratory of Neurological Disorders, IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri", Via Giuseppe La Masa, 19, 20156 Milan, Italy

ARTICLE INFO

Article history:
Received 22 January 2016
Received in revised form 2 March 2016
Accepted 2 March 2016
Available online 4 March 2016

Keywords:
Epilepsy
Burden
Incidence
Prevalence
Comorbidity
Prognosis
Mortality

ABSTRACT

Epilepsy is a heterogeneous clinical condition characterized by recurrent unprovoked seizures, their causes and complications. The incidence, prevalence and mortality of epilepsy vary with age, place and time contributing to a variable extent to the burden of the disease. Diagnostic misclassification may have strong impact on personal and societal reflections of the disease in light of its clinical manifestations and the need for chronic treatment. Epilepsy accounts for a significant proportion of the world's disease burden ranking fourth after tension-type headache, migraine and Alzheimer disease. Among neurological diseases, it accounts for the highest disability-adjusted life year rates both in men and in women. Although epilepsy is self-remitting in up to 50% of cases, variable long-term prognostic patterns can be identified based on the response to the available treatments. Epilepsy carries an overall increased risk of premature mortality with variable estimates across countries. Premature mortality predominates in patients aged less than 50 years, with epilepsies due to structural/metabolic conditions, with generalized tonic-clonic seizures, and seizures not remitting under treatment. Among deaths directly attributable to epilepsy or seizures, included are sudden unexpected death in epilepsy (SUDEP), status epilepticus, accidents, drowning, unintentional injuries, and suicide. Somatic and psychiatric disorders prevail in patients with epilepsy than in people without epilepsy. Asthma, migraine and cerebral tumors tend to occur more frequently in younger adults while cardiovascular disorders, stroke, dementia and meningioma predominate in the elderly. As being a fairly common clinical condition affecting all ages and requiring long-term (sometimes lifelong) treatment, epilepsy carries high health care costs for the society. Direct costs peak in the first year after diagnosis and then vary according to the severity of the disease, the response to treatment, and the presence of comorbidity. Although in several countries the costs of epilepsy are met by the national health systems, out-of-pocket costs may be a relevant fraction of the overall costs, especially in countries where the public management of health care is suboptimal or non-existent. Epilepsy strongly affects patients' independence, psychological health and emotional adjustment. Epilepsy impairs all aspects of health-related quality of life. Awareness and attitudes of the public about epilepsy may significantly affect the burden of the disease. All these factors add to the burden of the disease. However, many of the factors implicated in the onset of epilepsy, its course and treatment can be favorably addressed with appropriate strategic plans. More research is needed to investigate and manage the medical and psychosocial implications of epilepsy.

1. Introduction

Epilepsy is a highly heterogeneous clinical condition characterized by recurrent unprovoked seizures with their causes and biological, psychological and social complications. All these factors add to the burden of the disease and represent a relevant source of needs for patients, caregivers and caring physicians, and have a heavy economic impact at the societal level. The incidence, prevalence and mortality of epilepsy vary with age, place and time contributing to the variability of the burden of the disease. The observed differences can be explained by diagnostic misclassification, the population's and patient's genetic background, the distribution of some environmental risk factors, the socio-cultural context, the access to treatments and, not least, the definitions used for the diagnosis of the disease.

2. Definitions of seizures and epilepsy

One of the problems with the burden of epilepsy is represented by misdiagnosis. Diagnostic misclassification is one possible explanation for the inconsistencies between incidence and lifetime prevalence of epilepsy when comparing developed and developing countries [1]. The absence of diagnostic aids (laboratory tests, EEG and imaging studies) in developing countries may result in

E-mail address: ettore.beghi@marionegri.it

http://dx.doi.org/10.1016/j.phrs.2016.03.003
1043-6618/

Table 1
Age-standardized and absolute DALYs for epilepsy and proportion of DALYs attributable to epilepsy.

Variable	Value
Age-standardized DALYs (per 100,000), 1990, men	261.6
Age-standardized DALYs (per 100,000), 1990, women	226.0
Age-standardized DALYs (per 100,000), 2010, men	269.3
Age-standardized DALYs (per 100,000), 2010, women	232.9
Absolute DALYs	17,400,000
Proportion of total (all cause) DALYs (%)	0.7
Proportion of mental, neurological, and substance use DALYs (%)	6.8

Source: Whiteford et al. [8].
DALYs, disability-adjusted life years.

erroneously classifying as epileptic seizures psychogenic non-epileptic seizures (PNES) and other paroxysmal events. Even in countries where the diagnostic resources are fully available, misdiagnosis is not uncommon. Interrater reliability for the diagnosis of PNES by video-EEG monitoring is only moderate [2]. Misclassification may also refer to seizure type. Acute symptomatic seizures, defined as clinical seizures occurring at the time of a systemic insult or in close temporal association with a documented brain insult [3], are sometimes included in epidemiological studies, leading to the increase of all epidemiological indexes, and inevitably lead to overtreatment and to avoidable negative attitudes and stigma. The burden of epilepsy may also vary depending on the inclusion of single unprovoked seizures. Although the International League Against Epilepsy (ILAE) has recently included single unprovoked seizures in the definition of epilepsy [4,5], the risk of recurrence of a single unprovoked seizure is significantly lower than the risk of recurrence of a second seizure [6,7].

2.1. Epilepsy as part of the global burden of disease

Historically, health policy has been informed by mortality statistics. Although premature mortality has been an important source for the understanding of clinical conditions leading to premature mortality, only recently the focus on the burden of diseases has been moved to chronic disabling disorders. Epilepsy is one such disease. Chronic neurological disorders, including epilepsy, account for a significant proportion of the world's disease burden [8].

The Global Burden of Disease Study is a comprehensive analysis of the burden of 291 diseases and injuries and 67 risk factors in 187 countries and 21 world regions comparing the years 1990, 2005 and 2010 [9]. In this comprehensive review, burden estimates were obtained from all available epidemiological data using published reports and statistical methods to model the epidemiological data when unavailable, to quantify disability, and to adjust for comorbidities. The burden of disease was measured by disability-adjusted life years (DALYs), a health metric capturing the years lived with disability (LDs), the non-fatal component, and the years of life lost (YLLs) due to premature mortality. Mental, neurological and substance use disorders were the fifth cause of DALYs and the leading cause of YLDs [10]. Neurological disorders accounted for 3% of DALYs and 5.6% of YLDs [11].

As with other diseases, disability weights were calculated for epilepsy based on the availability of treatments and the presence of seizures [8]. With reference to published reports and modeling, a total of 28,300,000 prevalent cases are expected to live with epilepsy in the entire world. The disease ranks fourth after tension-type headache (1,432,500,000), migraine (1,014,000), and Alzheimer disease (43,000,000). The DALYs attributable to epilepsy are illustrated in Table 1. Among neurological diseases, epilepsy accounts for the highest age-standardized DALY rates both in men and in women, followed by migraine and Alzheimer disease. The disease accounts for 0.7% of total DALYs and for 6.8% of DALYs due mental, neurological and substance use disorders. A 16% increase of DALYs has been observed both in men and in women when comparing the years 1990 and 2010 (Table 1). This increase was largely due to changes in population growth and aging.

2.2. Prevalence of epilepsy

The prevalence of epilepsy varies substantially between developed and developing countries. In a systematic review and *meta*-analysis of published reports, the median lifetime prevalence for developed countries was 5.8 per 1000 compared to 15.4 per 1000 for rural and 10.3 per 1000 for urban studies in developing countries [12]. The median prevalence of active epilepsy, i.e. having experienced seizures in the previous five years and/or being treated, was 4.9 per 1000 for developed countries and 12.7 per 1000 and 5.9 per 1000 in rural and urban studies in developing countries. Along with sample size and age of study participants, poor health care and lack of specialized medical personnel and diagnostic equipment can explain the differences between developed and developing countries and between urban and rural areas. The higher lifetime prevalence of epilepsy in developing countries can be also due to higher incidence [13], which could in turn be attributable to traumatic brain injury (TBI) and infectious etiology, particularly in rural areas [14,15]. Rural areas of developing countries also have a large proportion of untreated patients possibly due to stigma, beliefs and attitudes towards epilepsy. Furthermore, recall of seizure events over a 5-year period may be poorer in rural areas due to low literacy levels and may lead to underestimation of prevalence [16].

2.3. Incidence of epilepsy

The estimated median worldwide incidence of epilepsy is 50.4 per 100,000 population per year [12]. However, significant differences can be found when comparing developing to developed countries (incidence, 81.7 vs. 45.0). The differences can be explained, at least in part, by the level of income in the country. The higher incidence of TBI, infections and infestations of the CNS in developing countries contribute to the increased incidence of the disease [14,15]. Familial clustering and differences in polymorphisms between developing and developed countries should be also considered [13].

The incidence of epilepsy varies with age with peaks in children under one year and predominantly in the elderly [17]. Annual incidence rates as high as 180 per 100,000 population in patients aged 85 years or older have been calculated [17]. The increase in the incidence of epilepsy with age is largely explained by the increased incidence of common clinical conditions in the elderly, like stroke and neurodegenerative disorders [18]. Silent strokes may also account for the occurrence of unprovoked seizures and epilepsy in this age group. Even acute symptomatic seizures predominate in the elderly [19], adding to the burden of the disease. Thus, with the increase of life expectancy, the number of individuals with epilepsy is going to increase in the future [18].

2.4. Prognosis and mortality of epilepsy

Epilepsy is a self-remitting clinical condition in up to 50% of cases [20]. Seizure remission is the main explanation for the difference between lifetime prevalence and incidence. However, when incidence and lifetime prevalence are compared in the same study, other factors need to be considered. These include premature mortality, socioeconomic factors, and stigma [1].

Epilepsy carries an overall increased risk of premature mortality. However, variable estimates have been provided across countries. The variability in such estimates can be attributed principally to

actual differences in risk of premature death among the various populations studied and to differences in study methods. All population-based studies reported an increased risk of premature mortality among people with epilepsy compared to general populations, with a three-fold pooled standardized mortality ratio (SMR), i.e. the ratio of observed deaths in epilepsy to that expected in the general population [21]. SMRs are especially high among people with epilepsy aged less than 50 years, among those with epilepsies due to structural/metabolic conditions, with generalized tonic-clonic seizures, and seizures not remitting under treatment. Among deaths directly attributable to epilepsy or seizures, important immediate causes include sudden unexpected death in epilepsy (SUDEP), status epilepticus, accidents, drowning, unintentional injuries, and suicide. SUDEP is the most common cause of epilepsy-related deaths and individuals with epilepsy have 27-fold higher rates of sudden death than controls [22]. In a pooled analysis of published reports [23], an overall crude annual incidence of 0.81 cases and an overall prevalence of 7.1 per 100,000 of SUDEP was estimated. Numbers were low in the first decade of life, were highest in the third and fourth decades, and declined markedly in the sixth decade. Based on the available numbers, in 2013 SUDEP accounted for 2750 deaths in the united States and 3994 deaths in the European Union.

2.5. The burden of epilepsy comorbidity

A comorbid condition is one that occurs in association with a given disease. The number of comorbidities tends to increase with age and rises to six in individuals aged 65 years or older [24]. The association of another clinical condition with epilepsy has substantial effects on morbidity and mortality, quality of life, demand on health services and, consequently, financial costs. The mechanisms of the association between epilepsy and other diseases include a causal association and shared risk factors, each represented by genetic or environmental factors. Several population-based studies, some of them using administrative databases, have addressed the comorbidity of epilepsy consistently showing a higher prevalence of somatic and psychiatric disorders in patients with epilepsy than in people without epilepsy (Table 2; see Ref. [25] for review). Psychiatric symptoms are common complaints in patients with epilepsy and the majority of studies using a control group report increased psychiatric problems in epilepsy cases than in controls [26]. The immune system is also relevant in epilepsy, as shown by the pathogenic role of specific antibodies in some syndromes, the good response to immune therapies, and the association with some autoimmune diseases [27]. Asthma, migraine and cerebral tumors tend to occur more frequently in younger adults while cardiovascular disorders, stroke, dementia and meningioma predominate in the elderly [28]. Compared to women without epilepsy, women with epilepsy are at increased risk of spontaneous miscarriage, antepartum or post-partum haemorrhage, hypertension, induction of labor, caesarean section, preterm birth, and fetal growth restriction [29]. The most significant differences in the frequency of comorbidity between epilepsy and controls can be explained by a causal relationship. This is particularly true for stroke, tumors, dementia and Alzheimer disease. Other associations (gastrointestinal disorders, cardiac arrhythmia, allergy and perhaps endocrine diseases) can be explained by the effects of antiepileptic drugs. Shared risk factors may be implicated in the association between epilepsy, heart disease, diabetes, and asthma. Epilepsy, dementia, major depression, anxiety and migraine may reflect underlying bidirectional mechanisms but, particularly for neurobehavioral disorders, symptoms reactive to the negative physical and social effects of the disease and its treatment cannot be excluded [30]. A comorbid psychotic illness is also common, with peaks in temporal lobe epilepsy [31]. Other associations cannot be easily explained

Table 2
Somatic and psychiatric comorbidities in patients with epilepsy.

Comorbidity	% (epilepsy vs. controls)		Prevalence ratio	
	Min	Max	Min	Max
Tumor (unspecified)	11.1 vs. 7.9	11.3–8.1	1.2	2.4[a]
Diabetes mellitus	7.7 vs. 5.7	13.0–7.7	1.0	1.6[a]
Thyroid disease (unspecified)	–	–	1.3	1.6[a]
Major depression	17.4 vs. 10.7		1.3[a]	2.0[a]
Anxiety	22.8 vs. 11.2		1.6[a]	2.0[a]
Dementia (unspecified)	–		4.3[a]	6.3[a]
Alzheimer disease	–		8.1[a]	
Migraine	34.7 vs. 16.2		1.4[a]	3.0[a]
Glaucoma	–		1.1	1.2
Cataract	–		1.2	2.4[a]
Stroke (unspecified)	9.4 vs. 2.2	15.7 vs. 2.4	3.9[a]	7.7[a]
Heart disease (unspecified)	8.4 vs. 4.6	18.3 vs. 11.3	1.8[a]	2.5[a]
Arterial hypertension	28.8 vs. 24.8	34.2 vs. 29.0	1.0	1.9[a]
COPD	5.2 vs. 1.9		1.9[a]	2.9[a]
Chronic bronchitis	7.5 vs. 4.1		1.7[a]	
Emphysema	5.5 vs. 1.7		1.3	
Asthma	19.2 vs. 12.6	21.9 vs. 12.6	1.1	1.8[a]
Peptic ulcer	12.4 vs. 6.2		1.9[a]	2.7[a]
Crohn & ulcerative colitis	–		2.0[a]	3.3[a]
Allergy (unspecified)	–		1.2[a]	1.6[a]
Back pain (unspecified)			1.4[a]	1.5[a]
Fibromyalgia	–		1.5	2.0[a]
Arthritis (unspecified)	30.9 vs. 21.4	43.0 vs. 28.0	1.4[a]	2.3[a]
Urinary incontinence	–		3.2[a]	4.4[a]

COPD, chronic obstructive pulmonary disease.
The identification and the prevention of several risk factors involved in the occurrence of seizures can significantly contribute to the reduction of the burden of epilepsy.
[a] Significant value. Modified from Keezer et al. [25].

but the possibility exists that patients with epilepsy, compared to the rest of the population, tend to report more frequently their complaints or undergo more intensive investigations of their health problems. The presence of comorbidity affects mortality in people with epilepsy. About two thirds of premature deaths can be attributed to comorbidity [32].

When assessing comorbidity in epilepsy, the presence of biological plausibility does not confirm per se a causal relationship. In fact, the possibility exists that epilepsy occurs spontaneously even at the presence of an epileptogenic CNS injury. For example, compared to the general population, patients with severe TBI are at higher risk of experiencing unprovoked seizures only during the first 20 years after the event [33]. The SMR is significantly increased in the first 15 years in patients with coexisting cerebrovascular disease, but only after 20 years of follow-up in those with ischemic heart disease [34].

2.6. Antiepileptic drugs as a source of disease burden

Antiepileptic drugs are an unreplaceable resource for the management of epilepsy. However, an incorrect use of antiepileptic drugs may be per se a source of disease burden. This issue is addressed in greater detail elsewhere in this volume. Suffice to say here that the available drugs could provoke discomfort and even put the patient at risk of serious adverse events if incorrectly included in the treatment regimen or if undue attention is paid to the side effect profiles or drug interactions. The use of carbamazepine in patients with generalized seizures, valproate in women of childbearing potential, and GABAergic drugs in patients with depression should be cautioned. Patients with drug-resistant epilepsy are at high risk of experiencing adverse treatment events because of the drug load and the number of coprescribed drugs [35]. Children, pregnant women and the elderly are the categories of patients in which an incorrect use of antiepileptic drugs may be a source of adverse events. Antiepileptic drugs can induce both

anatomical, cognitive and behavioral teratogenicity, with variable results depending on the designated compound, the daily dose and the number of products in the therapeutic schedule [36].

Quality of life has been found to be affected to a greater extent by adverse treatment effects than by an inadequate control of seizures [37].

2.7. The economic burden of epilepsy

As being a fairly common clinical condition affecting all ages and requiring long-term (sometimes lifelong) treatment, epilepsy carries high health care costs for the society. Included are direct costs, ie the expenditures met by patients and caregivers for the management of the disease, and indirect costs, ie the costs represented by productivity losses. While direct costs can be fairly easily calculated, indirect costs are difficult to measure because the extent of productivity losses depends on a number of variables, including the welfare state and the individual's education and socio-economic background. In 2010, the total cost of brain disorders in Europe was €798 billion, of which direct health care costs were 37%, direct non-medical costs 23%, and indirect costs 40% [38]. Average cost per inhabitant was €5.550 (ranging from €285 for headache to €30,000 for neuromuscular disorders). The total annual cost for epilepsy was 13.8 billion. The total cost per patient was €5221 (direct, €2461; direct non-medical, €625; indirect, €2136). Direct costs of epilepsy are even higher in the United States where, in the general epilepsy population, total healthcare costs per person ranged from $10,192 to $47,862 and epilepsy-specific costs ranged from $1022 to $19,749 [39]. Direct costs peak in the first year after diagnosis and then vary according to the severity of the disease, the response to treatment, and the presence of comorbidity [40]. These costs are highest in surgical candidates, followed by patients with drug-resistant epilepsy, active non drug-resistant epilepsy, newly diagnosed epilepsy, epilepsy with occasional seizures, and epilepsy in remission [41]. The main cost drivers include hospital admissions, drugs (mostly second and third-generation compounds), surgery and vagal nerve stimulation. The economic aspects of epilepsy differ with the age of the affected individuals [42]. Differences are also reflected by the inclusion of incident or prevalent epilepsy populations. Costs also vary with epileptic syndromes, antiepileptic drugs, hospital admissions, diagnostic tests and referral to epilepsy specialists and other healthcare professionals. In addition, children require the help of a caregiver, for whom lost work days or under-employment are frequent occurrences.

Out-of-pocket costs may also represent a relevant fraction of the overall costs, especially in countries where the public management of health care is suboptimal or non-existent.

2.8. The burden of epilepsy: patients' and caregivers' views

Epilepsy strongly affects patients' independence, psychological health and emotional adjustment. Educational attainment, driving and job restrictions and stigma may have strong emotional impact and significant effects on self-esteem, relationships with peers and family members, and even personal finances [43]. The social, psychological and emotional consequences of the disease and patients' reported outcomes are important aspects of the burden of epilepsy. The social implications of epilepsy have been assessed in a large European cohort study comparing individuals with epilepsy to non-epileptic controls in Italy, Germany, Spain, the Netherlands, England, Portugal, and Russia [44]. Patients with epilepsy were better educated than controls. However, more patients than controls were single or unemployed while fewer patients than controls held a driver's license or practiced sports. The distribution of social variables varied across countries but, with few exceptions, the differences between patients and controls were fairly similar.

Epilepsy impairs all aspects of health-related quality of life (HRQOL). The burden of epilepsy is perceived by patients and caregivers. The degree of parents' concerns and the severity of the disease correlate with deterioration of HRQOL both in children and in their family members [45]. This results in conflicts within the family and affects occupation, leisure activities, peer relationships and economy. Parents frequently admit increased apprehensiveness, even when not justified by the low severity of the disease. As with children, the care of an adult with epilepsy has a profound psychosocial impact on caregivers [46]. Included are increased levels of stress, social dissatisfaction, individual isolation, worry, helplessness, depression, marital problems, joblessness, and fear during seizures.

Awareness and attitudes of the public about epilepsy may significantly affect the burden of the disease. Knowledge about epilepsy, its clinical features, and attitudes towards its social/individual implications were tested in a nationwide telephone interview in Italy [47]. Almost all respondents declared knowing epilepsy, 56.6% knew a person with epilepsy, and 45.1% saw someone seizing. However, only 50.4% were unaware of the causes of the disease, 56.1% said epilepsy was a psychological/psychiatric disease, 36.5% a form of insanity, and 4.1% even an evil spirit possession. Epilepsy was incurable according to 35.5%. Moderate-to-severe restrictions to driving, regular employment, military career, and leisure activities, and even marriage and procreation were suggested by relevant proportions of interviewees. Knowledge and attitudes varied with education, age and gender. These findings are partly in keeping with other worldwide reports [47] and may justify experienced and perceived stigma, which predominates in developing countries and forces people with epilepsy to conceal their disease [48]. Patients' and caregiver views vary when comparing children and adults with epilepsy. The former may experience problems at school and when facing their first emotional and social activities while the latter may have difficulties in the labor market, with driving, marriage and procreation.

2.9. Unmet needs and future directions

The first and foremost action to reduce the burden of epilepsy is to minimize diagnostic errors. Misdiagnosis is common in developing countries but cannot be excluded even in developed countries. Adequate diagnostic aids and educational tools should be made available in developing countries. Efforts should be made to improve diagnostic accuracy in patients with paroxysmal events by devising proper algorithms [49]. Well-defined clusters of symptoms and signs differentiating epileptic seizures from PNES are awaited to favor a correct diagnosis in the absence of other diagnostic tests. Misdiagnosis should not only be intended as a missed diagnosis of epilepsy but also as an erroneous epilepsy label in patients experiencing other types of paroxysmal events. Misdiagnosis, with its negative reflections (which include stigma, unduly exposure to a chronic drug treatment, and "false" drug-resistance), will perhaps increase after the adoption of the new definition of epilepsy, issued by the International League, which may simply require the occurrence of a single unprovoked seizure in patients judged at high risk of recurrence [4,5].

The use of incorrect treatments is another source of disease burden. Another substantial action for the reduction of the burden of epilepsy is the elimination of seizures. Studies done in untreated individuals from developing countries have shown that the proportion of epilepsies entering remission is similar to epilepsies in countries in which virtually all patients receive appropriate treatment [50,51]. As treatment gap may be greater than 75% [52], the higher prevalence of active epilepsy is developing countries may

be explained at least in part by undertreatment. This unmet need can be properly addressed and perhaps successfully abated by providing drugs to patients living in developing countries.

Another effective intervention to reduce epilepsy burden is the prevention of symptomatic epilepsies. A report of the US Institute of Medicine emphasized the importance of the early identification of comorbidities [53]. Early detection may lead prevention of several complications of seizures and epilepsy, including antiepileptic drugs, with important reflections on quality of life of patients and caregivers, and on economic savings for the health systems. The treatment of comorbidities can also have effects on the prevention of seizures. Randomized trials of antidepressant drugs showed that the incidence of seizures as adverse events was less among patients receiving active treatment as compared to placebo [54].

Although in developing countries the proportion of people living in poverty is substantial, social deprivation is associated with risk factors for epilepsy, risk for developing epilepsy, and increased mortality [1]. Low socioeconomic status is associated with an increased prevalence of epilepsy in Brazil [55], in the United States [56] and in the United Kingdom [57]. Low socioeconomic status is also associated with stroke [58], TBI [59], congenital malformations [60], CNS infections [61], alcohol abuse [62], brain neoplasm [63], and Alzheimer's disease [64]. These causes of epilepsy are also associated with an increased mortality and some of them (stroke, TBI, CNS infections, alcoholism) can be prevented.

The increasing life expectancy in developing countries will perhaps have strong effects on the incidence of epilepsy because the elderly population is going to increase. Early detection and prevention of epileptogenic conditions is thus mandatory even in these countries.

Epilepsy-related mortality remains underappreciated and public health interventions are inadequate [65]. Despite increasing awareness of the excess mortality faced by people with epilepsy, epilepsy-related deaths cannot be accurately estimated nor effectively reduced. The prevention of epilepsy-related mortality will require quantifying epilepsy deaths in the community and measuring change over time.

Patient, caregiver, medical student, and physician education about SUDEP remains poor [66,67]. A collaborative effort is needed to promote awareness and education about epilepsy-related mortality and to develop, evaluate, and implement effective preventive measures.

The attribution of costs to epilepsy is difficult to disentangle from the cost of the underlying epileptogenic conditions [68]. For each clinical condition with epileptogenic potential well-designed prospective studies are needed comparing patients with and without seizures and followed for prolonged periods of time are awaited.

In countries with limited resources, the economic burden on households may be unsustainable, leading to undertreatment or even treatment discontinuation. Further research is needed to explore the burden of out-of-pocket costs, mostly in developing countries but even in countries where universal coverage arrangements are in place.

Caregiver burden constitutes an unmet need. Positive family support is needed for children and adults with epilepsy. This includes developing effective educational materials suited to individual family members, encouraging the use of support groups, and offering psychotherapy to family members.

3. Conclusions

Epilepsy is a chronic disease with differing phenotypes and relevant physical, psychological, emotional and social implications for the affected individuals and their families and caregivers. All these factors add to the burden of the disease. However, many of the factors implicated in the onset of epilepsy, its course and treatment can be favorably addressed with appropriate strategic plans. More research is needed to investigate and manage the medical and psychosocial implications of epilepsy. Epilepsy priorities have been outlined in a recent report by the ILAE-IBE Epilepsy Advocacy Europe Task Force [69]. In that document, suggestions were made to develop specific research programs focusing on pediatric and aging populations and on comorbidities and to reduce stigma and social burden through targeted initiatives at national and regional levels. Identified priorities also include, among others, therapeutic strategies aimed at improving prevention and cure of epilepsy.

Conflict of interest

Dr Beghi serves on the editorial boards of *Amyotrophic Lateral Sclerosis, Clinical Neurology & Neurosurgery,* and *Neuroepidemiology*; has been an associate editor of *Epilepsia*; has received money for board membership from VIROPHARMA and EISAI; has received funding for travel and speaker honoraria from UCB-Pharma, Sanofi-Aventis, GSK; has received funding for educational presentations from GSK; reports grants from the Italian Drug Agency and from the Italian Ministry of Health.

Acknowledgement

None.

References

[1] E. Beghi, D. Hesdorffer, Prevalence of epilepsy—an unknown quantity, Epilepsia 55 (2014) 963–967.
[2] S.R. Benbadis, W.C. La France Jr., G.D. Papandonatos, K. Korabathina, K. Lin, H.C. Kraemer, NES Treatment Workshop, Interrater reliability of EEG-video monitoring, Neurology 73 (2009) 843–846.
[3] E. Beghi, A. Carpio, L. Forsgren, D.C. Hesdorffer, K. Malmgren, J.W. Sander, T. Tomson, W.A. Hauser, Recommendation for a definition of acute symptomatic seizure, Epilepsia 51 (2010) 671–675.
[4] R.S. Fisher, W. van Emde, W. Boas, C. Blume, P. Elger, P. Genton, P. Lee, J.Jr Engel, Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), Epilepsia 46 (2005) 470–472.
[5] R.S. Fisher, C. Acevedo, A. Arzimanoglou, A. Bogacz, J.H. Cross, C.E. Elger, J. Engel Jr., L. Forsgren, J.A. French, M. Glynn, D.C. Hesdorffer, B.I. Lee, G.W. Mathern, S.L. Moshé, E. Perucca, I.E. Scheffer, T. Tomson, M. Watanabe, S. Wiebe, ILAE official report: a practical clinical definition of epilepsy, Epilepsia 55 (2014) 475–482.
[6] A.T. Berg, S. Shinnar, The risk of seizure recurrence following a first unprovoked seizure: a quantitative review, Neurology 41 (1991) 965–972.
[7] W.A. Hauser, S.S. Rich, J.R. Lee, J.F. Annegers, V.E. Anderson, Risk of recurrent seizures after two unprovoked seizures, N. Engl. J. Med. 338 (1998) 429–434.
[8] H.A. Whiteford, A.J. Ferrari, L. Degenhardt, V. Feigin, T. Vos, The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010, PLoS One 10 (2015) e0116820.
[9] C.J.L. Murray, T. Vos, R. Lozano, M. Naghavi, A.D. Flaxman, et al., Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet 380 (2012) 2197–2223.
[10] H.A. Whiteford, L. Degenhardt, J. Rehm, A.J. Baxter, A.J. Ferrari, et al., The global burden of mental and substance use dusorders, 2010, Lancet 382 (2013) 1575–1586.
[11] T. Vos, A.D. Flaxman, M. Naghavi, R. Lozano, C. Michaud, et al., Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis of the Global Burden of Disease Study 2010, Lancet 380 (2012) 2163–2196.
[12] A.K. Ngugi, C. Bottomley, I. Kleinschmidt, J.W. Sander, C.R. Newton, Estimation of the burden of active and life-time epilepsy: a meta-analytic approach, Epilepsia 51 (2010) 883–890.
[13] A.K. Ngugi, S.M. Kariuki, C. Bottomley, I. Kleinschmidt, J.W. Sander, C.R. Newton, Incidence of epilepsy. A systematic review and meta-analysis, Neurology 77 (2012) 1005–1012.
[14] P.M. Preux, M. Druet-Cabanac, Epidemiology and etiology of epilepsy in sub-Saharan Africa, Lancet Neurol. 4 (2005) 21–31.
[15] J.G. Burneo, J. Tellez-Zenteno, S. Wiebe, Understanding the burden of epilepsy in Latin America: a systematic review of its prevalence and incidence, Epilepsy Res. 66 (2005) 63–74.

[16] S.P. Saha, B. Sushanta, B.K. Roy, A. Basu, T. Roy, B. Maity, S.K. Das, A prospective incidence study of epilepsy in a rural community of West-Bengal, India, Neurol. Asia 13 (2008) 41–48.
[17] A.W. Hauser, J.F. Annegers, L.T. Kurland, Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984, Epilepsia 34 (1993) 453–468.
[18] M.J. Brodie, A.T. Elder, P. Kwan, Epilepsy in later life, Lancet Neurol. 8 (2009) 1019–1030.
[19] J.F. Annegers, W.A. Hauser, J.R. Lee, W.A. Rocca, Incidence of acute symptomatic seizures in Rochester Minnesota, 1935–1984, Epilepsia 36 (1995) 327–333.
[20] J.F. Annegers, W.A. Hauser, L.R. Elveback, Remission of seizures and relapse in patients with epilepsy, Epilepsia 20 (1979) 729–737.
[21] O. Nevalainen, H. Ansakorpi, M. Simola, J. Raitanen, J. Isojärvi, M. Artama, A. Auvinen, Epilepsy-related clinical characteristics and mortality: a systematic review and meta-analysis, Neurology 83 (2014) 1968–1977.
[22] A.G. Holst, B.G. Winkel, B. Risgaard, J.B. Nielsen, P.V. Rasmussen, S. Haunsø, A. Sabers, P. Uldall, J. Tfelt-Hansen, Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study, Epilepsia 54 (2013) 1613–1620.
[23] D.J. Thurman, D.C. Hesdorffer, J.A. French, Sudden unexpected death in epilepsy: assessing the public health burden, Epilepsia 55 (2014) 1479–1485.
[24] A.R. Feinstein, The pre-therapeutic classification of co-morbidity in chronic disease, J. Chronic Dis. 23 (1970) 455–468.
[25] M.R. Keezer, S.M. Sisodiya, J.W. Sander, Comorbidities of epilepsy: current concepts and future perspectives, Lancet Neurol. 15 (2016) 106–115.
[26] W.A. Swinkels, J. Kuyk, R. van Dyck, P. Spinhoven, Psychiatric comorbidity in epilepsy, Epilepsy Behav. 7 (2005) 37–50.
[27] R. Nabbout, Autoimmune and inflammatory epilepsies, Epilepsia 53 (Suppl. 4) (2012) 58–62.
[28] A. Gaitatzis, K. Carroll, A. Majeed, J.W. Sander, The epidemiology of the comorbidity of epilepsy in the general population, Epilepsia 45 (2004) 1613–1622.
[29] L. Viale, J. Allotey, F. Cheong-See, D. Arroyo-Manzano, D. Mccorry, M. Bagary, L. Mignini, K.S. Khan, J. Zamora, S. Thangaratinam, EBM CONNECT Collaboration, Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis, Lancet 386 (2015) 1845–1852.
[30] J.J. Lin, M. Mula, B.P. Hermann, Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan, Lancet 380 (2012) 1180–1192.
[31] M.J. Clancy, M.C. Clarke, D.J. Connor, M. Cannon, D.R. Cotter, The prevalence of psychosis in epilepsy; a systematic review and meta-analysis, BMC Psychiatry 14 (2014) 75.
[32] A. Gaitatzis, J.W. Sander, The mortality of epilepsy revisited, Epileptic. Disord. 6 (2004) 3–13.
[33] J.F. Annegers, W.A. Hauser, S.P. Coan, W.A. Rocca, A population-based study of seizures after traumatic brain injuries, N. Engl. J. Med. 338 (1998) 20–24.
[34] A. Neligan, G.S. Bell, A.L. Johnson, D.M. Goodridge, S.D. Shorvon, J.W. Sander, The long-term risk of premature mortality in people with epilepsy, Brain 134 (2011) 388–395.
[35] M.P. Canevini, G. De Sarro, C.A. Galimberti, G. Gatti, L. Licchetta, A. Malerba, G. Muscas, A. La Neve, P. Striano, E. Perucca, SOPHIE Study Group, Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy, Epilepsia 51 (2010) 797–804.
[36] K.J. Meador, D.W. Loring, Developmental effects of antiepileptic drugs and the need for improved regulations, Neurology 86 (2016) 297–306.
[37] F.G. Gilliam, A.J. Fessler, G. Baker, V. Vahle, J. Carter, H. Attarian, Systematic screening allows reduction of adverse antiepileptic drug effects: a randomized trial, Neurology 62 (2004) 23–27.
[38] J. Olesen, A. Gustavsson, M. Svensson, H.U. Wittchen, B. Jönsson, European Brain Council, The economic cost of brain disorders in Europe, Eur. J. Neurol. 19 (2012) 155–162.
[39] C.E. Begley, T.L. Durgin, The direct cost of epilepsy in the United States: a systematic review of estimates, Epilepsia 56 (2015) 1376–1387.
[40] K. Allers, B.M. Essue, M.L. Hackett, J. Muhunthan, A. Anderson, K. Pickles, F. Scheibe, S. Jan, The economic impact of epilepsy: a systematic review, BMC Neurol. 15 (2015) 245.
[41] E. Beghi, L. Garattini, E. Ricci, D. Cornago, F. Parazzini, EPICOS Group, Direct cost of medical management of epilepsy among adults in Italy: a prospective cost-of-illness study (EPICOS), Epilepsia 45 (2004) 171–178.
[42] E. Beghi, B. Frigeni, M. Beghi, P. De Compadri, L. Garattini, A review of the costs of managing childhood epilepsy, Pharmacoeconomics 23 (2005) 27–45.
[43] C. Kerr, A. Nixon, M. Angalakuditi, The impact of epilepsy on children and adult patients' lives: Development of a conceptual model from qualitative literature, Seizure 20 (2011) 764–774.
[44] The RESt-1 Group, Social aspects of epilepsy in the adult in seven European countries, Epilepsia 41 (2000) 998–1004.
[45] C. Cianchetti, P. Messina, E. Pupillo, G. Crichiutti, M.G. Baglietto, P. Veggiotti, N. Zamponi, S. Casellato, L. Margari, G. Erba, E. Beghi, TASCA study group, The perceived burden of epilepsy: impact on the quality of life of children and adolescents and their families, Seizure 24 (2015) 93–101.
[46] F. Saada, Z.S. Wang, R.E.D. Bautista, In focus: the everyday lives of families of adult individuals with epilepsy, Epilepsy Behav. 50 (2015) 10–13.
[47] O. Mecarelli, G. Capovilla, A. Romeo, G. Rubboli, P. Tinuper, E. Beghi, Past and present public knowledge and attitudes toward epilepsy in Italy, Epilepsy Behav. 18 (2010) 110–115.
[48] D. Bhalla, K. Chea, H. Chamroeun, C. Vichea, P. Huc, C. Samleng, R. Sebbag, D. Gérard, M. Dumas, S. Oum, M. Druet-Cabanac, P.M. Preux, Comprehensive evaluation of the psychosocial parameters of epilepsy: a representative population-based study in Prey Veng (Cambodia), Epilepsia 54 (2013) 1342–1351.
[49] T.U. Syed, W.C. LaFrance Jr., E.S. Kahriman, S.N. Hasan, V. Rajasekaran, D. Gulati, S. Borad, A. Shahid, G. Fernandez-Baca, N. Garcia, M. Pawlowski, T. Loddenkemper, S. Amina, M.Z. Koubeissi, Can semiology predict psychogenic nonepileptic seizures? A prospective study, Ann. Neurol. 69 (2011) 997–1004.
[50] M. Placencia, S.D. Shorvon, V. Paredes, C. Bimos, J.W. Sander, J. Suarez, S.M. Cascante, Epileptic seizures in an Andean region of Ecuador, Brain 115 (1992) 771–782.
[51] A. Nicoletti, V. Sofia, G. Vitale, S.I. Bonelli, V. Bejarano, F. Bartalesi, D.S. Tran, P.M. Preux, M. Zappia, A. Bartoloni, Natural history and mortality of chronic epilepsy in an untreated population of rural Bolivia: a followup after 10 years, Epilepsia 50 (2009) (2009) 2199–2206.
[52] A.C. Meyer, T. Dua, J. Ma, S. Saxena, G. Birbeck, Global disparities in the epilepsy treatment gap: a systematic review, Bull. WHO 88 (2010) 260–266.
[53] M.J. England, C.T. Liverman, A.M. Schultz, L.M. Strawbridge, Epilepsy across the spectrum: promoting health and understanding. A summary of the Institute of Medicine report, Epilepsy Behav. 25 (2012) 266–276.
[54] K. Alper, K.A. Schwartz, R.L. Kolts, A. Khan, Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports, Biol. Psychiatry 62 (2007) 345–354.
[55] A.L.A. Noronha, M.A. Borges, L.H.N. Marques, D.M. Zanetta, P.T. Fernandes, H. de Boer, J. Espíndola, C.T. Miranda, L. Prilipko, G.S. Bell, J.W. Sander, L.M. Li, Prevalence and pattern of epilepsy treatment in different socioeconomic classes in Brazil, Epilepsia 48 (2007) 880–885.
[56] S.L. Shamansky, G.H. Glaser, Socioeconomic characteristics of childhood seizure disorders in the New Haven area: an epidemiologic study, Epilepsia 20 (1979) 457–474.
[57] C.L. Morgan, Z. Ahmed, M.O. Kerr, Social deprivation and prevalence of epilepsy and associated health usage, J. Neurol. Neurosurg. Psychiatry 69 (2000) 13–17.
[58] S. Claiborne Johnston, S. Mendis, C.D. Mathers, Global variation in stroke burden and mortality: estimates from monitoring, surveillance, and modeling, Lancet Neurol. 8 (2009) 345–354.
[59] C. Cubbin, F.B. LeClere, G.S. Smith, Socioeconomic status and the occurrence of fatal and nonfatal injury in the United States, Am. J. Public Health 90 (2000) 70–77.
[60] M. Vrijheid, H. Dolk, D. Stone, L. Abramsky, E. Alberman, J.E. Scott, Socioeconomic inequalities in risk of congenital anomaly, Arch. Dis. Child. 82 (2000) 349–352.
[61] I.R. Jones, G. Urwin, R.A. Feldman, N. Banatvala, Social deprivation and bacterial meningitis in north east Thames region: three year study using small area statistics, BMJ 314 (1997) 794–795.
[62] T. Hemmingsson, I. Lundberg, F. Diderichsen, The roles of social class of origin, achieved social class and intergenerational social mobility in explaining social-class inequalities in alcoholism among young men, Soc. Sci. Med. 49 (1999) 1051–1059.
[63] F. Faggiano, T. Partanen, M. Kogevinas, P. Boffetta, Socioeconomic differences in cancer incidence and mortality, IARC Sci. Publ. 138 (1997) 65–176.
[64] A. Karp, I. Kareholt, C. Qiu, T. Bellander, B. Winblad, L. Fratiglioni, Relation of education and occupation based socioeconomic status to incident Alzheimer's disease, Am. J. Epidemiol. 59 (2004) 175–183.
[65] O. Devinsky, T. Spruill, D. Thurman, D. Friedman, Recognizing and preventing epilepsy-related mortality: a call for action, Neurology (2015), http://dx.doi.org/10.1212/WNL.0000000000002253, Dec 16. [Epub ahead of print].
[66] D. Friedman, E.J. Donner, D. Stephens, C. Wright, O. Devinsky, Sudden unexpected death in epilepsy: knowledge and experience among U.S. and Canadian neurologists, Epilepsy Behav. 35 (2014) 13–18.
[67] W.R. Miller, N. Young, D. Friedman, J.M. Buelow, O. Devinsky, Discussing sudden unexpected death in epilepsy (SUDEP) with patients: practices of health-care providers, Epilepsy Behav. 32 (2014) 38–41.
[68] C.E. Begley, E. Beghi, R.G. Beran, D. Heaney, J.T. Langfitt, C. Pachlatko, H. Silfvenius, M.R. Sperling, S. Wiebe, ILAE commission on the burden of epilepsy, subcommission on the economic burden of epilepsy: final report 1998–2001, Epilepsia 43 (2002) 668–673.
[69] M. Baulac, H. de Boer, C. Elger, M. Glynn, R. Kälviäinen, A. Little, J. Mifsud, E. Perucca, A. Pitkänen, P. Ryvlin, Epilepsy priorities in Europe: a report of the ILAE-IBE Epilepsy Advocacy Europe Task Force, Epilepsia 56 (2015) 1687–1695.