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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

daily dose (DDD) ratios for each AED included in the treatment regimen,[22] where DDD corresponds to the assumed average maintenance daily dose of a drug prescribed for its main indication. Two separate subgroup analyses were, therefore, performed to check for differences between patients on monotherapy or polytherapy and on the total drug load. Secondly, as side-effects of AEDs may differ over time, another subgroup analysis was performed to check for differences between children and adults.

In addition, a sensitivity analysis was performed to assess uncertainty. As different methods can be used to put a value on productivity losses, we corrected for the methodological uncertainty by calculating productivity losses on the basis of the friction cost method (FCM) instead of the HCA. The FCM is based on the assumption that an organization needs a certain time span to replace the absent worker. The definitive number of days absent from work is limited to the duration of the friction period, determined in The Netherlands to be 23 weeks.[17]

3. Results

In total, 210 patients from the tertiary epilepsy center completed the questionnaire. Although we asked patients only to fill out the questionnaire if they had experienced any side-effect during the previous 12 months, seven questionnaires were returned which described neither side-effects nor costs and so they were excluded from the analysis. The characteristics of all included participants are shown in Table 1.

All patients included in the analysis had experienced one or more side-effects due to AEDs during the previous 12 months, in most cases (85%) related to general health. Cognitive side-effects are the second most commonly reported problem among participants (77%), followed by the categories behavioral (68%), cosmetic (42%) and other (7%).

Table 2 lists the reference prices per unit and the arithmetic mean total costs per category. Table 3 shows the bootstrapped

Table 1
Demographic characteristics ($N = 203$).

	N	%
Age mean (range)	38 (2–81)	
0–19 years of age	52	25.6
20–39 years of age	49	24.1
40–59 years of age	66	32.5
60 years of age or older	36	17.7
Female	102	50.2
Education		
No education	20	9.9
Too young for school	13	6.4
At primary school	1	0.5
Special education	17	8.4
Primary education	18	8.9
Lower level secondary education	31	15.3
Higher level secondary education	11	5.4
Secondary vocational education	52	25.6
Higher education	40	19.7
Paid work	56	27.6
Number of different AEDs per patient		
One	59	29.1
Two	66	32.5
Three	47	23.2
Four	21	10.3
Five	6	3.0
Six	3	1.5
Seven	0	0
Eight	1	0.5

Table 2
Unit prices and annual mean costs per patient.

	Unit price (€)	Per side-effect category					Total[e]
		Cognitive $N = 157$	Cosmetic $N = 85$	Behavior $N = 139$	General health $N = 172$	Other $N = 15$	$N = 203$
Health care costs							
GP visits	29.56[a]	22.78	23.65	21.48	35.40	165.54	84.46
Specialist visits	76.02[a]	189.81	89.44	182.12	224.08	391.40	527.73
Blood sample	23.50[a]	20.66	13.27	15.38	28.01	86.17	62.17
Paramedic visits	32.73[a]	62.75	14.25	30.85	65.27	21.82	132.53
Psychologist visits	81.30[a]	84.41	8.61	159.09	36.40	319.78	232.29
Alternative care	53.85[b]	41.16	3.17	42.23	39.14	0.00	95.23
General hospital	459.29[a]	196.00	59.44	0.00	216.29	0.00	359.74
Academic hospital	607.1[a]	3.87	7.14	0.00	225.90	0.00	197.38
Epilepsy center	459.29[a]	175.52	32.42	489.03	376.51	183.72	816.77
Psychiatric care	244.95[a]	3.12	0.00	1.76	0.00	0.00	3.62
Day care (half day)	125.64[a]	13.60	67.99	20.79	167.28	16.75	196.20
Home care	36.95[a]	522.24	0.00	826.46	642.54	256.19	1533.15
Social services	59.59[a]	72.49	1.40	60.45	9.35	11.92	106.85
Occupational health services	55.00[b]	25.57	12.29	20.97	26.54	47.67	65.30
Prescribed medication	Variable[c]	1.51	80.48	10.25	3.16	466.93	79.06
OTC medication	Variable[c]	1.61	15.82	1.92	16.25	3.33	23.20
Total health care costs		**1437.11**	**429.37**	**1882.78**	**2112.11**	**1971.21**	**4475.27**
Patient and family costs							
Informal care	13.20[a]	4111.31	1815.00	5002.70	2840.70	8770.08	10,420.08
Out of pocket	Variable[d]	6.22	0.00	1.44	4.12	32.00	11.66
Total patient and family costs		**4117.53**	**1815.00**	**5004.14**	**2844.82**	**8802.08**	**10,472.14**
Other costs							
Production losses	31.72[a]	748.90	274.66	1386.89	967.67	118.42	2472.49
Daily routine losses	13.2[a]	952.84	319.91	1347.43	1536.09	2424.69	3274.18
Total other costs		**1701.73**	**594.57**	**2734.32**	**2503.76**	**2543.11**	**5746.67**
Total costs		**7256.38**	**2838.94**	**9621.23**	**7460.70**	**13,316.40**	**20,694.09**

Note: GP: general practitioner, OTC: over-the-counter. Costs are expressed in Euros, index year 2012. Exchange rate 1 EUR = 1.2855 USD.

[a] Dutch guidelines for costing studies.

[b] Respective providers or professional organizations.

[c] Dutch pharmaceutical therapeutic compass.

[d] Costs mentioned by participants.

[e] Mean annual costs due to side-effects per patient. Total $N = 203$ represents the number of patients. As patients may have experienced more than one side-effect, the numbers mentioned per side-effect category do not add up to 203.

Table 3
Bootstrapped annual mean costs per patient (confidence interval) base case and sensitivity analyses.

	Per side-effect category					Total[a]
	Cognitive *N* = 157	Cosmetic *N* = 85	Behavior *N* = 139	General health *N* = 172	Other *N* = 15	*N* = 203
Health care costs						
GP visits	23.02 (13–36)	23.41 (13–35)	21.40 (12–32)	34.20 (23–51)	160.13 (45–369)	84.22 (57–117)
Specialist visits	189.67 (136–251)	90.07 (52–134)	181.29 (138–232)	223.50 (164–299)	392.15 (249–569)	527.25 (420–648)
Blood sample	20.67 (13–31)	13.19 (7–20)	15.46 (9–23)	27.90(21–36)	85.27 (24–174)	62.31 (46–82)
Paramedic visits	63.34 (19–129)	14.07 (4–27)	30.32 (7–61)	64.36 (21–123)	21.43(0–65)	132.71 (69–211)
Psychologist visits	84.11 (51–121)	8.58 (1–19)	158.77 (77–261)	35.80 (18–59)	313.79 (0–905)	229.82 (139–334)
Alternative care	40.41 (12–79)	3.12 (0–9)	42.10 (11–91)	39.71 (9–81)	0.00	96.22 (29–197)
General hospital	189.20 (34–423)	59.25 (5–139)	0.00	215.75 (83–377)	0.00	357.45 (118–688)
Academic hospital	3.80 (0–12)	7.12 (0–21)	0.00	230.80 (4–565)	0.00	193.53 (9–490)
Epilepsy center	174.03 (57–342)	32.17 (0–80)	499.25 (149–899)	373.36 (128–697)	187.57 (31–398)	811.08 (391–1349)
Psychiatric care	3.16 (0–10)	0.00	1.72 (0–5)	0.00	0.00	3.64 (0–10)
Daycare (half day)	13.70 (7–22)	65.62 (3–184)	21.19 (5–49)	165.45 (3–476)	17.27 (0–50)	200.07 (31–489)
Home care	522.47 (50–1295)	0.00	837.50 (180–1933)	653.89 (39–1917)	266.95 (0–1025)	1562.01 (564–2863)
Social services	70.97 (17–142)	1.44 (0–4)	60.20 (26–99)	9.35 (2–20)	11.63 (0–36)	114.86 (52–197)
Occupational health services	25.92 (12–42)	12.07 (1–30)	20.60 (6–38)	26.38 (13–42)	48.22 (0–139)	65.62 (30–113)
Prescribed medication	1.50 (0.1–3)	82.16 (10–209)	10.29 (2–23)	3.15 (0–7)	471.45 (18–1285)	80.56 (22–166)
OTC medication	1.62 (0–4)	15.66 (5–30)	1.82 (0–5)	16.55 (8–26)	3.33 (0–10)	23.31 (13–34)
Total health care costs	**1421.15** (790–2213)	**432.49** (256–649)	**1887.24** (1061–2955)	**2119.69** (1153–3321)	**1980.87** (721–3576)	**4458.30** (3051–6034)
Patient and family costs						
Informal care	4113.53 (2695–5740)	1830.70 (205–4190)	5031.12 (2887–7604)	2841.91 (1494–4558)	8690.13 (945–19,786)	10,440.68 (6364–15,217)
Out of pocket	6.11 (0–13)	0.00	1.53 (0–4)	4.11 (1–8)	31.20 (0–96)	11.75 (3–23)
Total patient and family costs	**4111.98** (2473–6082)	**1820.71** (166–3985)	**5029.84** (2877–7539)	**2803.82** (1525–4449)	**8782.78** (945–19,577)	**10,526.12** (6348–15,549)
Other costs						
Production losses	760.16 (158–1564)	274.40 (0–702)	1351.80 (392–2585)	977.92 (260–1817)	118.66 (0–355)	2460.95 (732–4447)
Daily routine losses	968.95 (496–1535)	321.08 (4–829)	1340.97 (683–2099)	1535.99 (947–2232)	2404.40 (542–4961)	3311.08 (2050–4680)
Total other costs	**1703.01** (805–2712)	**598.63** (90–1284)	**2758.02** (1532–4124)	**2496.19** (1589–3638)	**2575.75** (672–5277)	**5761.00** (3719–8324)
Total costs	**7284.59** (5109–9844)	**2845.24** (1120–5295)	**9689.01** (7030–12,770)	**7454.17** (5265–9890)	**13,228.42** (3850–25,071)	**20,751.20** (15,049–27,196)
Sensitivity analyses						
Monotherapy total costs	2678.75 (1551–3925)	1002.11 (511–1878)	7154.23 (3419–12,337)	6134.73 (2846–9937)	*N.a.*	12,951.49 (6624–23,228)
Polytherapy total costs	9012.12 (5993–12,290)	3388.79 (1014–6489)	10,497.58 (6876–14,534)	8028.52 (5309–11,168)	*N.a.*	24,515.68 (17,291–33,676)
Difference polytherapy vs. monotherapy	6333* (3111–9844)	2268* (245–5327)	3413 (−2495 to 8471)	1894 (−2531 to 6255)	*N.a.*	11,564 (−1069 to 22,324)
Age 1–18 total costs	9164.14 (4388–14,698)	992.74 (269–1962)	10,689.29 (5114–17,768)	6844.33 (2467–12,230)	*N.a.*	24,368.92 (12,120–40,332)
Age > 18 total costs	6785.27 (4342–9682)	3372.30 (1005–6273)	9257.84 (6294–13,072)	7716.22 (5236–10,501)	*N.a.*	19,482.15 (13,391–26,078)
Difference age > 18 vs. age 1–18	−2379 (−8425 to 3453)	2380 (−151 to 5336)	−1431 (−9459 to 5453)	872 (−5387 to 6162)	*N.a.*	−4887 (−22,124 to 9615)
FCM production losses	575.89 (73–1194)	273.73 (0–655)	1063.47 (366–1919)	617.68 (198–1163)	118.66 (0–355)	1917.58 (765–3379)
FCM total costs	7104.20 (4882–9705)	2844.16 (1064–5090)	9266.24 (6543–12,186)	7206.38 (5205–9495)	13,223.24 (10,041–16,631)	20,070.83 (14,750–26,571)

Note: CI: confidence intervals based on the 2.5th percentile and the 97.5th percentile, GP: general practitioner, OTC: over-the-counter, Na: not applicable, FCM: friction cost method. Costs are expressed in Euros, index year 2012. Exchange rate 1 EUR = 1.2855 USD.

[a] Mean annual costs due to side-effects per patient. Total *N* = 203 represents the number of patients. As patients may have experienced more than one side-effect, the numbers mentioned per side-effect category do not add up to 203.

* Significant.

Table 4
Number of AEDs, mean drug load and bootstrapped annual mean costs per patient ($N = 162$).

Number of AED	Drug load	SD	Total[a]	CI
One	0.74	±0.51	10,499.58	6176–15,772
Two	1.39	±1.0	16,953.17	9772–29,208
Three	2.37	±1.27	26,883.80	12,065–47,156
Four or more	3.68	±2.1	30,215.72	10,142–57,502

Note: AED: antiepileptic drug, SD: standard deviation, CI: confidence intervals based on the 2.5th percentile and the 97.5th percentile, $N = 162$: represents the number of patients aged 16 years or over. Costs are expressed in Euros, index year 2012. Exchange rate 1 EUR = 1.2855 USD.
[a] Bootstrapped mean annual costs due to side-effects per patient.

mean total costs of all categories and their 95% confidence intervals. The arithmetic mean costs are comparable to the bootstrapped mean costs. On the whole, most costs are generated in the patient and family sector compared to costs in health care and other sectors. Overall, informal care is the main cost driver accounting for 51% of the total annual costs per patient. Production losses account for 43% of the other sector costs, but only for 12% of the overall total costs. However, only 28% of the patients had a paid job and were, therefore, responsible for the costs of production losses. Patients without a paid job generated the costs of daily routine losses.

Table 3 shows the differences in costs between the side-effect categories. As can be seen, admissions to a general or academic hospital are frequently categorized under general health side-effects, while behavioral problems lead to numerous admissions to the epilepsy center. Resource use related to daycare occurs most often in the general health category; homecare is an expensive factor in the cognitive, behavioral and general health side-effects categories. Prescribed medication only leads to high costs in the category 'other'. This is in fact due to one individual who underwent treatment with Teriparatide injections for osteoporosis during the previous 12 months (total costs > 5000 Euros, US$6428).[18]

Overall, total costs per patient in the category 'other side-effects' are the highest. These are based on a small group ($n = 15$) of patients of whom a few experienced side-effects due to AEDs which specifically led to high costs of informal care and many losses in daily routine.

3.1. Subgroup and sensitivity analyses

Table 3 shows the bootstrapped means of the subgroup analyses. Firstly, mean costs are calculated separately for patients on monotherapy and those on polytherapy. Of the 203 participants, 61 were on monotherapy. Overall, mean costs due to side-effects per patient are considerably higher in the polytherapy group. For the categories cognitive and cosmetic side-effects, the mean costs for a polytherapy patient is three times more than for a patient on monotherapy (€2679 (US$3444) vs. €9012 (US$11,585) resp. €1002 (US$1288) vs. €3389 (US$4357)). The difference between mean costs for monotherapy and polytherapy in the categories behavioral side-effects and general health side-effects are less prominent and statistically not significant (€7154 (US$9196) vs. €10,498 (US$13,495) and €6135 (US$7887) vs. €8029 (US$10,321)). As there are only two patients on monotherapy who have experienced any other side-effects, bootstrapping is impossible and presenting the arithmetic mean would be incorrect.

Table 4 shows the bootstrapped means of the subgroup analysis performed when taking the total drug load into account. We applied the average adult DDD, used for the main indication as reflected by the ATC code to calculate total drug load.[23] For medicinal products approved for use in children, dose recommendations will differ according to age and body weight. We, therefore, included only patients aged 16 years and over in this subgroup analysis. AED loads increased with increasing number of AEDs in the treatment regimen, from 0.7 ± 0.5 for patients on monotherapy to 1.4 ± 1, 2.4 ± 1.3 and 3.7 ± 2.1 for those on two, three and ≥4 AEDs, respectively. Moreover, total costs of side-effects also increase when drug loads rise.

Secondly, total mean costs were calculated separately for children and adolescent patients (aged 1–18) and for adult patients over 18 years of age. Of the 203 participants, 50 patients were aged between 1 and 18 years. Overall, total mean costs per patient due to side-effects seem to be higher in children and adolescents. However, in the categories cosmetic and general health, side-effect costs were higher in the adult group. No statistically significant differences in costs were found in the different side-effect categories. Again, showing the bootstrapped or the arithmetic mean of this subgroup analysis in the other side-effects category would be incorrect as the group is small (4 children vs. 11 adults).

Furthermore, Table 3 shows the result of the bootstrapped means of the sensitivity analysis. When using the FCM instead of the HCA to calculate productivity losses in a sensitivity analysis, total costs of all side-effects decreased to €20,071 (US$25,801). The FCM was applied in four patients in whom the maximum length of the friction period (23 weeks) was exceeded. More specifically, costs of cognitive side-effects decreased from €7285 (US$9365) to €7104 (US$9132), of behavioral side-effects from €9689 (US$12,455) to €9266 (US$11,911) and of general side-effects from €7454 (US$9582) to €7206 (US$9263). As the patients who exceeded the maximum length of the friction period did not report any cosmetic or other side-effects, these costs remained the same.

4. Discussion

Based on reports on use of resources (in the categories health care, patient and family, and other) by 203 epilepsy patients with side-effects, the general societal costs of common side-effects in 2012 due to antiepileptic drugs is estimated to be €20,751 (US$26,675) per patient. Patient and family costs were on the whole higher than the cost of health care or the costs in the 'other' sector. Examining the different categories of common side-effects separately, other side-effects generated the most (€13,228; US$17,005) and cosmetic side-effects the least costs (€2845; US$3657) per patient per year. Behavioral effects generated the second highest costs per patient per year (€9689; US$12,455) closely followed by costs of general health side-effects (€7454; US$9582) and cognitive side-effects (€7285; US$9365). Furthermore, several subgroup analyses only showed significant differences in costs between patients on monotherapy and those on polytherapy within the cognitive and the cosmetic side-effects categories.

Although many articles dealing with 'cost of epilepsy' have been published in the literature, we did not find any studies focusing on the cost of common side-effects due to AEDs. It can be stated that the economic burden of common side-effects is considerable compared with the costs of the disease itself. For example, estimates show total costs of epilepsy per patient per year ranging between €625 and €4292 (US$803–5517) in The Netherlands,[24]

€8275 (US$10,638) in Sweden,[25] €14,575 (US$18,736) in Denmark,[26] and €7738 (US$9947) in Germany.[27] Although these cost of illness studies used different methods, databases and study periods, they included roughly the same cost categories (e.g. direct and indirect) as those used in this article. For example, Pugliatti et al.[28] estimated the cost of epilepsy in Europe based on a review with economic modeling and also concluded that costs outside the formal health care sector were the single most costly resource item, productivity losses being the most dominant cost category. In his review of twelve cost of epilepsy studies, Strzelczyk et al.[29] found that indirect costs comprised between 12% and 85% of the total costs. These results are, however, highly dependent on the method used to measure this cost category. Moreover, the lack of standardization of productivity cost methodology is a serious concern. Applying different methods can lead to (large) variations in productivity cost estimates, and so the trustworthiness of outcomes may become a matter of debate. Furthermore, patients are treated differently depending on whether they are employed on a full-time or part-time basis or have no work at all. E.g. consider a patient who has severe seizures or side-effects which do not allow him/her to take a job. No productivity losses due to side-effects are calculated for this patient as he/she has no paid work. Whereas an epilepsy patient with better controlled epilepsy and/or side-effects can create high loss of productivity costs whenever he/she is not able to work due to seizures or side-effects. As a result the calculated costs might lead to incorrect conclusions. However, as we chose to follow existing Dutch guidelines for costing, we tried to reduce the problems of productivity loss calculations to a minimum. Additional methodological differences between our study and other cost of illness studies, concern the sources of information and cost components included. To be more specific, in contrast to most other cost of illness studies, we included informal care costs, the component which proved to be the most dominant direct cost category outside the health care sector in our study. The euro value of the burden associated with informal care may have been even higher than estimated, as we assumed a minimum wage for all informal care providers.

Our results confirm that from an economic perspective, it is very important that the treatment of epilepsy patients is primarily concerned with balancing seizure control and adverse effects. Side-effects exert a high burden, not only for society, but also for the individual patient. One study showed that patients are willing to pay €879 (US$1130; £709, £1 = €1.24, 2012 exchange rate) per month to achieve 100% seizure reduction with no adverse effects, but only €216 (US$278; £174) per month for a drug that provided seizure freedom but also caused hair loss.[30]

As mentioned earlier, we found a significant difference in costs between patients on monotherapy and polytherapy. Early studies emphasized that polytherapy is usually detrimental, since it is associated with a considerable burden due to side-effects, with only modest advantages in terms of seizure control.[31] However, there is also evidence that AED toxicity may be related to total drug load rather than to the number of AEDs administered.[22] Canevini et al.[32] provided evidence that adverse events did not differ between monotherapy and polytherapy patients, and did not correlate with AED load. Although our primary aim was not to contribute to this debate, our data show that drug load increased with an increase in the number of AEDs included in a polytherapy regimen. Furthermore, costs due to side-effects increased with increase in drug load and number of AEDs administered.

Relevant within the scope of this paper, but not touched upon due to the lack of data, is the high cost related to (pharmacological) treatment of and productivity losses due to chronic side-effects of long-term AED treatment. For instance, in patients undergoing AED treatment which carries a high risk of osteoporosis (e.g. enzyme inducing drugs), side-effect costs will increase as those patients eventually have to use additional (pharmacological) treatments in order to overcome these chronic side-effects or bring them to a halt. Another example which might induce long-term costs is the patient with cognitive impairments due to long-term AED treatment who becomes unable to hold down a job. Research using longitudinal data is needed to further explore the costs and influences of chronic side-effects due to long-term AED treatment.

Our study does have certain limitations. Firstly, only subjective symptoms and related health care use of resources reported by patients were used. It has been proven that the frequency at which side-effects of antiepileptic drugs are reported in a given population is dependent on the method of assessment. Reliance on unstructured interviews or spontaneous reporting underestimates the burden of toxic effects of antiepileptic drugs, whereas use of screening measures, such as questionnaires or checklists, can result in overestimation.[33] Furthermore, caution should be exercised when relying on patient-recorded cost data[34]; recall bias is to be expected especially considering the chosen time scale (12 months). Using a cost questionnaire, however, enabled us to obtain actual data on patient and family costs, including informal care, which cannot be captured through other sources such as hospital databases and patient records.

Secondly, since we did not include a control group in our analyses, we were not able to compare health care costs in people with epilepsy with the health care costs of those without epilepsy. It has, however, already been proven that patients suffering from epilepsy are associated with higher expenditure, both because of being more likely to have expenses and because the average expense is higher. In a comparison of health care expenditure of people with epilepsy and non-epileptics, Yoon et al.[35] found that the average excessive direct health care expenditure due to epilepsy was €3518 (US$4523). Furthermore, they found that adults with epilepsy received significantly more informal care than people without epilepsy. Jennum et al.[26] showed that the direct net annual health care and indirect costs were €14,575 (US$18,736) for patients and €1163 (US$1495) for controls, i.e. a consequent excess cost of €13,412 (US$17,241).

Thirdly, our study has a potential bias toward severely affected patients at an epilepsy center as only 30% of the patients were on monotherapy. Moreover, we had a participation rate of only 15% which can lead to possible selection bias. This low response rate is mainly due to a combination of factors: patients without any side-effects and/or patients unwilling to participate in the study. Furthermore, only 18% of the participants was 60 years or older which may mean the costs are underestimated as chronic side-effects due to long-term AED usage (e.g. osteoporosis) can result in high costs.

In conclusion, this study, despite its limitations, demonstrates the economic burden induced by patients with antiepileptic side-effects as viewed from societal perspective in The Netherlands. Assuming that in The Netherlands, more than 80,000 people have epilepsy,[36] that about 88% of the patients experience side-effects[37] and that the demonstrated costs can be as high as €20,751 (US$26,675) per patient per year, side-effects due to antiepileptic drugs will have a major impact on health care costs. These figures should be considered along with the costs associated with drug acquisition, delivery and treatment of all clinical successes and failures, in the overall assessment of the economic impact of pharmacotherapy.

Conflict of interest statement

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved

in ethical publication and affirm that this report is consistent with those guidelines.

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