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Side-effects of antiepileptic drugs: The economic burden

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ABSTRACT

Purpose: Antiepileptic drugs are a potentially effective treatment for epilepsy. Side-effects are, however, common and the negative consequences necessitate treatment ranging from minor interventions to very expensive hospitalization. This analysis has been conducted to provide insight into the costs of side-effects due to antiepileptic drugs in The Netherlands from a societal perspective.
Method: Resources allocated to care (grouped according to health, patient and family and other) for five different categories of side-effect were measured using a questionnaire. Standard cost prices were derived from the Dutch costing manual. Chronic epilepsy patients were invited to complete the questionnaire if they had experienced side-effects during the previous 12 months.
Results: Based on data from 203 patients, the total societal costs of common side-effects in 2012 are estimated to be €20,751 CI:15,049–27,196 (US$26,675 CI:19,345–34,960) per patient per year. These consist of: health care costs (mean €4458; US$5731), patient and family costs (i.e. informal care, mean €10,526; US$13,531) and other costs (i.e. productivity losses, mean €5761; US$7406). Examining the different categories of side-effects separately, ranging from the most to the least expensive category, the cost estimates per patient per year were as follows: other (mean €13,228; US$17,005), behavioral (mean €9689; US$12,455), general health (mean €7454; US$9582), cognitive (mean €7285; US$9365) and cosmetic side-effects (mean €2845; US$3657). Subgroup analyses showed significant differences in costs between patients using monotherapy and those using polytherapy when looking at cognitive and cosmetic side-effects.
Conclusion: These estimates should be considered in the overall assessment of the economic impact of a pharmacotherapy.

1. Introduction

Antiepileptic drugs (AEDs) are potentially an effective treatment for patients with epilepsy. Treatment failure and poor adherence are, however, very common in patients experiencing side-effects due to AEDs. In approximately 25% of the patients, side-effects lead to treatment discontinuation[1–3] and have a substantial, negative impact on the quality of life.[3,4] Furthermore, the negative consequences of side-effects can significantly affect the lives of relatives and friends of the patient, as well as society in general.

Commonly occurring side-effects of AEDs are memory problems, fatigue, tremors, gastrointestinal symptoms, osteoporosis, depression, drowsiness, dizziness, weight change, nausea, etc.[5] These may require medical treatment ranging from a minor intervention to very expensive specialist care and hospital admission. In addition to these health care costs, patient and family costs (i.e. informal care) and costs in other sectors (e.g. loss of employment) can be substantial.

Numerous studies have calculated the economic burden of epilepsy in many countries.[6–12] Only one study assessed the direct costs of severe idiosyncratic reactions due to antiepileptic drugs in hospitalized patients from an institutional perspective.[13] None focused on the economic burden of the commonly occurring side-effects due to AEDs in their analyses. In order to accurately reflect

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the total economic burden of epilepsy on society, costs related to side-effects should be included in the analysis.

The overall objective of this study is, therefore, to estimate the annual health care costs, the patient and family costs and costs in other sectors of commonly occurring side-effects due to AEDs in The Netherlands.

2. Methods

All epilepsy patients using antiepileptic drugs, who visited the tertiary epilepsy center Kempenhaeghe, Heeze, The Netherlands, between September 2011 and November 2011, received a patient information letter by mail including an invitation to complete a questionnaire (N = 1386). The letter contained information about the content of the questionnaire and the purpose of the study. Furthermore, the letter stated that participation was completely voluntarily and that participant's data would be anonymously analyzed and reported. Participants were invited to complete the questionnaire only when they had experienced side-effects during the previous 12 months. For young children and patients with severe mental retardation, proxy measures were taken. The questionnaire could either be completed digitally via the internet or on paper. All participants (patients, parents or caregivers) gave their informed consent.

2.1. Questionnaire

The Side-effects of AED treatment (SIDAED)[14] was used as the basis for the questionnaire. The ten original side-effect categories of the SIDAED were compressed into four categories, in order to focus on the most common side-effects and to condense the questionnaire. The categories used in this study were: cognition (e.g. memory problems, slowing of thought process, feeling drowsy or sleepy, etc.), cosmetic (e.g. weight problems, skin rash, surplus saliva, etc.), behavioral (e.g. depressed, irritated, pressurized or excitable, etc.) and general health (e.g. general CNS, vision, headache, gastrointestinal, sexuality/menses complaints). A fifth category was added ('other' complaints) to allow patients to report side-effects that they could not classify within one of the aforementioned categories.

The questionnaire starts with some basic demographic questions (age, sex, education, employment, and AED usage). Then the opening question of the first subdivision of the questionnaire is: 'Have you experienced any cognitive side-effects, such as slow reaction or memory and concentration problems, during the last 12 months?' If not, the questions about cognitive side-effects can be skipped and the patient can go on to the subdivision of the questionnaire dealing with cosmetic side-effects and answer whether or not they have encountered, for example, skin rash, hair loss or weight gain, during the last 12 months, etc. If a patient has experienced cognitive side-effects, he or she is asked to describe their symptoms and to respond to all the questions about use of resources belonging to this specific category. All categories of the questionnaire are dealt with in this way. The questions about resource use are exactly the same for all five categories. As the cost analysis is performed from a societal perspective, the measurement of resources has to be broad, i.e. it must encompass all related costs, irrespective of who pays. Use of resources in the categories health care, patient and family and other sectors are, therefore, measured. Health care usage includes visits to the general practitioner, specialists, psychologists, alternative health care practitioners, paramedics (i.e. dietician, speech therapist, physiotherapist), admission to a general, academic or psychiatric hospital or to an epilepsy center, care received, including day care, occupational care, social services, home care, prescribed and over-the-counter (OTC) medication for side-effects. Patient and family resource use includes informal care and out of pocket expenses. The sector 'other resource use' includes loss of productivity and absenteeism from activities of daily life.

2.2. Analyzing costs

The total costs were estimated using a bottom-up approach, where information on each element of service used was multiplied by an appropriate standardized unit cost and summed to provide an overall total cost.[15] The index year for the study was 2012 (consumer price index (inflation) number: 111.39; exchange rate 1.00 EUR = 1.2855 USD)[16] and standard cost prices were derived from the Dutch Manual for Costing[17] or (if not available) calculated mean cost prices according to providers were used. In accordance with these guidelines, medication costs were calculated based on daily defined dosage taken from the Dutch pharmaceutical therapeutic compass combined with the Dutch consumer reimbursement price of medication.[18] When data on medication was diverse, lowest cost prices for the specific medication were used.

Costs of informal care and absenteeism from daily activity were calculated using standardized cost prices based on shadow prices. 'Shadow pricing' is a method used to impute values on cost items for which no market prices are available. In this case, the minimum wage rate of The Netherlands was used to estimate the cost of informal care provided by relatives or friends of the patient and losses of daily activity. For out-of-pocket payments, costs declared by the patient were used.

Productivity losses from paid work were quantified in terms of net cumulative number of days of sick leave over a period of 12 months. In the case of partial sick leave, we assumed that subjects were 100% productive during the hours of partial work resumption. Productivity losses were calculated based on the Human Capital Approach (HCA). The cumulative number of calendar days of sick leave was converted into work-hour equivalents based on the mean number of work-hours per week registered by the patients. The costs of production losses were calculated by multiplying the number of sick leave hours by the estimated reference cost of production loss for an employee per hour of sick leave.[17]

Despite the usual skewness in the distribution of costs, arithmetic means are generally considered to be the most appropriate measures for describing cost data.[19,20] Therefore, arithmetic means are presented. However, to check for sample uncertainty, non-parametric bootstrapping was used. This method is based on random sampling, with replacement based on the participant's individual data.[21] Non-parametric bootstrapping avoids the need to make assumptions about the shape of the distribution, such as normality, and instead uses the observed distributions of the cost data in the study being analyzed. In this study, the non-parametric bootstrap resample method was applied with 1000 replications. The bootstrap replications were used to calculate 95% confidence intervals around the costs, based on the 2.5th and 97.5th percentiles. The data on costs were analyzed using the statistical package IBM SPSS 20.0 (SPSS, IBM Corporation, Chicago, USA) and MS-Excel 2010 (Excel, Microsoft Corporation, Washington, USA).

2.3. Subgroup and sensitivity analyses

Subgroup analyses were performed to check for differences between groups. Firstly, a combination of AEDs can produce negative interactions which can lead to side-effects. There is, however, evidence that AED toxicity may show a greater correlation with total drug load than with the number of AEDs administered.[22] Drug loads for each individual patient were estimated as the sum of the prescribed daily dose (PDD)/defined