

Systematic Adverse Drug Reaction Monitoring of Patients Under Newer Antiepileptic Drugs Using Routine Clinical Data of Inpatients

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Abstract

Background Based on data of clinical trials, new agents are receiving approval to the pharmaceutical market, for which information concerning safety issues under real-life conditions is not yet available.

Objectives The aim was to evaluate the tolerability of newer antiepileptic drugs (AEDs), such as topiramate, levetiracetam, zonisamide, pregabalin, extended-release oxcarbazepine, lacosamide and eslicarbazepine, under real-life conditions by means of an assessment of routine clinical data of inpatients.

Method Over 2.75 years data of all inpatients receiving one of the newer AEDs were documented. Occurring adverse drug reactions (ADRs) were classified according to the WHO-UMC Causality Assessment concerning their likely relationship to the prescribed AEDs. For each AED,

the total number of patients without and with ADRs, assessed as at least possibly related to the particular drug, was calculated and corresponding incidences compared with reference data provided in the Summary of Product Characteristics (SmPC). For statistical evaluation Spearman correlation (r_s), estimated relative risk and logistic regression analysis were used.

Results In total, the data of 562 patients were assessed, of which 90 % received up to six different AEDs. The proportion of off-label use with regard to dosage varied between 6.4 and 64.7 %. Levetiracetam and oxcarbazepine as an extended-release formulation were most commonly used, and levetiracetam showed the best tolerance. By using logistic regression, the occurrence of ADRs was significantly associated with the number of AEDs ($p < 0.001$) as well as the defined daily doses ($p = 0.003$). In total, ADRs of AEDs were documented for 318 patients (56.6 %). The most common referred to electrolyte imbalance, e.g., low sodium ($n = 79$, 14.1 %) and potassium ($n = 25$, 4.4 %) levels, the central nervous system, including dizziness ($n = 61$, 10.9 %), disturbed vision ($n = 47$, 8.4 %), fatigue ($n = 40$, 7.1 %), nystagmus ($n = 36$, 6.4 %) and ataxia ($n = 29$, 5.2 %), or cognitive deficits, especially disturbance of speech ($n = 37$, 6.6 %), memory impairment ($n = 36$, 6.4 %) and mental slowing ($n = 32$, 5.7 %). By comparing the assessed ADR incidences with specification data, for some ADRs, a probable underestimation by the SmPC of respective risk could be assumed.

Conclusion During inpatient treatment, valuable data are generated, which are currently rarely utilized for pharmacoepidemiologic or pharmacovigilance purposes. A systematic evaluation of these data can increase the probability of detecting ADRs and can promote real-life-related drug surveillance.

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Key Points

Summary of Product Characteristics data may underestimate the risk of adverse drug reactions.

Continuous tolerability and safety surveillance is necessary to align approval data with real-life experience.

Frequent risk evaluation of drugs by means of routine clinical data could provide a new quality of drug surveillance.

1 Introduction

Based on submitted quality, efficacy and safety data, dozens of new agents are receiving approval to the pharmaceutical market every year. Despite their promising advantage to medical care, at the time of approval, there can be no certainty that these drugs are completely safe [1]. Information about specific population groups can frequently be assumed to be missing as well as data about rare adverse drug reactions (ADRs) or drug interactions. It is therefore necessary to establish methods of large-scale post-marketing surveillance to gather real-life data especially with regard to safety issues. In most countries a spontaneous reporting system (SRS) for collecting data of suspected ADRs is used. Reported data are assessed by the responsible authority in a global database, which thus contains a vast data pool of ADRs relating to a wide range of drugs, in support of its main objective of generating signals of unknown, rare or serious ADRs [2–4]. This is a very cost-effective method. However, this kind of drug safety monitoring also has many limitations, the most frequently mentioned being the subject of underreporting. The mentioned reasons for this are manifold, including lack of time, large effort, fear of being prosecuted, unawareness of the requirement to report or the estimation that a particular ADR is not worth noting [3–5]. Also, SRSs are often believed to be exclusively designed for detecting rare and serious ADRs, but for general drug safety, the monitoring of all undesirable reactions is necessary [4]. For the most accurate relative risk (RR) assessment, exact data of application or drug utilization is required, which, however, is only available by approximation. Thus, an SRS has not got the impact to determine the prevalence rate of a specific ADR reliably and bears a risk of delay in signal detection.

In the case of diseases requiring lifelong treatment, more detailed knowledge about the efficacy and tolerability of a

drug, attention to ADRs as well as awareness of patients' needs are necessary to achieve the best therapeutic outcome. For epilepsy, as one of these diseases, the occurrence of ADRs has been shown to have an important influence on patients' quality of life [6–9]. Approximately 20 % of all patients with epilepsy, in the case of refractory epilepsy, even about 50 %, are on polytherapy, bearing an increased risk for ADRs and drug interactions [10–13]. Many of these patients have tried most of the available drugs and are therefore a target group for new treatment options aimed at reducing seizure frequency while maintaining or even optimizing tolerability. Especially in patients suffering from seizure recurrence, optimizing therapy can be a balancing act between increasing the drug dosage to maximize the therapeutic effect and running the risk of ADRs [14, 15]. Over the past 25 years, more than 15 new antiepileptic drugs (AEDs) with modified acting mechanisms and/or side effect profiles have become available for epilepsy treatment, resulting in a major challenge for health professionals and post-marketing surveillance in respect of specified knowledge about tolerability and drug interaction. Such a level of competence can hardly be generated by relying only upon a tool like an SRS for monitoring drug safety. In fact, long-term supervision of medicated patients, increased sensitivity towards recognizing accumulation of specific ADRs and deriving remedial measures from these observations are recommended as vital for a comprehensive risk–benefit evaluation [14]. Accordingly, the systematic assessment and evaluation of routine inpatient data was assumed to be one way of obtaining this relevant knowledge and was therefore investigated in this survey.

2 Methods

2.1 Data Collection

Between May 2008 and December 2010, an in-house pharmacist attended the Consultants' ward round once a week on four different wards of the Bethel Epilepsy Centre, Bielefeld, Germany, a tertiary reference center for epilepsy. All information taken as part of clinical routine during the ward round was documented in the patients' chart as usual and, for later digitalization, concurrently transcribed to an adjusted record form by the pharmacist. For every patient a new record form was used for each week. All inpatients receiving one of the newer AEDs, i.e., topiramate (TPM), levetiracetam (LEV), zonisamide (ZNS), pregabalin (PGB), extended-release oxcarbazepine [OXC(ER)], lacosamide (LCM) and eslicarbazepine (ESL), were included. Documented data comprised the specific drug, all AEDs in use, corresponding daily dosages and serum levels, if available, age, gender, concomitant

medication, patient and actual case number. In addition, all patient-reported and medically diagnosed ADRs were documented in an unstructured format, and for each one, the current causality concerning the administered AEDs was assessed by interprofessional exchange (i.e., physician, pharmacist, nursing staff). To this end, the temporal pattern of association between its occurrence and change of medication and all available information concerning concomitant disorders, diseases or medication were taken into account. For the classification of causality, the WHO-UMC Causality Categories were used (see the electronic supplementary material, Online Resource 1) [16]. Any severe or unknown suspected ADRs were immediately reported via the SRS to the responsible regulatory authority.

2.2 Data Entry

All relevant data were recorded by the pharmacist in an internal database, using IBM SPSS for Windows 20.0. Patient data were documented by assigning an individual patient number, case number, gender, age and date of observation. In order to enable the evaluation, the initially documented ADRs were coded numerically according to the system organ classes (SOCs) of the MedDRA (*Medical Dictionary for Regulatory Activities*) terminology, and the specific symptom. Also, corresponding causality categories were entered numerically. For every documented ADR and week, a single data set containing patient details, medication, daily dosage and causality category for every given AED was generated. Where the same ADR was documented more than once for one patient, the first documented observation and accordingly the one with the lowest AED dosages was included for analysis only. For patients without ADRs, the highest AED dosage was considered. To rule out possible input errors, the data were entered twice at different times. Asserted discrepancies were clarified by re-checking the record forms.

2.3 Data Evaluation

Demographic and clinical characteristics of the patients were evaluated by using the first documented contact after hospitalization. For every newer AED, the total number of patients without and with ADRs, assessed with at least possible causality, and the corresponding dosages were calculated. Additionally, the same analysis was performed including only data sets of patients being treated off-label with regard to the maximum recommended daily dosage in the Summary of Product Characteristics (SmPC). In both analyses, every patient was included only once. Furthermore, for every AED, the incidence of the respective ADR was determined with reference to the number of patients experiencing this ADR while taking the particular AED

divided by the total number of patients where this AED was part of the therapy. All estimated incidence rates were compared with the respective data provided in the SmPC of each AED [17–23]. The correlation between the number of AEDs and the total drug load, calculated as sum of the defined daily doses (DDD), was determined by Spearman correlation. For assessing the impact of number of AEDs and sum of DDDs on the occurrence of ADR, logistic regression was used.

Concerning tolerability of each AED, the RR of ADR occurrence was calculated. For this purpose, the data of LEV were used as the reference, as being the most frequently applied AED in this survey, the first recommended for treatment of focal epilepsy out of this selection and also proven as well tolerated [24–28].

3 Results

In total, data of 562 cases were assessed, which equals around one quarter of the total number of in-house patients on the attended wards in the same time period. The corresponding patients' characteristics, length of stay and number of AEDs in concomitant usage [mean, median and standard deviation (SD)] are summarized in Table 1. For further specification of the antiepileptic therapy, the number and percentage distribution of patients receiving antiepileptic monotherapy versus polytherapy of up to six different AEDs were evaluated on the basis of each initially documented observation per patient. Hence, 57 patients (10.1 %) were on monotherapy, 192 patients (34.2 %) were treated with two different AEDs, 205 patients (36.5 %) with three, 88 (15.7 %) with four, 19 (3.4 %) with five and just one patient (0.2 %) with six. The number of AEDs correlated significantly with the total drug load as sum of DDDs ($r_s = 0.661$, $p < 0.001$). The mean drug load (\pm SD) per patient increased with an increasing number of AEDs from 1.15 ± 0.60 in patients on monotherapy to 2.42 ± 0.98 in patients on two concomitant AEDs, 3.33 ± 1.33 in those on three, 4.50 ± 1.35 in those on four and 5.56 ± 1.28 in those on five or six.

In monotherapy, as well as in a combination of two different AEDs, OXC(ER) and LEV were the ones most commonly used. This is the case for more than 40 % of the patients. For further information concerning the percentage of each AED in antiepileptic polytherapy see Fig. 1. LEV and OXC(ER) were further the most frequently used at all, with applications documented for 367 and 183 patients, respectively. For TPM and LCM, the data of 109 and 102 patients were assessed, whereas ZNS (68 patients), PGB (61 patients) and ESL (17 patients) were a less frequently used component of the antiepileptic therapy.

Table 1 Patients' characteristics^a of 562 in-house patients treated at the tertiary reference center for epilepsy who were receiving at least one of the newer AEDs

	N	Total (%)	Mean	Median	SD	Min.	Max.
Gender							
Male	293	52.1					
Female	269	47.9					
Epilepsy syndrome							
Focal	446	79.4					
Generalized	83	14.8					
Focal + generalized	24	4.3					
Non-epileptic disorder ^b	9	1.6					
Age (years)	562		37.2	36.0	14.6	16.0	89.0
Length of stay (days)	562		60.6	51.0	38.7	6.0	238.0
No. of AEDs per patient	562		2.64	3.00	1.00	1.00	6.00
Drug load of AEDs (DDD) ^c	562		3.14	3.02	1.53	0.25	10.82

AED antiepileptic drug, DDD defined daily dose, SD standard deviation

^a Calculated by including every first documented observation of each patient

^b Differential diagnosis of a paroxysmal non-epileptic disorder obtained during hospitalization

^c Sum of DDD according to the WHO DDD list

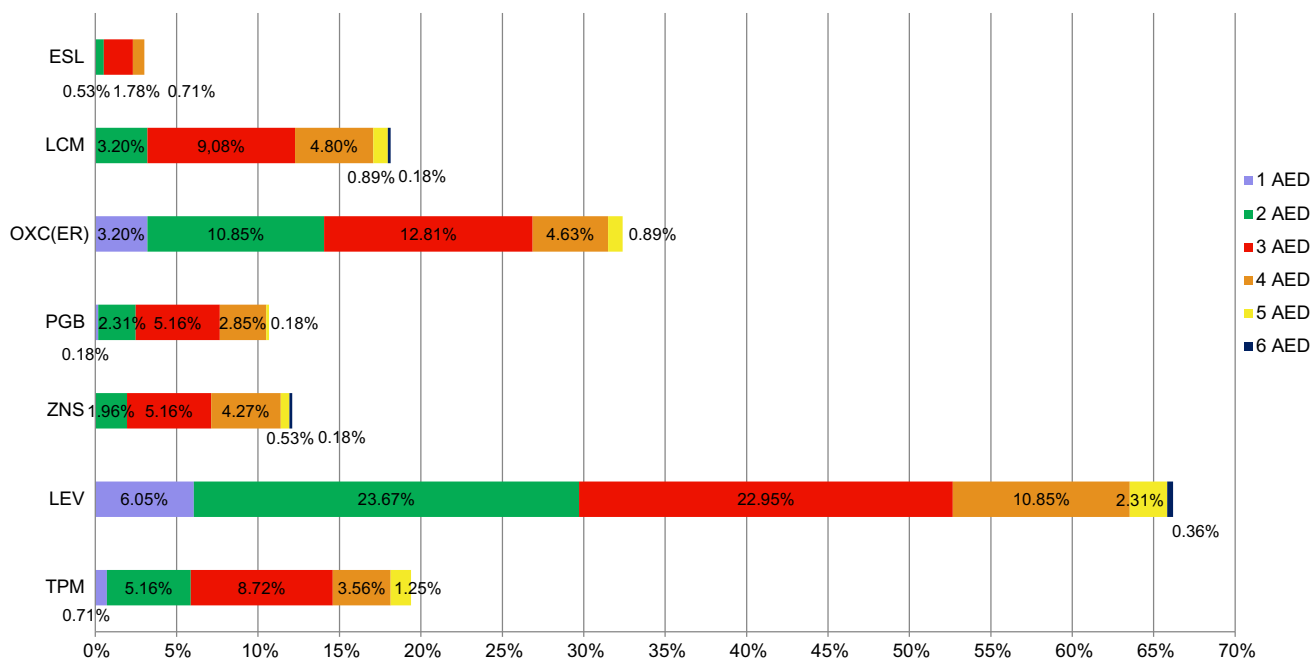


Fig. 1 Percentage of patients treated with the respective AED, stratified by monotherapy and the different kinds of polytherapy (left to right). Total percentage of patients taking respective drug either as monotherapy or part of polytherapy: LEV 66.19 %, OXC(ER) 32.38 %, TPM 19.4 %, LCM 18.15 %, ZNS 12.1 %, PGB 10.68 %,

and ESL 3.02 %. AED antiepileptic drug, ESL eslicarbazepine, LCM lacosamide, LEV levetiracetam, OXC(ER) oxcarbazepine extended-release formulation, PGB pregabalin, TPM topiramate, ZNS zonisamide

In total, ADRs of AEDs were documented for 318 patients (56.6 %). Logistic regression indicated that the occurrence of ADRs was significantly associated with the number of AEDs in polytherapy regime ($p < 0.001$) as well as the total drug load as sum of DDDs ($p = 0.003$), whereas each predictor was analyzed separately.

For each of the focused AEDs, the number of cases without and with an ADR of at least possible causality and corresponding dosages are listed in Table 2. For none of these AEDs the sum of percentage of cases without and with possibly related ADRs achieved 100 %. The differences, ranging from 4 to 15 %, represent ADRs assessed as

Table 2 Patients without and with at least possibly related ADRs, stratified by the respective AEDs, including details of particular daily dosages

	N	Total ^a (%)	RR ^b	CI	Daily dosage (mg)					
					Mean	Median	SD	Min.	Max.	
LEV										
Without ADR	203	55.3	[1.00]		2596	3000	1107	250	6000	
With possible ADR	120	32.7			2465	2500	1096	250	7000	
PGB										
Without ADR	26	42.6	1.31	0.89–1.93	487	600	187	75	750	
With possible ADR	28	45.9			321	275	194	75	750	
ZNS										
Without ADR	26	38.2	1.40	0.98–2.02	256	250	164	50	600	
With possible ADR	32	47.1			338	300	148	100	600	
OXC(ER)										
Without ADR	73	39.9	1.57	1.26–1.95	1715	1800	677	450	3850	
With possible ADR	97	53.0			1646	1800	530	450	3000	
LCM										
Without ADR	37	36.3	1.63	1.24–2.13	326	350	144	50	600	
With possible ADR	55	53.9			269	250	139	50	600	
TPM										
Without ADR	31	28.4	1.97	1.56–2.47	223	150	203	25	800	
With possible ADR	65	59.6			213	200	119	50	500	
ESL										
Without ADR	2	11.8	2.30	1.75–3.02	1800	1800	849	1200	2400	
With possible ADR	14	82.4			1514	1600	501	800	2400	

AED antiepileptic drug, ADR adverse drug reaction, CI confidence interval, ESL eslicarbazepine, LCM lacosamide, LEV levetiracetam, OXC(ER) oxcarbazepine extended-release formulation, PGB pregabalin, RR relative risk for the occurrence of possibly related ADRs compared with the occurrence of these under levetiracetam, SD standard deviation, TPM topiramate, ZNS zonisamide

^a For calculation, the total number of documented cases per AED was used; the missing percentage up to 100 % fall upon ADRs assessed as unlikely, conditional or not causally linked to the particular AED

^b For calculation of RR, patients taking both of the specifically compared AEDs were excluded

unlikely, conditional or not causally linked to the particular AED. In the case of TPM, this applied to 13 patients, for LEV to 44, PGB to seven, ZNS to ten, OXC(ER) to 13, LCM to ten and ESL to just one patient.

By referring exclusively to the overall tolerability, LEV emerged as best tolerated. The calculated RRs of ADR occurrence per AED compared with LEV, which was set as reference, ranged between 1.31 and 2.30, whereas again just the total number of possibly related ADRs was taken into account, not the clinical relevance of every single ADR nor other tolerability influencing factors.

By means of the maximum applied dosages (Table 2), it becomes apparent that in some cases the maximum applied AED dosage exceeded the maximum permissible dosage according to the particular SmPC [17–23]. For LCM, that dosage was specified as 400 mg per day, for TPM and ZNS, as 500 mg/day each, and for PGB, as 600 mg/day; for ESL, OXC(ER) and LEV, the maximum approved dosage was determined as 1200, 2400 and 3000 mg/day, respectively. The proportion of off-label usage concerning

the maximum recommended daily dosage in the SmPC varied between 6.4 and 64.7 % with regard to the total number of patients the respective AED was part of therapy. For further differentiation, the corresponding data of every single AED, with and without ADR, is summarized in Table 3. Comparing the calculated RR for each AED used off-label to its application as recommended by the SmPC revealed no relevant risk change. Though, the number of patients for these evaluations was small.

Concerning the documented ADRs, the most common were related to electrolyte imbalance, e.g., low sodium ($n = 79$, 14.1 %) and potassium ($n = 25$, 4.4 %) levels, the central nervous system, including dizziness ($n = 61$, 10.9 %), disturbed vision ($n = 47$, 8.4 %), fatigue ($n = 40$, 7.1 %), nystagmus ($n = 36$, 6.4 %) and ataxia ($n = 29$, 5.2 %), or cognitive deficits, especially disturbance of speech ($n = 37$, 6.6 %), memory impairment ($n = 36$, 6.4 %) and mental slowing ($n = 32$, 5.7 %). In 24 patients (4.3 %), the observed ADRs were considered as severe, rare, very distinctive or currently unknown and

Table 3 Patients under off-label use concerning dose, without and with at least possibly related ADRs, stratified by the respective AEDs, including details of particular daily dosages

	N	Total ^a (%)	RR	CI	Daily dosage (mg)					
					Mean	Median	SD	Min.	Max.	
TPM										
Off-label use	7	6.4								
Without ADR	4	3.7	0.49	0.16–1.54	638	600	111	550	800	
With possible ADR	2	1.8			650	650	71	600	700	
LCM										
Off-label use	18	17.6								
Without ADR	8	7.8	0.84	0.50–1.40	513	500	58	450	600	
With possible ADR	8	7.8			500	500	53	450	600	
LEV										
Off-label use	91	24.8								
Without ADR	50	13.6	0.95	0.68–1.33	3945	4000	408	3500	6000	
With possible ADR	27	7.4			4102	4000	701	3500	7000	
PGB										
Off-label use	6	9.8								
Without ADR	3	4.9	0.96	0.42–2.24	725	750	43	675	750	
With possible ADR	3	4.9			708	700	38	675	750	
OXC(ER)										
Off-label use	20	10.9								
Without ADR	8	4.4	1.02	0.68–1.52	2994	3000	401	2550	3850	
With possible ADR	11	6.0			2832	2700	316	2500	3600	
ESL										
Off-label use	11	64.7								
Without ADR	1	5.9	1.03	0.78–1.36	2400	2400		2400	2400	
With possible ADR	9	52.9			1822	1600	353	1600	2400	
ZNS										
Off-label use	7	10.3								
Without ADR	2	2.9	1.21	0.66–2.23	600	600	0	600	600	
With possible ADR	4	5.9			588	600	25	550	600	

AED antiepileptic drug, ADR adverse drug reaction, CI confidence interval, ESL eslicarbazepine, LCM lacosamide, LEV levetiracetam, OXC(ER) oxcarbazepine extended-release formulation, PGB pregabalin, RR relative risk for the occurrence of possibly related ADRs comparing off-label use concerning dose to the particular applications of the same drug used on-label, i.e., according to the recommended dosage by the Summary of Product Characteristics, SD standard deviation, TPM topiramate, ZNS zonisamide

^a For calculation, the total number of documented cases per AED was used

therefore reported via the SRS to the responsible regulatory authority. Among these reports were one case of an arrhythmia absoluta under the combination of LCM and LEV as a potentially life-threatening ADR, three of suicidal ideation (two under LEV, one under the combination of OXC(ER)/LCM), three of myoklonia [two under OXC(ER), one under LEV], two of peripheral edema under OXC(ER), one of paresthesia under LEV, one of anorexia under TPM and one case of anxiety under LEV.

For comparing the frequency of occurrence of particular ADRs in relation to the information mentioned in the SmPC, the incidence of the ADR was calculated for each

AED separately. The detailed results are shown in Table 4. Although, SmPC data express a very rough classification for ADR frequency by using categories differing by one power of ten only, e.g., $\geq 0.1\%$ for an uncommon and $\geq 10\%$ for a very common occurrence, for some registered ADRs probable underestimation was assumed. This, for example, was apparent in the case of cognitive impairment related to TPM and electrolyte imbalance concerning potassium under therapy with an carbonic anhydrase (CA) inhibitor (i.e., TPM, ZNS) or sodium level by application of dibenzazepine anticonvulsants (i.e., OXC, ESL).

Table 4 Incidence rates of all ADRs, assessed as at least possibly related to the antiepileptic drug, compared with corresponding frequency data by the SmPC (nonexhaustive list; occurred ADRs mentioned only)

	TPM		LEV		PGB		ZNS		OXC(ER)		LCM		ESL	
	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC
<i>Metabolism and nutrition disorders</i>														
Weight gain														
<i>N</i>			3		7				2					
%		≥1	0.8	≥0.1	11.3	≥1		N/A	1.1	N/A		N/A		N/A
Weight loss														
<i>N</i>	9		2				3							
%	8.2	≥10	0.5	≥0.1		≥0.1	4.5	≥1		N/A		N/A		≥0.1
Decreased appetite/anorexia														
<i>N</i>	5		5				3							
%	4.5	≥1	1.4	≥1		N/A	4.5	≥1		N/A		N/A		≥1
Hypokalemia														
<i>N</i>	11		3				9		1		3		1	
%	10.1	≥0.1	0.8	N/A		≥0.1	13.2	≥0.1	0.6	N/A	2.9	N/A	5.9	N/A
Hyponatremia														
<i>N</i>			3		1				67		3		10	
%		N/A	0.8	≥0.01	1.6	N/A		N/A	37.0	≥1	2.9	N/A	58.8	≥1
<i>Psychiatric disorders</i>														
Sleep disturbance/insomnia														
<i>N</i>			2		1		1						1	
%		≥1	0.5	≥1	1.6	≥1	1.5	≥1		N/A		≥1	5.9	≥1
Nervousness/agitation														
<i>N</i>	1		5		1		1		3		4		1	
%	0.9	≥1	1.4	≥1	1.6	≥0.1	1.5	≥10	1.7	≥1	3.9	≥0.1	5.9	≥0.1
Irritability														
<i>N</i>	2		10						1					
%	1.8	≥1	2.7	≥1		≥1		≥10	0.6	N/A		≥1		≥0.1
Aggressive reaction														
<i>N</i>	2		11		1		2		2		1			
%	1.8	≥1	3.0	≥1	1.6	≥0.1	3.0	≥0.1	1.1	N/A	1.0	≥0.1		N/A
Anxiety														
<i>N</i>			4		1									
%		≥1	1.1	≥1	1.6	N/A		≥1		N/A		N/A		N/A
Listlessness/apathy														
<i>N</i>			2		1				1					
%		≥0.1	0.5	N/A	1.6	N/A		N/A	0.6	≥1		N/A		≥0.1
Mood swings/depressed mood														
<i>N</i>	2		8				3		1		2			
%	1.8	≥10	2.2	≥1		≥0.1	4.5	≥10	0.6	≥1	1.9	≥1		≥0.1
Confusion														
<i>N</i>			2						1					
%		≥1	0.5	≥0.1		≥1		≥10	0.6	≥1		≥1		≥0.1
Suicidal ideation														
<i>N</i>	1		4						1		1			
%	0.9	≥0.1	1.1	≥1		N/A		≥0.1	0.6	N/A	1.0	≥0.1		N/A
<i>Nervous system disorders</i>														
Fatigue/tiredness														
<i>N</i>	5		25		5		6		12		6		2	
%	4.5	≥10	6.8	≥10	8.1	≥10	9.0	≥10	6.6	≥10	5.8	≥1	11.8	≥10
Dizziness														
<i>N</i>	5		23		7		5		24		25		5	
%	4.5	≥10	6.3	≥1	11.3	≥1	7.5	≥10	13.3	≥10	24.3	≥10	29.4	≥10

Table 4 continued

	TPM		LEV		PGB		ZNS		OXC(ER)		LCM		ESL	
	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC
Nystagmus														
<i>N</i>	4		10		5		2		13		19		4	
%	3.6	≥1	2.7	N/A	8.1	≥0.1	3.0	≥1	7.2	≥1	18.4	≥1	23.5	≥0.1
Tremor														
<i>N</i>	2		17		3		2		3		8		1	
%	1.8	≥1	4.6	≥1	4.8	≥1	3.0	≥1	1.7	≥1	7.8	≥1	5.9	≥1
Balance disorder/ataxia														
<i>N</i>	3		10		2		2		12		11		2	
%	2.7	≥1	2.7	≥1	3.2	≥1	3.0	≥10	6.6	≥1	10.7	≥1	11.8	≥1
Disturbance in concentration/attention														
<i>N</i>	16		3				2		2		1			
%	14.7	≥1	0.8	≥0.1		≥1	3.0	≥1	1.1	≥1	1.0	≥1		≥1
Memory impairment														
<i>N</i>	25		11		2		6		3		2			
%	22.9	≥1	3.0	≥0.1	3.2	≥1	9.0	≥10	1.7	≥1	1.9	≥1		≥0.1
Disturbance of speech														
<i>N</i>	31		4				3		4		2			
%	28.4	≥1	1.1	N/A		≥0.1	4.4	≥1	2.2	N/A	1.9	≥1		≥0.1
Mental slowing/bradyphrenia														
<i>N</i>	17		10		1		8		4		4			
%	15.6	≥1	2.7	N/A	1.6	≥0.1	11.9	≥1	2.2	N/A	3.9	≥1		N/A
Headache														
<i>N</i>	1		6		1				7		4		1	
%	0.9	N/A	1.6	≥10	1.6	≥10		N/A	3.9	≥10	3.9	≥10	5.9	≥1
Dysgeusia														
<i>N</i>			1		1									
%		≥1	0.3	N/A	1.6	≥0.1		N/A		N/A		N/A		N/A
Paresthesia														
<i>N</i>	3		2											
%	2.7	≥10	0.5	N/A		≥1		≥1		N/A		≥1		≥0.1
Eye disorders														
Blurred vision/diplopia														
<i>N</i>	6		13		5		5		23		17		4	
%	5.5	≥1	3.5	≥0.1	8.1	≥1	7.5	≥10	12.6	≥10	16.5	≥10	23.5	≥1
Ear and labyrinth disorders														
Tinnitus														
<i>N</i>	1		1											
%	0.9	≥1	0.3	N/A		N/A		N/A		N/A		≥1		≥0.1
Gastro-intestinal disorders														
Nausea/vomiting														
<i>N</i>	3		4		1				13		15		2	
%	2.7	≥10	1.1	≥1	1.6	≥1		≥1	7.2	≥10	14.6	≥10	11.8	≥1
Diarrhea														
<i>N</i>	1		1								1			
%	0.9	≥10	0.3	≥1		≥1		≥1		≥1	1.0	≥1		≥1
Obstipation														
<i>N</i>	1				1		2		4		2			
%	0.9	≥1		N/A	1.6	≥1	3.0	≥1	2.2	≥1	1.9	≥1		≥0.1
Flatulence														
<i>N</i>									1		4			
%		≥0.1		N/A		≥1		N/A	0.6	N/A	3.9	≥1		≥0.1

Table 4 continued

	TPM		LEV		PGB		ZNS		OXC(ER)		LCM		ESL	
	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC	Obs.	SmPC
<i>Hepatobiliary disorders</i>														
Increase in liver enzymes														
<i>N</i>			6		1		2		6		2		2	
<i>%</i>		≥0.1	1.6	≥0.1	1.6	≥0.1	3.0	≥1	3.3	≥0.1	1.9	≥0.1	11.8	≥0.1
<i>Skin and subcutaneous tissue disorders</i>														
Hypersensitivity/pruritus														
<i>N</i>			2						1		1			
<i>%</i>		≥1	0.5	≥0.01		≥0.1		≥1	0.6	≥0.001	1.0	≥1		≥0.1
Alopecia														
<i>N</i>	1		2						2		1			
<i>%</i>	0.9	≥1	0.5	≥0.01		N/A		≥1	1.1	≥1	1.0	N/A		≥0.1
<i>Musculoskeletal disorders</i>														
Myoclonia														
<i>N</i>			1				1		2					
<i>%</i>		≥1	0.3	N/A		≥0.1	1.5	N/A	1.1	N/A		≥1		N/A
<i>General disorders</i>														
Peripheral edema														
<i>N</i>					4				2				1	
<i>%</i>		N/A		N/A	6.5	≥1		≥1	1.1	N/A		N/A	5.9	≥0.1
Total														
<i>N</i>	109		367		61		68		183		102		17	
<i>%</i>	100		100		100		100		100		100		100	

ADR adverse drug reaction, ESL eslicarbazepine, LCM lacosamide, LEV levetiracetam, N/A not available, Obs. observed, OXC(ER) oxcarbazepine extended-release formulation, PGB pregabalin, SmPC Summary of Product Characteristics, TPM topiramate, ZNS zonisamide

4 Discussion

4.1 AED Usage and ADR Incidence

Of the various AEDs of interest in this survey, OXC(ER) and LEV were most frequently used. To our knowledge, no study has so far investigated this selection of newer AEDs, but there are three different papers reporting on the nationwide prescription patterns of AEDs in Italy (data included until 2007), Norway (until 2009) and Germany (until 2010) [13, 29, 30]. Extracting the data related to the AEDs focused on in this survey also reveals the tendency towards LEV being the most frequently used, followed by OXC(ER), TPM, ZNS and PGB. LCM and ESL were the most recently approved AEDs, which is why no reliable data were available.

With regard to every first documented observation per patient in this evaluation, almost 90 % were on polytherapy. Compared with the studies of Canevini et al. and Malerba et al. in which 22.5 and 21 %, respectively, of drug refractory patients were being managed on a single AED [30, 31], a proportion of 10.1 % is small. However, in our survey only patients recently admitted to in-house treatment were included, for whom, other than severe epilepsy, the need for a complex therapy management,

including administration of antiepileptic medication for acute use and the change in therapy by gradual cross-over of AEDs, can be assumed. By considering the calculated mean data for the length of stay, number of concomitant AEDs and AED load, defined as the sum of DDDs (Table 1), this assumption can be substantiated.

It is still a matter of debate if antiepileptic polytherapy compared with monotherapy is generally associated with more frequent ADRs. The correlation between AED toxicity and total drug load rather than the number of concomitant AEDs is also still under discussion [31–34]. In this survey, both factors were significantly associated with a more frequent occurrence of ADRs, whilst also both were strongly correlated with each other. However, in view of the numerical extent of association, the total number of AEDs seemed to be of greater impact. The reasons for this can be manifold, including the absence of a rigid dosing scheme, a gradual cross-over of AEDs, and the value of DDD as an imperfect measure of drug exposure itself [15, 31, 35]. Testing for serum concentration-dependent tolerability was also considered for this survey, but ultimately rejected as therapeutic drug monitoring of the newer AEDs often was applied in selected cases only [36] and, therefore, corresponding serum concentrations were not available in every documented data set.

The overall incidence of ADRs was calculated as 56.6 %, based on 318 patients for whom adverse reactions were documented. With regard to the method of assessment and the investigated patient population, this result corresponds well with that of other studies. Canevini et al., who also analyzed patients with drug-resistant epilepsy at tertiary referral centers, identified ADRs in 36.5 % of patients, based on spontaneous reporting, compared with 95.5 % when a validated screening questionnaire was used [31]; similar results were summarized in a review of Perucca and Gilliam [37]. Considering that the detection of ADRs in clinical routine is derived from spontaneous reporting complemented by medical examination and lab diagnostics, and in view of the findings by Baker et al., which indicate a prevalence underestimation of ADRs when based on spontaneous reporting versus overestimation when using checklists, the extent of prevalence in this survey can be considered plausible for a real-life hospital setting [38].

Concerning the overall tolerability, LEV emerged as best tolerated, which, similarly, was reported by Cramer et al. [28]. This may be a reason for it being first recommended and therefore frequently used, as also indicated by the high number of patients under LEV in this survey. The calculated RRs of ADR occurrence for each AED compared with LEV varied between 1.31 and 2.30. But these values should be treated with caution; for the evaluation, only the total number of possibly related ADRs was taken into account, and not the type nor the clinical relevance of the ADR, nor other tolerability influencing factors. The impact of associated ADRs can be very different, which is why by using this kind of RR calculation only the overall tolerability can be estimated and has to be reviewed in every single case [31, 37]. Furthermore, all patients were preselected due to real-life conditions, and the total number of patients treated with particular AEDs varied widely, which in itself may have had an impact on the estimated RR.

An interesting finding of this survey was the rather high proportion of off-label use concerning maximum recommended daily dosage (Table 3). So far, there are not many studies investigating off-label use by dose in drug resistant epilepsy. One study by Franco et al. focused on this question by means of a diagram, showing proportions of off-label use of between 0 and 25 % [39]. The values in our survey ranged from 6.4 % for TPM up to 64.7 % for ESL. By comparing the calculated RR for each AED used off-label to its application as recommended by the SmPC, no considerable change of ADR occurrence was seen. However, the documented extent of off-label use showed an obvious relevance for clinical practice, indicating the need of further investigations on potential risks and benefits to alleviate physicians' and patients' uncertainty whilst using a drug out of its specification [39].

As already mentioned, antiepileptic therapy often means a balancing act between optimizing therapeutic outcome and running the risk of ADRs [6–8, 14, 15, 31, 37, 40–42]. It is therefore important to be aware of the side effect profiles of every considered AED in order to choose the best therapy option for every patient. The comparison of incidences of ADRs with possible causality in relation to the information mentioned in the SmPC, which, to our knowledge, was first performed in this survey, is very valuable to provide a supplementary assessment of particular risk. Even though, SmPC data present a very rough estimate for ADR frequency by using categories differing by one power of ten only, e.g., ≥ 0.1 % for an uncommon and ≥ 10 % for a very common occurrence, for some of the documented ADRs, a probable underestimation was determined. For example, in the case of cognitive impairment related to TPM or electrolyte imbalance under therapy with a CA inhibitor (i.e., TPM, ZNS) or dibenzazepine anticonvulsants (i.e., OXC, ESL), the discrepancy was particularly apparent.

It is a well known fact that the detection of specific ADRs can be influenced by physicians' expectations as to the likelihood of occurrence [8, 31]. Therefore, it cannot be excluded that applied targeted testing, such as close control of lab values, will cause a detection bias.

TPM and ZNS are known as inhibitors of CA, which has a considerable share in regulating the acid–base balance and therefore influences the electrolyte status. In this survey, low potassium levels (< 3.6 mEq/L) were assessed for 11 and nine patients on TPM and ZNS (10.1 and 13.2 %), respectively, although the SmPC of both drugs mention this to be an uncommon occurrence (≥ 0.1 and < 1 %) [17, 20]. A similar result for TPM was found in a systematic review by Dell'Orto et al., indicating hypokalemia as concomitant with metabolic acidosis for 10 % of the cases [43]. To our knowledge, there are no comparable investigations referring to potassium levels under ZNS treatment, but a study by Mirza et al. indicated similar inhibitor potency to CA isoforms by TPM and ZNS, both inducing renal tubular acidosis [44]. Therefore, it seems plausible to detect an also increased frequency of hypokalemia under ZNS. Further investigations are definitely necessary to verify these results, but until then, the potential risk of CA inhibitors should be considered, particularly in patients with comorbidity or co-medication influencing electrolyte balance.

The same applies to treatment regimes with OXC(ER) or ESL, for which a higher incidence of hyponatremia, compared with SmPC data, was documented [21, 23]. As possible reasons, the previously mentioned detection bias or other influencing factors, like vomiting, diuretic or psychotropic medication, heart or kidney insufficiency, etc., should be also taken into account. Furthermore, the varying reference values applied for the definition of

hyponatremia in different studies (here <135 mEq/L) and the highly selected patient population in this survey should be considered. Apart from this, there are many studies mentioning the frequency of decreased sodium serum levels in about 10–30 % of the patients under OXC treatment, which in turn substantiates an assumed higher risk [45–50]. At the time of approval, ESL was promoted as bearing a lower hyponatremia risk compared with OXC. However, studies by Ley et al. and Gupta et al. could not substantiate this claim [51, 52]. In our survey, almost all patients with ESL stopped OXC(ER) because of decreased sodium levels prior. Therefore, the previous experience of hyponatremia could be an explanation for the high incidence even under ESL. But interesting in this context, data concerning hyponatremia mentioned in the SmPC have, since approval, been adjusted to a common frequency (≥ 1 and <10 %), therefore, indicating the same risk as for OXC(ER), by now [23, 53].

With regard to cognitive impairment (e.g., psychomotor slowing, difficulty with concentration/attention, difficulty with memory, speech or language problems, particularly word-finding difficulties), this is a well described problem in patients on TPM [42, 54–59]. Being aware of that, neuropsychological testing and retesting (investigating cognitive processing, memory, language) are more often applied in conjunction with TPM therapy, as for example, recommended by Lee et al. [60]. This may have induced an overestimation of the particular risk in this survey, since cognitive impairment is also known to be influenced by seizure frequency and an increased number and dosage of AEDs [56]. However, a review by Mula, investigating the evidence of cognitive impairment under TPM, established that approximately 10 % of the patients experienced cognitive problems [58]. Of these, as also confirmed in our survey, speech problems mainly concerning verbal fluency were the most prominent [58, 61], a fact, which should be considered in individual treatment plans, especially for patients actively working or studying.

In conclusion, the results of this survey show that a systematic evaluation of inpatient data allows for even more information to be gained than could be extracted from clinical trials or SRS. Therefore, this kind of surveillance can provide a decisive contribution to future adjustments of risk data, applied to align approval data with real-life experience, which is an ongoing process, as the comparison of SmPC data from 2011 and 2015 reflects [17–23, 53, 62–67].

4.2 Methodological Considerations

Within this project, data were collected weekly by a pharmacist as part of the Consultants' ward rounds. It cannot be excluded that short-stay patients were missed, which could have biased the selection of patients towards more complex

therapies. For this reason and to avoid time-consuming re-documentation of paper notes, the implementation of electronic patient records is to be recommended. For ADR documentation, no standardized questionnaire was used in this survey, which may have underrated some ADR incidences. However, by using this method, the ADR assessment remained as close to clinical routine as possible, and is therefore assumed to reflect the problems and concerns of practical relevance. A challenge, which is inherent in the system, is the real-life data assessment itself. Influencing factors, such as dose adjustment, change of therapy regime, co-morbidity or concomitant drug use, etc., do not follow a precise study plan under these conditions. Thus, the causality assessment and calculation of RRs concerning ADR are only methodical approaches to deal with these data, and the corresponding results should be judged in context and treated with caution. Due to this, not every pointed question of scientific interest can be proven or rejected. Moreover, neither the applied method nor all of the results can be translated to patients treated at primary care level or those being well controlled concerning seizure frequency and tolerability. But by this approach, treatment issues relevant to all patients can be identified and used as guidance for further investigation.

The major advantage of this method lies in the prospectively orientated full assessment of patients. It provides reliable application data, and the rather long-term observation period, the accumulation of medical information and the opportunity of monitoring progress, encourage the evaluation of causal relations between ADRs and suspected drugs.

5 Conclusion

For patients depending on lifelong treatment, optimized therapies adapted to individual needs are of great importance. For this purpose, established expertise in the advantages and disadvantages of each drug is indispensable. It has been shown that during inpatient treatment, valuable data are generated. A systematic assessment and continuous evaluation of these data can constitute a chance for perpetual risk and treatment evaluation under real-life conditions and therefore support individualized therapy management. Accordingly, even if this approach may need more methodological reasoning, it would certainly provide a new quality of drug surveillance.

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Author contributions Annika Hilgers was involved in the conception of this study, collected all relevant data prospectively, developed the internal database, ran the analyses, and drafted the

manuscript. Marion Schaefer was involved in the conception of this study and reviewed and provided critical revisions to the manuscript.

Compliance with Ethical Standards

Ethical approvals For this type of study, ethical approval was not required. Data were collected as part of clinical routine and the use of patients' medical records was in accordance with the Gesundheitsdatenschutzgesetz (GDSD NRW, German law of healthcare data protection). The study was performed in accordance with the ethical standards of the Declaration of Helsinki.

Informed consent For this study, no informed consent was collected from the patients as all information was extracted from routine medical records and used anonymously.

Conflict of interest Annika Hilgers and Marion Schaefer have no conflicts of interest.

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