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ORIGINAL RESEARCH ARTICLE

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

Annika Hilgers[1,2,3] · **Marion Schaefer**[3]

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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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✉ Annika Hilgers
annika.hilgers@evkb.de

[1] Ev. Krankenhaus Bielefeld gGmbH, Bethesdaweg 10, 33617 Bielefeld, Germany

[2] Epilepsiezentrum Bethel, Krankenhaus Mara gGmbH, 33617 Bielefeld, Germany

[3] Charité Universitätsmedizin Berlin, Institut für klinische Pharmakologie, 10115 Berlin, Germany

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 (DDDs), 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 (± 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

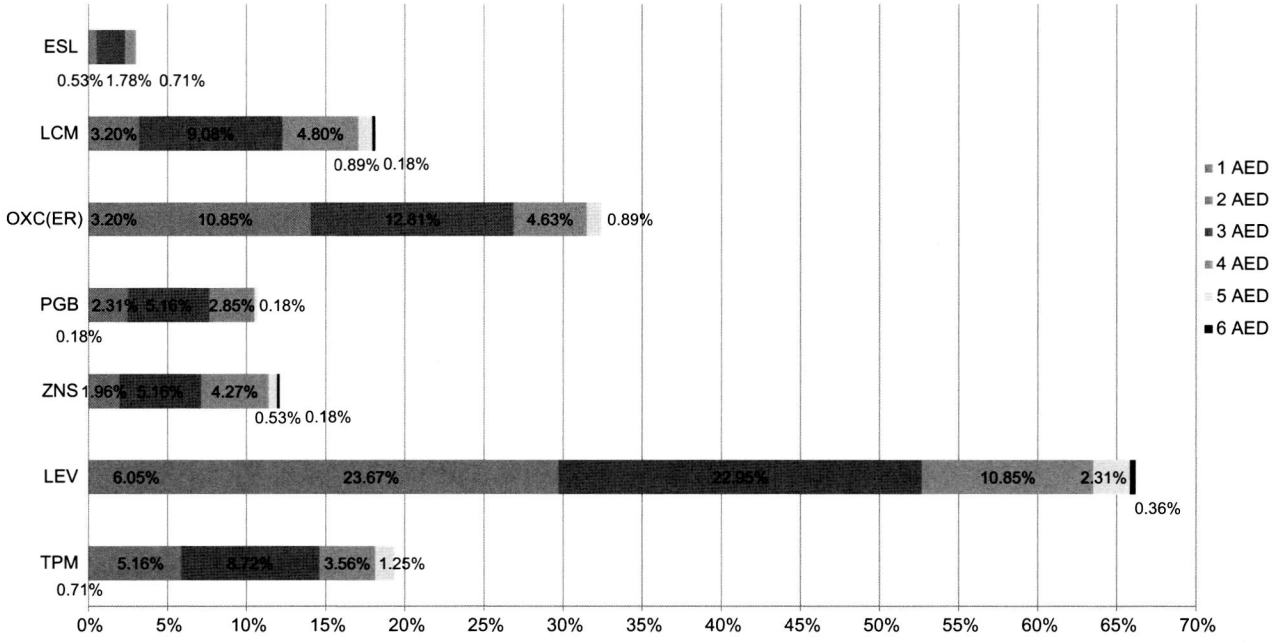

Fig. 1 Percentage of patients treated with the respective AED, stratified by monotherapy and the different kinds of polytherapy (*left to right*). Total percentage of patients taking respective drug either as monotherapy or part of polytherapy: LEV 66.19 %, OXC(ER) 32.38 %, TPM 19.4 %, LCM 18.15 %, ZNS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

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