



## Evaluation of costs of epilepsy using an electronic practice management software in Germany

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### ABSTRACT

**Purpose:** This study used an electronic practice management software in daily routine to gather long-term disease and cost-of-illness (COI) data in patients with epilepsy in Germany.

**Methods:** Data on socio-economic status, course of epilepsy as well as direct and indirect costs were recorded using practice software-based questionnaires.

**Results:** In 2011 we enrolled 359 patients (170 male (47.4%); mean age  $50.5 \pm 20.7$  years) in six neurological practices. The majority of patients had been in long-term seizure remission for more than one year ( $n = 200$ , 55.7%) and in more than two-thirds the anti-epileptic drug (AED) monotherapy ( $n = 248$ , 69.1%) was used. Levetiracetam (31%), lamotrigine (26%) and valproate (24%) were the drugs prescribed most frequently.

Total annual direct costs amounted to €1698 per patient with anticonvulsants (59.9% of total direct costs) and hospitalization (30.0%) as the main cost factors. Of the patients enrolled 252 (70.2%) were of working age and indirect annual costs due to absenteeism amounted to €745 per patient.

Potential cost-driving factors were seizure frequency and a recent diagnosis of epilepsy associated with higher costs. Anticonvulsant treatment in patients aged 65 years and older was associated with lower drug costs due to prescription of older AEDs.

**Conclusion:** We were able to demonstrate that electronic practice management software can easily be used to perform long-term health economic evaluations with a bottom-up approach. The combination of both physician- and patient-based electronic databases will facilitate performing less expensive studies, but at the same time simplify large, prospective and multicentre clinical trials.

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### 1. Introduction

Epilepsy is a common and chronic neurological disorder that imposes a substantial burden on individuals and society as a whole. The initial diagnosis of epilepsy is associated with costs of diagnostic procedures and inpatient admission. In the further clinical course the majority of patients require an anticonvulsant treatment for an extended period of time and up to 30% of patients

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### 3. Results

#### 3.1. Clinical and sociodemographic characteristics

During the study period 359 (170 male (47.4%); 189 female) consecutive outpatients treated for epilepsy by neurologists in outpatient offices were recruited. The mean age was  $50.5 \pm 20.7$  years (range 18–99 years). Half of the patients suffered from focal epilepsy ( $n = 186$ , 51.8%) the remaining from idiopathic generalized epilepsies ( $n = 56$ , 15.6%) and other or unknown epilepsy syndromes ( $n = 117$ , 32.6%). The majority of patients were in long-term seizure remission for more than one year ( $n = 200$ , 55.7%) and in more than two-thirds AED monotherapy ( $n = 248$ , 69.1%) was used. Table 1 shows detailed clinical characteristics. None of the surveyed patients died during the study period. Further socio-demographic characteristics in terms of marital status, residential situation, employment status, disability level, nursing needs and reported difficulties in daily life are presented in Table 2.

#### 3.2. Direct and indirect costs

Table 3 shows the epilepsy-specific costs of patients during a one-year evaluation period in 2011. Total annual direct costs amounted to €1698 (SD €2247, range €52–15,377) per patient, with anticonvulsants (59.9% of total direct costs) and hospitalization (30.0%) as the main cost factors. Anticonvulsant monotherapy was associated with mean costs of €651 ( $n = 248$ ) with levetiracetam (mean annual costs €1507,  $n = 59$ ), lamotrigine (€257,  $n = 48$ ), valproate (€203;  $n = 42$ ), carbamazepine (€140;  $n = 24$ ) and oxcarbazepine (€759;  $n = 19$ ) as the main five monotherapies of choice.

During the evaluation period in 2011 fifty patients (13.9%) were admitted to a hospital for 1–29 days (mean hospital stay 8.1 days) with mean costs of €3650 per admission. Nine patients (2.5%) were admitted for rehabilitation to a hospital for 9–48 days (mean hospital stay 22.4 days) with mean costs of €3973 per admission.

The estimate of mean indirect costs was based on patients with a working age of below 65 years. This amounted to 252 patients

(70.2%) of working age, and indirect annual costs due to days off amounted to €745 (SD €3587) per patient. Thirty patients (11.9%) had to take days off due to seizures. The mean annual duration of work absenteeism was  $4.8 \pm 24.6$  days (range: 0–230).

Table 4 presents each cost factor for patients in seizure remission of more than one year and for patients with active epilepsy.

#### 3.3. Prescription patterns and medication costs

Costs and daily dosages of different AEDs are listed in Table 5. The mean AED costs were €1017 (SD €1224, range €23–8334) per one year. Levetiracetam (31%), lamotrigine (26%) and valproate (24%) were the drugs prescribed most frequently. Sixty-nine per cent of the patients received AED in monotherapy. Zonisamide, lacosamide and levetiracetam were associated with the highest costs, along with infrequently prescribed AEDs such as eslicarbazepine acetate ( $n = 2$ ), retigabine ( $n = 1$ ) or vigabatrin ( $n = 1$ ). The proportion of enzyme-inducing anticonvulsants was 18.1% (89 out of 491 prescribed drugs). Likewise the share of so-called 'older' AEDs was 35.8% (176/491).

#### 3.4. Cost-driving factors

Potential cost-driving factors were identified by univariate analysis as well as post hoc tests and are presented in Table 6. We found a positive correlation of seizure frequency with increased medication, hospitalization, and direct and indirect costs. Epilepsy syndrome and gender did not influence costs in this analysis. A recent diagnosis of epilepsy in the first two years correlates with higher hospitalization and indirect costs than an established diagnosis of more than three years. Analysis of total direct ( $p = 0.057$ ), AED ( $p = 0.087$ ), hospital ( $p = 0.371$ ) and indirect ( $p = 0.577$ ) costs did not reveal a significant correlation with the treating neurologist.

Anticonvulsant treatment in patients aged 65 years and older was associated with lower drug costs. Elderly patients aged 65 years and older were treated mainly with monotherapy (92/107; 86%) and

**Table 1**  
Clinical characteristics.

			<i>n</i> = 359
<b>Age in years<sup>a</sup></b>			$50.5 \pm 20.7$ Range 18–99
<b>Disease duration in years</b>			% ( <i>n</i> )
	0–2 years		23.4 (84)
	3–5 years		10.9 (39)
	5–10 years		19.2 (69)
	>10 years		46.5 (167)
<b>Anticonvulsants</b>		Mean number of AEDs <sup>a</sup>	$1.4 \pm 0.6$
			% ( <i>n</i> )
	Monotherapy		69.1 (248)
	2 AEDs		25.1 (90)
	>3 AEDs		5.8 (21)
<b>Epilepsy syndrome</b>			% ( <i>n</i> )
	Focal epilepsy		51.8 (186)
	Idiopathic generalized epilepsy		15.6 (56)
	Unclassified or other syndromes		32.6 (117)
<b>Seizure frequency</b>			% ( <i>n</i> )
	Seizure remission > 1 year		55.7 (200)
	Active epilepsy		43.2 (155)
		1 seizure/year	14.4 (51)
		2–10 seizures/year	19.9 (73)
		>10 seizures/year	9.0 (31)
n.a.			1.1 (4)

<sup>a</sup> Mean  $\pm$  standard deviation.

**Table 2**

Detailed socio-demographic parameters.

	All patients <i>n</i> = 359 % ( <i>n</i> )
<b>Marital status</b>	
Married/living in relationship	48.7 (175)
Single	37.6 (135)
Divorced	7.0 (25)
Widowed	6.7 (24)
<b>Residential status</b>	
Lives with partner/family	70.8 (254)
Lives alone	13.1 (47)
Assisted living	1.9 (7)
Nursing home or clinic	14.2 (51)
<b>Employment situation</b>	
Employed	42.7 (157)
Ongoing school education	2.2 (8)
Vocational training	5.3 (19)
Unemployed	15.3 (55)
Early and old-age retirement	33.4 (120)
<b>Activities of daily life</b>	
No problems	54.3 (195)
Mild impairment	28.4 (102)
Severe impairment	17.3 (62)
<b>Nursing demand</b>	
None	76.6 (275)
Nursing care level 1 <sup>a</sup>	8.6 (31)
Nursing care level 2 <sup>a</sup>	5.8 (21)
Nursing care level 3 <sup>a</sup>	8.6 (31)
n.a.	0.3 (1)
<b>Disability level</b>	
None	48.5 (174)
0–50%	13.1 (47)
60–100%	38.4 (138)

<sup>a</sup> According to German statutory long-term care insurance.

were in seizure remission (61/107; 57%). Levetiracetam (mean annual costs €1462, *n* = 33), carbamazepine (€104; *n* = 16); phenytoin (€66; *n* = 14), gabapentin (€374; *n* = 13) and valproate (€220, *n* = 13) were the five most prescribed drugs in the elderly.

#### 4. Discussion

This study is the first evaluation to gather annual disease and COI data in patients with epilepsy using an electronic practice management software in daily routine. We were able to present recent data in 2011 prices and tariffs and confirm previous studies showing the difference in health-care utilization by patients in

seizure remission and those with active epilepsy. Furthermore we were able to demonstrate high hospitalization and indirect costs due to days off in the first two years upon diagnosis of epilepsy. This is likely due to inclusion of patients with newly diagnosed epilepsy causing high inpatient and indirect costs upon diagnosis, which is in line with previous long-term studies [30,31]. Comparison of the presented prescription patterns with previous German evaluations from 2003 [3], 2008 [19] and 2009 [32], demonstrates an increase in the prescription of 'newer' drugs and decrease in prescription of enzyme-inducing anticonvulsants.

This study was able to include a large subgroup (*n* = 107) of elderly patients, which tend to be neglected in field studies. Interestingly, anticonvulsant treatment in the elderly > 65 years was associated with lower costs as compared to patients aged 18–65 years. This subgroup is mainly treated with monotherapy (86%) as compared to patients aged 18–65 years with 62% on monotherapy (156/252); however, the proportion of seizure-free patients is similar, with 56% and 57% in both groups. Older AEDs such as carbamazepine, phenytoin and valproate are still widely used, as well as gabapentin which was formerly considered as the drug of choice in the elderly. This is in keeping with evaluations on a national level which still show a predominance of older AEDs such as carbamazepine, valproate, phenytoin and primidone being prescribed to the elderly [32]. This could be regarded as inappropriate treatment in this age group. However, a recent study of elderly epilepsy patients showed that elderly with chronic epilepsy seem to continue their treatment with phenytoin, carbamazepine and valproate, while a large proportion of patients are on lamotrigine and levetiracetam [33]. In contrast, those elderly with late-onset epilepsy are often started on levetiracetam or gabapentin [33]. Probably, in the course of time, mainly newer AEDs will be prescribed to the elderly with both chronic and late-onset epilepsies. On the other hand elderly patients caused higher costs for hospitalization possibly reflecting the need of admissions in the presence of frailty and other comorbidities.

The direct medical costs in our study were mainly caused by AEDs and hospitalization. The increasing utilization of newer and cost-intensive AEDs, such as levetiracetam is in line with recent studies confirming this trend towards an increased usage of newer AEDs [31–34]. This finding explains the high costs for anticonvulsants and confirms other recent COI studies [18,34,35], which showed that AEDs were becoming the main contributor to direct costs. However, inpatient costs are still a major cost component and studies with a top-down approach from Denmark [36] and the United States [37,38] proved hospitalization to be the major direct cost factor. Possibly, cost-intensive patients with status epilepticus [39,40] and patients undergoing video-EEG monitoring or epilepsy

**Table 3**

Annual direct and indirect costs in Euro (year 2011 values).

Direct cost components	Mean	SD	% of total direct costs	Minimum	Median	Maximum	Bootstrap 95% CI	
Hospitalization	510	±1622	30.0%	–	–	13,091	352	681
Rehabilitation	101	±736	5.9%	–	–	8498	36	182
Outpatient neurological care	72	±53	4.2%	29	58	288	67	79
Anticonvulsants – all patients	1017	±1224	59.9%	23	516	8334	887	1130
Monotherapy ( <i>n</i> = 248, 69.1%)	651	±791		23	309	5055	557	755
2 AEDs ( <i>n</i> = 90, 25.1%)	1585	±1321		107	1304	6015	1337	1841
≥3 AEDs ( <i>n</i> = 21, 5.8%)	2916	±2109		453	2662	8334	2092	3880
TOTAL DIRECT COSTS	1698	±2247	100%	52	716	15,377	1474	1907
INDIRECT COSTS (<65 y)	Mean	SD		Minimum	Median	Maximum	Bootstrap 95% CI	
Days off due to seizures ( <i>n</i> = 252)	745	±3587		–	–	29,763	391	1,169

SD: standard deviation, 95% CI: 95% confidence interval using the bootstrap bias corrected and accelerated method.

**Table 4**

Direct and indirect costs stratified according to seizure status.

Cost components	Seizure free > 1 year (n=200)		95% CI	Active epilepsy (n=155)		95% CI	p-Value
	Mean annual costs	SD		Mean annual costs	SD		
Hospitalization	€172	948	59; 316	€932	2123	636; 1263	<0.001
Rehabilitation	€56	628	0; 154	€160	855	54; 294	0.037
Outpatient neurological care	€65	47	59; 72	€82	59	73; 93	0.003
Anticonvulsants	€825	990	694; 952	€1.237	1415	1024; 1473	0.001
<b>TOTAL DIRECT COSTS</b>	<b>€1.117</b>	<b>1538</b>	<b>916; 1337</b>	<b>€2.404</b>	<b>2734</b>	<b>2029; 2830</b>	<b>&lt;0.001</b>
<b>INDIRECT COSTS (&lt;65 y)</b>							
	Seizure free > 1 year (n=139)		95% CI	Active epilepsy (n=109)		95% CI	p-Value
	Mean annual costs	SD		Mean annual costs	SD		
Days off due to seizures (n=252)	€456	3062	74; 916	€1.125	4165	443; 1930	<0.001

**Table 5**

Annual costs of anticonvulsants and prescription patterns (n=359, year 2011 values).

	n	Mean daily dose in mg ± SD <sup>a</sup>	Minimum in mg	Median in mg	Maximum in mg	Mean annual costs in Euro ± SD <sup>a</sup>
Levetiracetam (30.6%)	110	1434 ± 737	500	1000	3500	1619 ± 832
Lamotrigine (26.2%)	94	235 ± 163	25	200	800	261 ± 180
Valproate (24.2%)	87	1248 ± 722	300	1000	4200	231 ± 134
Carbamazepine (13.1%)	47	761 ± 373	100	800	1600	164 ± 80
Oxcarbazepine (10.9%)	39	1426 ± 856	75	1200	3600	817 ± 491
Phenytoin (6.4%)	23	226 ± 78	100	200	400	69 ± 24
Topiramate (5.3%)	19	183 ± 128	25	150	500	1242 ± 871
Gabapentin (4.7%)	17	1000 ± 412	600	900	2400	430 ± 177
Primidon (3.3%)	12	367 ± 220	100	350	750	85 ± 51
Lacosamide (2.5%)	9	333 ± 71	200	300	400	2031 ± 431
Phenobarbital (1.9%)	7	79 ± 42	25	75	150	135 ± 72
Zonisamide (1.9%)	7	329 ± 170	100	400	500	2351 ± 1219
other AEDs <sup>c</sup> (5.6%)	20					
Percentage of enzyme-inducing AEDs <sup>b</sup>		18.1%				
Percentage of 'old' AEDs <sup>b</sup>		35.8%				

<sup>a</sup> Mean ± standard deviation.<sup>b</sup> Enzyme-inducing AEDs: carbamazepine, phenobarbital, primidon, phenytoin; 'old' AEDs: valproate, carbamazepine, phenobarbital, primidon, phenytoin.<sup>c</sup> Other prescribed AEDs were pregabalin (n=6), clobazam (n=3), sultiame (n=3), eslicarbazepineacetate (n=2) ethosuximide (n=2), tiagabine (n=2), retigabine (n=1) and vigabatrin (n=1).**Table 6**

Cost and cost components stratified by potential cost-driving factors.

	n	Total direct costs	SD	p-Value <sup>a</sup>	AED costs	SD	p-Value <sup>a</sup>	Hospitalization costs	SD	p-Value <sup>a</sup>	n	Indirect costs	SD	p-Value <sup>a</sup>
<b>Gender</b>				0.097			0.032			0.527				0.603
Female	189	€1.693	2510		€954	1315		€533	1786		130	€743	3598	
Male	170	€1.704	1921		€1.088	1115		€486	1421		122	€747	3591	
<b>Age</b>				0.586			0.004 <sup>b</sup>			0.032				0.790
18–40 years	128	€1.790	2272		€1.165	1411		€409	1252		128	€909	4369	
41–65 years	124	€1.502	1618		€1.154	1290		€193	703		124	€577	2549	
>65 years	107	€1.817	2787		€683	766		€1.000	2460		–	–	–	
<b>Disease duration</b>				0.107			0.118			<0.001 <sup>b</sup>				0.001 <sup>b</sup>
0–2 years	84	€2.254	2870		€852	976		€1.188	2531		38	€2.406	7100	
3–5 years	39	€1.095	1401		€710	757		€313	999		21	€132	413	
5–10 years	69	€1.569	2014		€1.076	1243		€281	1143		50	€565	2629	
>10 years	167	€1.613	2101		€1.148	1392		€310	1181		143	€463	2543	
<b>Epilepsy syndrome</b>				0.057			0.188			0.381				0.814
Focal epilepsy	186	€1.900	2492		€1.047	1170		€672	1960		111	€306	1765	
Idiopathic generalized epilepsy	56	€1.322	1744		€981	1472		€153	533		53	€809	4219	
Unclassified or other syndromes	117	€1.558	2022		€988	1189		€424	1318		88	€1.269	4710	
<b>Seizure frequency</b>				<0.001 <sup>b</sup>			0.001 <sup>b</sup>			<0.001 <sup>b</sup>				0.001 <sup>b</sup>
Seizure remission > 1 year	200	€1.117	1538		€825	990		€172	948		139	€456	3062	
1 seizure/year	51	€2.534	3307		€901	928		€1.452	2806		29	€1.326	5222	
2–10 seizures/year	73	€2.054	2179		€1.172	1165		€545	1306		57	€1.077	3770	
>10 seizures/year	31	€3.013	2835		€1.944	2207		€976	2236		23	€987	3749	

<sup>a</sup> Mann–Whitney or Kruskal–Wallis test (two-sided), SD: standard deviation.<sup>b</sup> Significant p-values after Holm–Bonferroni correction.



surgery are neglected in bottom-up studies that recruit outpatients only. Studies with a top-down approach have the advantage of including all patients with epilepsy, irrespective of their ability to participate in field studies. However, it remains difficult to distinguish between epilepsy-specific costs and costs for comorbidities. In both studies from the United States [37,38] epilepsy-related costs for AEDs and claims for epilepsy or convulsions diagnoses accounted for only 32–46% of excess direct costs. Overall, these cost estimates rather represent the average costs of patients with epilepsy than the epilepsy-specific costs. Overall, the ongoing shift in direct cost components in our and other studies suggests that the costs of AEDs and hospitalization are continuously changing and depend on the research setting and health systems. On the one hand, the introduction of generic formulations will surely be associated with further decreasing AED costs. This is especially true for levetiracetam and lamotrigine, which are the drugs of choice in our study. On the other hand, the development of hospitalization costs is rather difficult to forecast and will need further evaluation.

We were able to demonstrate that electronic practice management software can easily be used to perform long-term health economic evaluations with a bottom-up approach. By that means time-consuming and labour-intensive implementation of field studies can be avoided while repeated or long-term evaluations are facilitated. Further use of electronic seizure diaries with direct information from the patient may allow the assessment of the clinical course in individual patients to be improved. Electronic seizure diaries have been proved to be reliable tools for clinical [41,42] and health economic evaluations [43]. The combination of both physician- and patient-based electronic databases will facilitate performing less expensive studies, but at the same time simplify large, prospective and multicentre clinical trials.

Despite the careful study design, this COI study suffers from certain limitations inherent to such investigations. In order to collect data regarding several direct cost components and indirect costs, the patients were asked about resource consumption at each visit and the possibility of incomplete patient recall cannot be excluded, which could have resulted in an underestimation of costs and a large variability in cost estimates. Also we did not record in detail all possible costs due to epilepsy-related comorbidities (e.g. depression, osteoporosis) or AED use [44], unless they resulted in a hospital admission. Due to recruitment from neurologists in private practice there might be a bias towards a referral population leading to higher costs. Further limitations of our study were due to the calculation of indirect costs using the human capital approach. In the current situation of underemployment in the general population, indirect costs may not exactly reflect the burden on society and may be overestimated [45]. However, due to the limitations of the friction cost approach [46], we retained the human capital approach, which is in accordance with the German and international recommendations for performing health economic evaluations [25].

## 5. Conclusions

We were able to demonstrate that electronic practice management software can easily be used to perform long-term health economic evaluations with a bottom-up approach.

Future studies should evaluate the development of direct cost components with a focus on hospitalization and anticonvulsants. From the societal perspective, major efforts should focus on the reduction of seizures for maintaining quality of care and reducing the need for hospitalization in epilepsy patients, thus improving the life quality of patients.

## Conflict of interest statement

Dr. R. Berkenfeld has served on the speakers' bureau of UCB Pharma.

Dr. D. Dennig has received honoraria as scientific advisor from Desitin, GlaxoSmithKline and Eisai and has served on the speakers' bureau of Eisai and UCB Pharma.

Dr. K. Menzler has served on the speakers' bureau of GlaxoSmithKline.

Dr. S. Knake has served on the speakers' bureau of Desitin and UCB Pharma.

Dr. F. Rosenow has received honoraria as scientific advisor from GlaxoSmithKline, Eisai, UCB Pharma and Pfizer. He has received speaker honoraria from UCB Pharma, GlaxoSmithKline, Eisai, Desitin, Medtronic and educational grants from Nihon-Kohden, UCB Pharma, Medtronics, Cyberonics and Cerbomed.

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None of the other authors did report conflict of interest to disclose regarding the content of the article. We confirm that we have read Seizure's position on ethics and procedures and confirm that this report is consistent with these guidelines.

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