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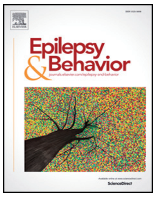

Editorial

Determining the cost of first-ever seizures: A narrative review and future directions

1. Introduction

First-ever seizures are life changing events that may inflict substantial emotional and financial strain through productivity loss, altered informal care needs, and modified occupational and social roles. They may impose a new health burden on previously well patients or further complicate the health of those with preexisting complex medical needs. A diverse range of conditions manifests as seizures, and therefore, first-ever seizures carry a wide range of implications for patients and healthcare systems alike. Broadly speaking, first-ever seizures may be categorized as provoked or unprovoked seizures. Acute symptomatic (or provoked) seizures occur in the presence of potentially life-threatening risk factors that require rapid identification and management. Unprovoked seizures may represent single events that never recur or, conversely, new-onset epilepsy with propensity for further seizures. Delineating between one-off seizures and new-onset epilepsy largely relies on an adequate period of follow-up, and so, for the purposes of this review, we refer to both eventualities when considering unprovoked seizures. The costs of first-ever seizures, irrespective of the underlying cause, are an important and understudied issue. This review considers first-ever seizure epidemiology and etiology; associated direct and indirect costs and effect on quality of life; potential future costs; and proposes research strategies to accurately quantify the substantial health economic burden of first-ever seizures to facilitate health budget planning.

2. Epidemiology of first-ever seizures

A systematic review reports the incidence of unprovoked seizures to be 50.8 per 100,000 [1], and up to 4.1% of people will experience one or more unprovoked seizures during their lifetime [2]. Acute symptomatic seizures occur in 39 per 100,000 person-years with a 3.6% lifetime risk [3]. This relatively high risk of seizures across a lifetime is reflected in healthcare system utilization: seizures account for 1–2% of presentations to emergency departments [4,5] and occur in 3.6% of hospitalized patients [6]. Determining the costs associated with these common events is crucial to appreciate and best manage their impact.

3. Cost of first-ever seizures

There are many ways in which first-ever seizures cost patients, caregivers, and society. These include direct medical costs, which include hospitalization, clinic visits, and medications; direct nonmedical costs including patients' out-of-pocket expenditures; and indirect costs due to loss of ability to perform paid and unpaid work. Quantifying quality of life, as assessed through patient-reported outcome measures (PROMS), is of paramount importance for those with first-ever seizures. Finally, unprovoked first-ever seizures, and to a lesser extent, acute symptomatic seizures, bear potential future costs associated with seizure recurrence.

3.1. Direct costs

Direct medical costs may be divided into costs associated with the incident seizure and subsequent costs. Incident seizure costs may include emergency department assessments, hospital admissions, routine laboratory tests, and neuroimaging. Subsequent costs may include outpatient visits to general practitioners and epilepsy specialists, diagnostic investigations such as dedicated functional and structural neuroimaging, electroencephalographs (EEG), and antiepileptic drug (AED) therapy.

Direct medical costs of epilepsy have been studied, but there is a paucity of data on costs associated with first-ever seizures. A good approximation of the direct medical costs of first-ever seizures are those related to the management of patients with newly diagnosed epilepsy; this cohort represents the intensive consultation and investigation typically required for the modern evaluation of new-onset seizures. A large prospective study reported that in the first year after epilepsy diagnosis, inpatient care accounted for two-thirds of direct costs, with the remaining direct costs associated with subsequent outpatient care including visits to neurologists (3%), investigations including EEG (3%), Computer tomography (CT) or magnetic resonance imaging (MRI) (10%), and AEDs (8%) [7]. A multicenter observational study reported that a cohort of patients referred to epilepsy specialists for newly diagnosed epilepsy incurred average costs of $US4473 per patient per year, compared with an 'old referral' cohort with established epilepsy diagnoses that incurred average costs of $US845 per patient per year [8].

Similar patterns were observed in a prospective Russian study, with direct medical costs due to newly diagnosed epilepsy outweighing direct medical costs of established and well-controlled epilepsy (€782 and €646 per person, respectively) [9]. In the 'new referral' cohort, direct medical costs accounted for 87.6% of total costs, mainly due to hospitalization (64%) and AEDs (11%) [8]. This was consistent with studies of patients with established epilepsy, for whom hospitalizations (32.3%–59.9%) and AEDs (26.7%–30%) were the main contributors of direct medical costs [10,11].

Underlying seizure etiology is likely to influence direct costs. Compared with unprovoked seizures, acute symptomatic seizures due to systemic disturbance or brain insults, or remote symptomatic seizures due to structural abnormalities such as brain tumors, likely require

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more intensive medical care. Studies report increased risk of death for patients with acute symptomatic seizures due to central nervous system infection, stroke, traumatic brain injury, anoxic encephalopathy, and metabolic derangement, and seizures in this setting may reflect the severe underlying illness [12,13]. Clearly, these conditions require hospital admission and intensive management; this is supported by a study that reported within the first year of epilepsy diagnosis, those with symptomatic etiology had direct costs almost three times higher compared with those with idiopathic etiology [7].

Healthcare utilization for patients with first-ever seizures has been compared with people with well-controlled epilepsy and patients with uncomplicated hypertension [14]. The first-ever seizure cohort had greater healthcare utilization compared with well-controlled epilepsy and uncomplicated hypertension cohort over a 12-month period, with 29% visiting a healthcare provider 4–6 times regarding their first-ever seizure and 71% visiting 1–3 times [14]. This did not include visits made to undergo tests and was not related to seizure recurrence, as patients with more than one seizure were excluded from the first-ever seizure cohort. Although the reasons for increased visits to healthcare providers was not specifically explored in this study, potential reasons may include thorough workup of first-ever seizure cause, review, and monitoring of those newly prescribed antiepileptic medication, and patient-initiated visits for reassurance and to allay anxiety.

There are few data regarding patients' out-of-pocket expenditure for epilepsy, and even less with regard to first-ever seizures. A meta-analysis identified six studies in epilepsy, which specifically reported out-of-pocket expenditure, from a range of countries with varying levels of health insurance [15]. Overall, the upfront out-of-pocket costs were found to pose a substantial financial burden on many households, including those with health insurance.

3.2. Indirect costs

Even less well studied are the indirect costs of first-ever seizures. These costs include reduced productivity because of sick leave (absenteeism), reduced work capacity while at work (presenteeism), and early retirement [16,17].

It has been shown that patients with first-ever seizure have lower employment rates and lower income when compared with controls. In one study, employment rates for the first-ever seizure cohort were 1–12% lower than that of controls at time of index seizure event, and this remained unchanged for duration of follow-up [18]. This may in part be due to higher morbidity in the first-ever seizure cohort, as measured by sickness periods and days of receiving disability pension [18]. Employment rates for patients with first-ever seizures may be further affected by limitations to undertake potentially dangerous activities, such as operating heavy machinery or driving, and these restrictions may be in place for up to 12 months [19]. If alternative work duties are not readily available, patients with first-ever seizures may need to retrain, change careers, or accept early retirement. A large UK study reported that almost 5% of people with first-ever seizures or newly diagnosed epilepsy had to change jobs because of their seizure(s) [20].

Informal care needs of first-ever seizure patients are likely underreported or underrecognized and may impose a considerable burden on families and caregivers. This may include driving patients to medical appointments, school, and work, and temporarily assuming household duties that may carry risk if there is a seizure recurrence such as bathing infants or cooking. The indirect costs of first seizures are understudied, and the true effect, including absenteeism, presenteeism, early retirement, and informal care needs may be substantially more than previously estimated.

3.3. Quality-of-life costs

Quality of life is an often overlooked yet important consideration to fully appreciate the far-reaching effect of first-ever seizures. Few studies have examined the neuropsychological effect of first-ever seizures, but from the scant literature that does exist, it is clear that the impact of first-ever seizures cannot be overstated. In a study of patients with first-ever seizures, 17% were moderately to extremely fearful of having a recurrent seizure, and 38% stated that twelve months after the event, the seizure still had a moderate to extreme impact on their quality of life [14].

Quality of life may be quantified using PROMS that consider general- and health-related quality of life, disease symptoms, and level of function. Patient-reported outcome measures may be evaluated with validated generic scales such as the EuroQoL five-dimension scale (EQ-5D) [21] or disease-specific scales such as the Quality of Life In Epilepsy Inventory (QOLIE) [22]. The EQ-5D assesses five domains including mobility, pain/discomfort, usual activities, self-care, and anxiety/depression, and patients rate these domains at five levels: 'no problems', 'slight problems', 'moderate problems', 'severe problems', and 'extreme problems'. The QOLIE, available in long (-89) and short (-31) versions, includes measures of overall quality of life, emotional well-being, work/driving/social function, cognitive abilities, worry about seizures, and health perceptions.

Although there are no PROMS questionnaires specific to first-ever seizures, scales such as EQ-5D and/or QOLIE may be reasonable options for baseline assessment. Routine collection of PROMS questionnaires for first-ever seizures is needed to increase recognition and provide quantifiable data regarding the substantial effect of first-ever seizures on well-being and quality of life.

3.4. Potential future costs

The decision to initiate AED therapy, and the appropriate timing for this, are crucial and difficult questions in the management of unprovoked first-ever seizures. Clinicians need to carefully balance the risk of missed opportunities for appropriate therapy against the risk of overtreatment with potential side effects and drug–drug interaction. The pivotal point in this decision-making process involves determining an individual's risk of subsequent seizures. The Multicentre trial for Early Epilepsy and Single Seizures (MESS) [23] is a large multinational trial that developed a prognostic model to estimate an individual's risk of subsequent seizures. Variables to consider include number of seizures prior to presentation, presence of a neurological disorder, and epileptiform activity on EEG. The MESS revealed that those at moderate- or high-risk for seizure recurrence would benefit from AED therapy; the evidence was less clear for those at lower risk of seizure recurrence. The MESS included some patients with prior seizures, fulfilling epilepsy diagnostic criteria, and so, the modeling is difficult to extrapolate to those with true first-ever seizures.

A Cochrane review and meta-analysis [24] found that AED initiated for unprovoked first-ever seizures reduced the risk of subsequent seizures but did not confer remission over the long term nor a mortality benefit. In addition, the review found that immediate treatment of unprovoked first-ever seizures was associated with a higher risk of adverse events. However, as is currently the case in clinical practice, this meta-analysis was unable to separate and compare patients based on those with one-off unprovoked events and those destined for future seizures. It is possible that the true benefits of immediate versus delayed AED therapy for these distinctly different prognostic groups differ from the findings of this Cochrane review.

A recent study used Markov decision modeling to compare differences in quality-adjusted life years (QALYs) between adult patients who had immediate versus deferred AED treatment after an unprovoked first-ever seizure [25]. This model determined that immediate AED treatment is preferable to deferred treatment in most scenarios, including for those patients traditionally considered to be at low risk of subsequent seizures. Specifically, the model found benefit in QALY for immediate AED therapy in those with 10-year seizure recurrence risk of 38.0% and above, as opposed to the 60% threshold used in current practice.

Robust algorithms are needed to confidently predict and triage patients into different prognostic groups. From this foundation, research may determine the appropriate seizure-risk threshold at which to initiate AED therapy in order to delay or prevent future seizures and their associated morbidity and mortality, and thus, reduce the potential future costs of unprovoked first-ever seizures.

4. Future directions

This review identifies important gaps in the literature regarding costs associated with first-ever seizures. Establishing studies that identifies these cost data are necessary to determine appropriateness and cost effectiveness of interventions in order to optimize efficiency of our healthcare system.

Seizures, like any other acute new medical symptom, are associated with additional expense for the healthcare system, and comprehensive evaluation of these costs will form the foundation for future research. Hospital clinical costing units, insurance claim databases, and data linkage to state and national datasets may provide information regarding health service utilization and costs associated with first-ever seizure presentations. This may include emergency department attendances and hospital admissions; laboratory tests, neuroimaging and EEGs; outpatient visits to general practitioners and specialists; and cost of AEDs. These data are necessary for comparing cost effectiveness of various health interventions, which in turn, may limit unnecessary use of low value, high-cost interventions.

Patients with first-ever seizure may be stratified into different 'at risk' groups, and these groups may require different levels of clinical management and resource utilization. There may be substantial differences in healthcare accessed by those with first-ever seizures because of new-onset epilepsy, neurodegenerative disease, or acute systemic or neurologic insults compared with those whose seizures are unrelated to these factors and/or never recur. However, we are yet to establish a robust prognostic model to help determine if an individual's seizure is likely to be the harbinger of related future healthcare expense or an isolated event. Such a model may be achieved through epidemiological studies and data linkage. Cost data may identify large areas of services or costs that may or may not be warranted in each group. Those in 'at risk' groups with higher likelihood of further seizures, increased hospital admissions, morbidity, and mortality may benefit from more intensive monitoring and additional health interventions. Conversely, lower risk groups may be spared unnecessary workup and costs.

The impact of first-ever seizures on quality of life is well-acknowledged but lacks formal quantification. This may be achieved through prospective, cross-sectional cohort studies with PROMS questionnaires. These could be administered in the outpatient clinic setting, with baseline and 6- and 12-month follow-up. This would provide objective data on severity and perseverance of the impact of first-ever seizures. In addition, these questionnaires may assess efficacy of interventions such as early referral to epilepsy support groups and care delivered by multidisciplinary teams with regard to improving quality of life.

Perhaps, the most impactful future research strategy is widespread establishment of national first-ever seizure registries. These clinical registries may answer many of the above questions and provide wide-reaching research opportunities. Clinical registries collect longitudinal data that may be used to monitor efficiency and efficacy of healthcare systems. Clinical registries may be linked to other datasets, for example, hospital clinical costing units and death registries, to comprehensively determine outcomes of interest including subsequent seizures, future hospital admissions, all-cause morbidity, and mortality. Finally, the non-randomized observational data collected in clinical registries may be used to evaluate effect of interventions, certain variables or exposures between two groups through propensity score matching (PSM). This method allows unbiased assessment that mimics particular characteristics of randomized controlled trials at a fraction of the cost of traditional clinical trials [26].

5. Conclusion

Establishing the cost of first-ever seizures is crucial if we are to optimally manage this common event. The limited research in this area suggest that the costs of first-ever seizures are underestimated, and further research is needed through clinical registries, data linkage, and prospective cohort studies. These cost data will help society invest in healthcare in a way that will identify opportunity costs and avoid preventable seizure recurrence, morbidity, and mortality.

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CRediT authorship contribution statement

Emma Foster: Conceptualization, Methodology, Investigation, Writing - original draft. **Zanfina Ademi:** Conceptualization, Supervision, Writing - review & editing. **Nicholas Lawn:** Writing - review & editing. **Zhibin Chen:** Writing - review & editing. **Patrick Carney:** Writing - review & editing. **Danny Liew:** Writing - review & editing. **Terence John O'Brien:** Writing - review & editing. **Patrick Kwan:** Writing - review & editing.

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Emma Foster
Department of Neurology, Alfred Health, Commercial Road, Melbourne, VIC 3000, Australia
Department of Neurology, The Royal Melbourne Hospital, Grattan Street, Parkville, VIC 3052, Australia
Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC 3000, Australia
Corresponding author at: Department of Neurosciences, Level 6 Alfred Centre, 99 Commercial Road, Melbourne, Victoria 3000, Australia.
E-mail address: emma.foster@monash.edu.

Zanfina Ademi
School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC 3000, Australia

Nicholas Lawn
Western Australian Adult Epilepsy Service, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia

Zhibin Chen
Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC 3000, Australia
Department of Medicine at Royal Melbourne Hospital, University of Melbourne, Parkville 3050, Australia

Patrick Carney
Department of Medicine, Monash University and Eastern Health, Melbourne, Australia
Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Danny Liew
School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC 3000, Australia

Terence John O'Brien[1]
Patrick Kwan[1]
Department of Neurology, Alfred Health, Commercial Road, Melbourne, VIC 3000, Australia
Department of Neurology, The Royal Melbourne Hospital, Grattan Street, Parkville, VIC 3052, Australia
Department of Neuroscience, Central Clinical School, Monash University, Melbourne, VIC 3000, Australia
[1] Equal senior author.

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