Outcome of antiepileptic drug treatment of 1282 patients with epilepsy, their pharmacovigilance reports and concomitant medication on CNS in an East-Hungarian adult database

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Abstract

Objective: The aim of this study was to determine the outcome of antiepileptic drug (AED) treatment based on seizure freedom, pharmacovigilance reports and effects of concomitant medication on the central nervous system (CNS) of adult epileptic patients registered in the East-Hungarian Epilepsy Database.

Methods: Prospective cross-sectional database was compiled from outpatient files between 1992 and 2011.

Results: The majority of 1282 treated patients were on monotherapy 894 patients (70%), 286 (22%) on bitherapy and 102 (8%) on polytherapy. Of all treated patients, seizure freedom was achieved by 603 (47%). Among the seizure free patients 464 (77%) were on monotherapy, 115 (19%) on bitherapy and only 24 (4%) on polytherapy. The overall rate of adverse drug reactions (ADRs) was 16.2%. From patients on AED, 279 (22%) took concomitant drugs acting on the CNS. In a logistic regression model, other CNS-related drugs and a number of prescribed antiepileptic drugs had a significant influence on the desired outcome of seizure freedom. On comparing the Proportional Reporting Ratio and 95%CI of older and newer AEDs, no significant superiority of newer AEDs was detected.

Conclusion: Careful drug selection for epileptic patients must be highlighted in order to improve outcome, reduce ADRs and improve patient compliance.

Keywords: epilepsy, database, antiepileptic drug treatment, seizure freedom, adverse drug reaction, pharmacovigilance

1. Introduction

Epilepsy is a complex issue that has an impact on the patients' quality of life [1]. Treating epilepsy means a life-time treatment, so real-life studies are important [2]. Uncontrolled seizures may increase the hospitalization rate even up to 35% [3]. Since financial support of antiepileptic treatment varies between countries it is important to have local databases. For tolerability and long term effectiveness these databases are also useful [4]. Camfield concluded that population-based research with large grouping had a considerable impact on the understanding of epilepsy [5]. Many factors, including comorbidities and their medication, could influence the outcome of antiepileptic treatment [6]. A number of drugs can predict patient adherence [7, 8]. Until new methods are available to predict the outcome, there is only a "reasonable chance" of good outcome, which can be described using data from ongoing treatments [9]. Alternative monotherapy and early add-on therapy showed the same effectiveness and adverse drug reaction (ADR) profile among persistent focal seizure patients in France [10].

ADRs are commonly experienced with antiepileptic drug (AED) treatment. Most of the ADRs are mild and tolerable, but severe effects have also been reported [11]. Due to long duration of treatment, various ADRs are seen, which requires change of medication and monitoring.

The prevalence of ADRs is described using Proportional Reporting Ratio (PRR) and Reported Odds Ratio (ROR) beside basic characteristics [12]. PRR means the portion of spontaneous report for a specified drug with certain ADR divided by the corresponding proportion of other drugs or group of drugs. PRR can be used as a direct measure of the strength of the signal and it can also be used to determine unexpectedness relative to the background of the rest of the database [13, 14]. ROR provides additional information over PRR, which can be important in evaluating the link between ADRs and drugs. Furthermore, ROR allows the estimation of relative risk and removal of biases [12].

Using PRR and ROR, signal of disproportionate reporting (SDR) can show the association between drug-event pair in the database which can be generated from spontaneous adverse drug reaction reporting systems based on European Medicines Agency (EMA) criteria [15].

The purpose of this study was to investigate the basic characteristics of patients registered in our East-Hungarian epilepsy database, the outcome of AED treatment, the effects of concomitant medication on the central nervous system (CNS), and pharmacovigilance report using PRR, ROR and SDR.

2. Methods

2.1 Database

Debrecen Epilepsy Database was created in order to analyse the data of patients through their case histories from out-patient files, covering the period between 1992 and 2011 in a cross-sectional view. In our database we registered all of the adult patients (2152) who were referred to our out-patient or in-patient department by general practitioners or other out-patient clinics (approximately 108 patients/year). Our epilepsy out-patient unit provides care for patients from 16 years of age. The majority of the patients are from Debrecen (approx. 70%) and the remainder are referred from 3-4 counties (700 000 catchment area).
We excluded those who had no seizures at all or their seizures were related to alcohol dependency. Most of the patients with alcohol problems understated or disclaimed alcohol consumption. Due to their poor adherence to instructions and treatment we excluded them from the final analysis. Eventually, 1528 patients with epileptic seizures were included in the database. Patients were coded with epilepsy diagnoses in accordance with the International Classification of Diseases by the World Health Organization [16].
Data were obtained from every patient at the first and subsequent out-patient visits, also from past medical records as well as family members. We collected 60 parameters per patient. Among others, the following data were entered into the database: gender, age at the first visit, age at the onset of epilepsy, family history of epilepsy, risk factors of epilepsy (including febrile convulsions), relevant details of past medical and neurological history such as congenital disorder, type of delivery, miscarriage, causes of symptomatic epilepsy, neurological and psychiatric comorbidities, influence of meteorological factors, classification of present and past seizures, frequency of each seizure type, EEG and imaging findings, past and present antiepileptic drug treatment, further drugs acting on the CNS, ADR and drug interactions, etc. We defined childhood between 0-14 years and adolescence between 15-20 years. Concomitant drugs acting on the CNS were prescribed by a neurologist / epileptologist, psychiatrist or general practitioner. During each visit, we monitored suicidal intent and behaviour and, if required, the Beck Depression Inventory (BDI) was used for measuring the severity of depression. Serum electrolyte levels, liver and kidney functions were evaluated regularly. In addition, therapeutic drug monitoring (TDM) was also required (valproate [VPA], carbamazepine [CBZ], phenytoin [PHT] continuously available, and lamotrigine [LTG] for some patients). In the current study, we focused on the effectiveness of current antiepileptic therapy, further drugs acting on the CNS and pharmacovigilance report.

All the patients with potential drug or alcohol-induced, psychogenic and heart-related seizures were excluded. The patients were classified as suffering from generalized, focal and unknown seizures according to the ILAE definition [17, 18].

The epileptologists chose the best treatment modality for each patient. In most cases the first two AEDs were prescribed as monotherapy. If monotherapy had failed a combination was considered. Doses were built up very carefully in accordance with the summary of product characteristics up to a medium dose range, and were further increased up to the maximally tolerated dose in case seizures occurred repeatedly. When needed, TDM (if available) was performed and assessed to guide dosage changes and, also, to test patient compliance. A patient was considered nonadherent (non-compliant) if he or a relative reported not taking their medication, the patient has changed the prescribed daily dose intentionally or TDM has revealed unmeasurable or very low plasma concentration of AED.

According to ILAE definition seizure freedom meant at least three times the interval of the longest previous interseizure duration (determined from seizures occurring within the past 12 months, or in any 12-month-period, whichever was longer) [19]. We followed up the patients' status for many years (until closing the database), to determine whether their seizures truly came under control. Drug resistant epilepsy was defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (either as monotherapies or in combination) to achieve sustained seizure freedom [19]. The seizure freedom and current therapy were determined at the last follow-up visit.

On the strength of patients' report, adverse drug reactions were recorded in the patients' files after the physician considered their causality. On the basis of the above, our database stores individual case safety reports (ICSRs).

We used the following criteria for generating a signal according to EudraVigilance [15, 20]:

a) When the PRR is displayed with its 95% confidence interval:

- the lower bound of the 95% confidence interval is greater than or equal to one
- the number of individual cases is greater than or equal to three

b) When the PRR is displayed with χ^2 statistic:

- the PRR > 2
- $\chi^2 > 4$
- the number of individual cases is greater than or equal to three.

Ethical approval was obtained from the Regional and Institutional Research Ethics Committee (DEOEC RKEB/IKEB: 2584A-2007).

2.2 Statistics

Statistical analysis was carried out using the SPSS for Windows 19.0 (SPSS Inc. Chicago, USA) and Microsoft Office Excel 2007.

Two-sample T test, and F test were used to analyse our patients' data. Categorical variables were assessed using Pearson χ^2 test and logistic regression.

As per standard pharmacovigilance practices, the values of the PRR and ROR were computed using 2x2 contingency table [13].

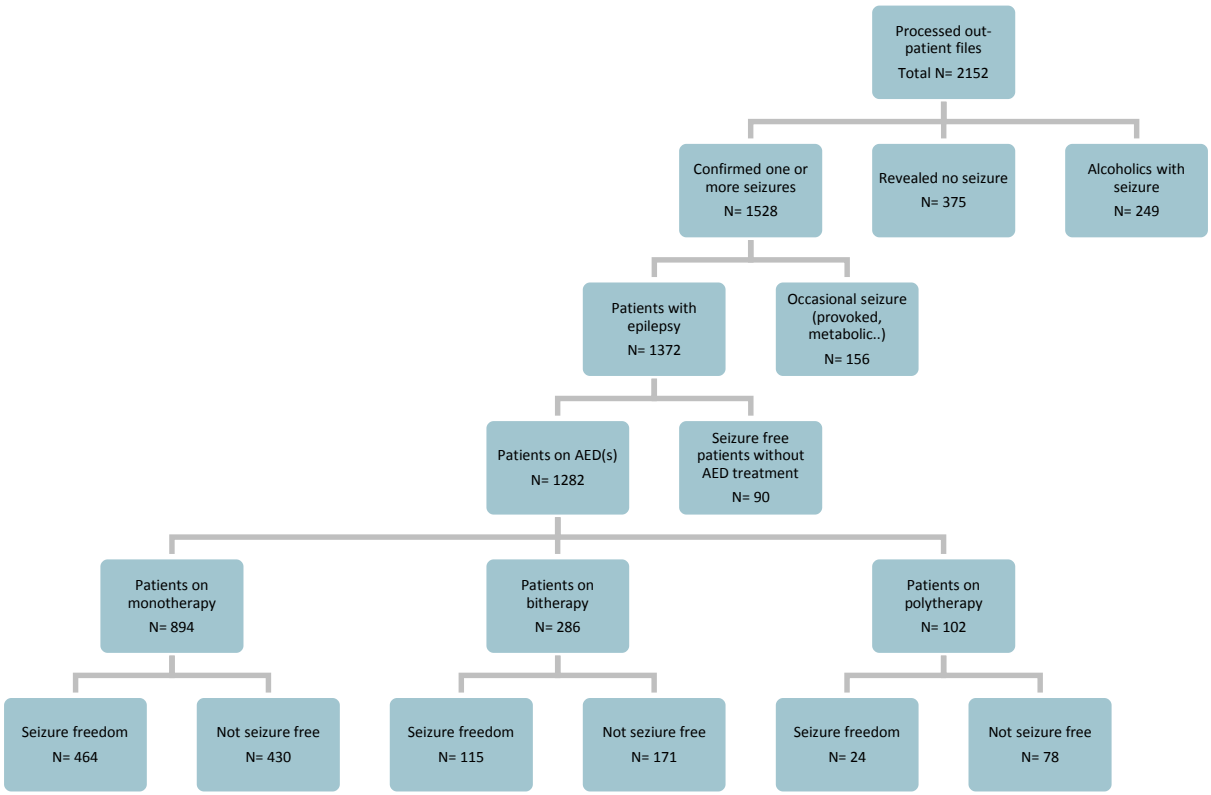
Significant differences were considered if $p<0.05$.

3. Results

3.1 Basic characteristics of patients

We registered 2152 patients in our database (Figure 1). We excluded all the patients who had no epileptic seizures (heart-related, pulmonological and other disorders were detected in 375 patients). Alcohol consumption or withdrawal of alcohol caused seizures in 249 patients.

Figure 1 Flow chart. Investigation and treatment of patients registered in the Epilepsy Database



We registered 1528 patients (760 males and 768 females) with one or more epileptic seizures. Mean age was 48.28 ±18.18 years with no significant difference (male: 49.25±17.9, female: 47.33±18.42 years). Patient age at first seizure showed male dominancy in adulthood. A significantly different sex ratio could be seen in the childhood onset groups (p=0.03; females were in majority in such groups). Approximately 1/5 and 1/6 of patients had their first seizure in childhood and adolescence, respectively. Cumulative incidence of epilepsy by age at the first registration and current age was parallel above 20 years and the number of the registered patients decreased by age after 50 years.

During the study period 106 (7%) patients died due to comorbidities but only three patients' deaths were related to epilepsy; two of them had epileptic status.

Recurring seizures were observed in 1372 (89.8%) patients so, in accordance with the ILEA definition, these patients had epilepsy, and 156 (10.2%) patients had provoked and/or metabolic failure-induced seizures. While 856 (56%) of the patients had generalized seizures, 602 (39.4%) had focal seizures (no significant difference in gender between seizure type *v.* all patients; p= 0.20 and p= 0.27 respectively) and 70 (4.6%) of the patients had unknown seizures. Gender ratios (male/female) were 1.09 in the generalized seizure group and 0.88 in focal seizure group (gender was significantly different, p=0.04).

Family history was positive for epilepsy in 107 (7.8%) out of 1372 patients. Idiopathic epilepsy affected 228 (16.6%) patients whereas symptomatic epilepsy was confirmed in 574 (41.8%) patients (stroke: 185 [32.2%], head injury: 155 [27%], congenital disorders: 76 [13.2%], tumour: 74 [12.9%], CNS infection: 57 [9.9%], other disorders such as cerebral atrophy or arachnoid cyst: 27 [4.7%]). Cryptogenic epilepsy and new onset epilepsy were diagnosed in 570 (41.2%) and 686 (50%) patients, respectively.

3.2 Treatment characteristics

Among the recruited patients, 1282 (93.4%) took AEDs but 90 (6.6%) did not due to 5-10 years of seizure free status (Figure 1).

According to the last follow-up visit 894 (70%) of the patients were on monotherapy, 286 (22%) on bitherapy and 102 (8%) on polytherapy (Table 1). Being on monotherapy, the majority of patients took CBZ, VPA and LTG (449 [50.2%], 197 [22%] and 118 [13.2%], respectively). PHT and phenobarbital (PB) prescriptions amounted to only 11 (1.2%) and 4 (0.4%) respectively. Newer AEDs were taken by 229 patients (25.6%); oxcarbazepine (OXC; 61 patients [6.8%]) and levetiracetam (LEV; 35 patients [3.9%]) were the most commonly prescribed ones in this group.

Table 1 Antiepileptic treatment and its relationship with adverse drug reaction (ADR)

Type of therapy	All patients (N=1282)	Male (N=608)	Female (N=674)	p-value
Monotherapy	894 (69.7%)	427 (33.3%)	467 (36.4%)	0.91
ADR	*147 (16.4%)*	*51 (5.7%)*	*96 (10.7%)*	*0.003**
Bitherapy	286 (22.3%)	137 (10.7%)	149 (11.6%)	0.94
ADR	*53 (18.5%)*	*18 (6.3%)*	*35 (12.2%)*	*0.06*
Polytherapy	102 (8%)	44 (3.4%)	58 (4.6%)	0.46
ADR	*24 (23.5%)*	*9 (8.8%)*	*15 (14.7%)*	*0.65*

*: significance between males and females.
ADR is significantly higher in females than in males using AED in monotherapy (p=0.003).

Among the patients on monotherapy (N=894), 464 patients (52%) took AEDs which had an enzyme-inducing effect on drug metabolizing enzymes (CYPs systems), 197 patients (22%) were prescribed with enzyme inhibiting AEDs, 62 patients (7%) used AEDs with both effects on enzyme systems and in 171 patients (19%) the AED had no effect on liver metabolizing systems.

Bitherapy included 15 AEDs prescribed in 45 different combinations. The most commonly used combinations were CBZ-VPA (66 patients [23.1%]), CBZ-LTG (29 patients [10.1%]), CBZ-LEV (28 patients [9.8%]), VPA-LTG (25 patients [8.7%]), CBZ-clonazepam (CZP; 22 patients [7.7%]), CBZ- gabapentin (GBP; 14 patients [4.9%]), LEV-OXC (13 patients [4.5%]), VPA-LEV (11 patients [3.8%]), LTG-LEV (8 patients [2.8%]) and VPA-CZP (8 patients [2.8%]). Old-old, old-new and new-new AED combinations were prescribed for 118 (41%), 133 (47%) and 35 (12%) patients, respectively. The prevalence of newer AEDs use was 35.5%. As for the number of participants, there was no significant difference between males and females on mono-, bi-, or polytherapy.

The enzyme inhibitor (only VPA) played the same role in mono-, bi-, and polytherapy (197 [22%], 122 [21.3%], and 65 [19.4%], respectively). In both groups on bi- and polytherapy, the second choice of AEDs was for an enzyme inducer and/or inhibitor.

Seizure freedom was achieved in 47% of all treated patients (Table 2). The overall seizure freedom was 693 (50.5%) including those patients (90, 6.6%) who did not take AEDs because of long-term seizure freedom. We calculated seizure freedoms in patients with generalized and partial epilepsy, 396 (52.1%) and 283 (49.8%), respectively. Seizure freedom was 48 (45.5%) among the patients with positive family history of epilepsy. In the subgroup idiopathic, symptomatic, cryptogenic and new onset epilepsy seizure freedom was 125 (55%),

258 (45%), 288 (50.5%) and 340 (49.5%) respectively. Differences were not significant. From them 584 (96.9%) patients were seizure free for more than one year, eight patients were seizure free less than six months (1.3%) and 11 (1.8%) patients were seizure free more than six months but less than one year. Among the seizure free patients 77% of the patients were given monotherapy, 19% received bitherapy and only 4% were on polytherapy. More than half of the patients receiving only one type of AED were seizure free. When taking a combination of three or more AEDs, only 24% of patients were seizure free. The proportion of seizure free patients was nearly the same in monotherapy, bitherapy and polytherapy in both genders. There was no significant difference between genders.

Table 2 Effectiveness of AED treatment using monotherapy, bitherapy and polytherapy, comparing males and females, and seizure freedom

Type of therapy	**Number and percentage (%) of patients taking AED(s)**	**Number and percentage (%) of all seizure free patients**	**Percentage (%) of seizure free patients within each group**	**p_1-value**	**Number and percentage (%) of seizure free males**	**Number and percentage (%) of seizure free females**	**p_2-value**
Monotherapy	894 (69.7)	464 (77)	52	0.60	221 (47.6)	243 (52.4)	0.08
Bitherapy	286 (22.3)	115 (19)	40	0.92	56 (48.7)	59 (51.3)	0.20
Polytherapy	102 (8)	24 (4)	24	0.94	12 (50)	12 (50)	0.50
Total	1282 (100)	603 (100)	47	NA	341 (49.2)	352 (50.8)	NA

p_1: significance between all seizure free patients and all patients taking AED(s).
p_2: significance between seizure free male and female patients.
NA: not applicable

We used logistic regression model in order to analyse what kind of factors influenced seizure freedom, where seizure freedom was the dependent variable and gender, age group, type of seizure, other drugs acting on the CNS, number of AEDs and ADR were the independent variables. In this model, the number of AEDs and other drugs acting on the CNS had a significant impact on seizure freedom (all $p<0.05$). No link was revealed with gender, age group, type of seizure or ADR. Increase in the number of AEDs and the presence of other drugs acting on the CNS reduced the chance of seizure freedom significantly ($p<0.05$). Nonadherence was associated with 12% of patients (154).

3.3 Adverse drug reaction (ADR)

Patients on AED monotherapy exhibited fewer ADRs than the patients on bi- or polytherapy. The differences between males and females were significant in the monotherapy group (p=0.003) (Table 1). There was an unfavourable but not significant trend in the occurrence of ADRs among female patients on bitherapy.

ADRs (incidence: 16.2%) were reported by 247 patients (male: 89 [36%], female: 158 [64%]). The vast majority (195; 80%) of the patients had one ADR and while 52 (20%) suffered two or more ADRs. The majority of patients with ADR were female. The differences were significant (1 ADR p= 0.008; 2 ADRs p= 0.009). Among those having ADRs, the number of seizure free patients and those with recurrent seizures were not significantly different.

Altogether 326 different ADRs were reported due to AED by our 247 patients. Most of them were women (217 [66.6%] reports from women, and 109 [33.4%] from men). The most common AEDs causing ADR were CBZ (42%; male *vs.* female, 37.2% *vs.* 62.8%), VPA (19.94%; male *vs.* female, 29.2% *vs.* 70.8%) and LTG (13.5%; male *vs.* female, 22.7% *vs.* 77.3%). Most commonly, CBZ caused toxicoderma, hepatotoxicity (an increase of over 2 N [upper limit of the normal range] in one or combination of the following: ALT, AST, gamma-GT and total bilirubin), dizziness, sleepiness, mild depression (with or without anxiety) and vomiting (or nausea). Similarly, VPA induced ADRs including weight gain, alopecia, tremor and hepatotoxicity and, infrequently, mild depression or anxiety. LTG-induced common ADRs were: toxicoderma and, rarely, mild depression or anxiety. OXC caused toxicoderma and dizziness. All other AEDs caused fewer than 5 symptoms. The occurrence of (usually mild) depression was 7% of all recorded ADRs. There was no suicidal attitude, behaviour or attack reported.

A pharmacovigilance report of the most commonly used AEDs can be found in Tables 3 and 4. All the patients having ever taken a certain AED according to out-patient files were included in the report. Surprisingly, newer AEDs (except LEV) showed higher values of PRR and ROR.

Table 3 Number of patient events who have ever taken a certain drug characterised by PRR and ROR

AED	Number of patients	PRR	ROR

CBZ	1042	1.28	1.32
CLB	43	1.03	1.03
CLZ	135	0.25	0.23
GPB	87	1.12	1.14
LEV	173	0.75	0.73
LTG	329	1.21	1.24
OXC	156	1.02	1.02
PHT	123	0.56	0.53
PRM	52	0.85	0.83
TPM	40	1.56	1.68
VPA	547	1.06	1.07
ZNS	19	2.35	2.83

Comparing PRR and 95% CI of old (PRR: 0.86; 95% CI [0.67-1.05], χ^2= 2.42, p=0.12) and new (PRR: 1.16; 95% CI [0.97-1.35], χ^2= 2.42, p=0.12) generation AEDs, we found no significant superiority of newer AEDs. Table 4 contains the signal detection of Adverse Drug Reactions in accordance with the EMA criteria.

Table 4 Signal detection of ADRs according to the EMA fulfilled criteria

AED and ADR	PRR	Lower 95% CI	χ^2	p-value
CBZ hepatotoxicity	4.63	3.87	19.57	<0.0001
CBZ itching	10.22	8.15	7.55	0.006
VPA tremor	4.06	3.0	7.7	0.006
VPA weight gain	16.59	15.51	47.62	<0.0001
VPA alopecia	6.1	5.14	17.43	<0.0001
OXC dizziness	3.03	2.16	6.16	0.01
GBP dizziness	3.73	2.81	7.52	0.006
TPM somnolence	3.84	2.81	6.17	0.01

3.4 Concomitant drugs acting on the CNS

As Table 5 shows, 279 (22%) patients took concomitant drug(s) acting on the CNS. Although no gender-based difference was established within the "monotherapy" group concerning patients with or without seizures, significant differences were confirmed regarding either one (p= 0.03) or ≥2 (p= 0.03) certain other medicines acting on the CNS. Comparing the number of patients with or without CNS co-medication the difference was even more pronounced (p=0.003).

There was a significant difference between all seizure free and all seizure-affected patients on AEDs taking two or more drugs acting on the CNS (p= 0.02).

Analysing and comparing all the patients who took at least one type of medicine acting on the CNS with the ones that did not, we found the difference was significant ($p=0.009$).
Only 22 (8%) of the 279 patients were on psychoactive drugs which could alter the effects of AEDs, CBZ, LTG, PHT and VPA being the AEDs in the focus of attention.

Table 5 Antiepileptic therapy with or without concomitant drug therapy acting on the CNS

Type of therapy and number of patients	No. of other CNS drugs	All patients	All male / All female	Seizure free	Male / Female	Not seizure free	Male / Female
Monotherapy (894)	***0***	726 (81.2%)	348 (47.9%) / 378 (52.1%)	394 (54.3%)	185 (47%) / 209 (53%)	332 (45.7%)	163 (49.1%) / 169 (50.9%)
	1	114 (12.8%)	56 (49.1%) / 58 (50.9%)	49 (43%)	26 (53.1%) / 23 (46.9%)	65 (57%)	30 (46.2%) / 35 (53.8%)
	≥2	54 (6%)	23 (42.6%) / 31 (57.4%)	21 (38.9%)	10 (47.6%) / 11 (52.4%)	33 (61.1%)	13 (39.4%) / 20 (60.6%)
Bitherapy (286)	***0***	209 (73.1%)	105 (50.2%) / 104 (49.8%)	81 (36%)	42 (52.4%) / 39 (47.6%)	128 (64%)	63 (47.3%) / 65 (52.7%)
	1	54 (18.9%)	21 (38.9%) / 33 (61.1%)	26 (48.1%)	10 (38.5%) / 16 (61.5%)	28 (51.9%)	11 (39.3%) / 17 (60.7%)
	≥2	23 (8%)	11 (47.8%) / 12 (52.2%)	8 (34.8%)	4 (50%) / 4 (50%)	15 (65.2%)	7 (46.7%) / 8 (53.3%)
Polytherapy (102)	***0***	68 (66.7%)	31 (45.6%) / 37 (54.4%)	16 (23.5%)	7 (43.8%) / 9 (56.2%)	52 (76.5%)	24 (46.2%) / 28 (53.8%)
	1	26 (25.5%)	11 (42.3%) / 15 (57.7%)	7 (26.9%)	5 (71.4%) / 2 (28.6%)	19 (73.1%)	6 (31.6%) / 13 (68.4%)
	≥2	8 (7.8%)	2 (25%) / 6 (75%)	1 (12.5%)	0 (0%) / 1 (100%)	7 (87.5%)	2 (28.6%) / 5 (71.4%)
N=1282	0	1003 (78%)		**603**		**679**	
	≥1	279 (22%)					

4. Discussion

4.1 Basic characteristics of patients

Gender distribution was nearly equal if all patient groups were examined but, in the childhood onset groups, there was a remarkable difference by gender, women being in majority. The mean duration from the first epileptic seizure was 9.54 years despite the fact that 686 patients were diagnosed with new onset epilepsy during the 20 years' study period. A probable explanation might be that our out-patient unit provides care only for adults, but approximately 1/5 and 1/6 of patients had their first seizure in childhood or adolescence, respectively.
There was not a second peak in the incidence of new onset seizures over 50 years of age, although, in adults, stroke was the most common cause of symptomatic epilepsy, which is quite common in this age group.
In our database, the ratio of generalised epilepsy was higher than in the adult epileptic population with newly diagnosed epilepsy, but we registered and attended patients after 16 years of age.
Stroke and head injury followed by congenital disorders were the most common causes of symptomatic epilepsy. The great majority of these patients had focal seizures which evolved into bilateral convulsive seizures.
Mortality rate was 6.9% primarily because of comorbidities.

4.2 Treatment characteristics

The choice of AEDs must be matched to the patient's seizure type(s) and / or epilepsy syndrome, age, gender, childbearing potential, weight, psychiatric and other comorbidities, concomitant medications and lifestyle [21, 22]. In all cases, the above were taken into consideration, nevertheless sometimes the cost / price of drugs was also of concern.
We found that most of the patients were on older AEDs such as CBZ, VPA and LTG; OXC and LEV belong to the family of newer AEDs. The drugs CBZ, VPA, LTG were prescribed either in generalized or focal seizures whereas OXC and LEV were administered only in focal seizures and in combination.
In contrast with certain data in the literature, PHT and PB prescriptions were quite uncommon [23]. Newer AEDs (taken by 25.6% of patients) were indicated frequently in both monotherapy and bitherapy.
One probable explanation for these differences in the literature might be that our epilepsy out-patient unit provides care for patients from the age of 16 and our female patients were

potentially in adolescent or childbearing age which was also taken into consideration. The severe side effects of VPA, PHT and PB have been widely known. Another explanation for differences in the literature and our findings might be that some patients have comorbidities at the onset of epilepsy and there are a number of newly evolving disorders requiring a switch to a non–enzyme-inducing AED (e.g. cancer therapy, osteoporosis, hyperlipidemia, sexual dysfunction and infertility). In all these cases the best possible AED therapy was chosen considering pharmacokinetics and the ADR profile.

A recent study reported 68% overall seizure freedom in generalized and partial seizure which was higher than our finding (50.5%) [24]. We did not find significant difference between patient groups with generalized and partial epilepsy (p=0.41).

More than 30% of patients were given two or more AEDs. In our database, 24% of these patients were seizure free, which is slightly higher than the figure (20.5%) in a study by Stephen LJ et al [25].

In our database, VPA, an enzyme inhibitor, played the same role in mono-, bi-, and polytherapy. Almost one in five patients took an AED without enzymatic effect in the monotherapy group. In both of the bi-, and polytherapy groups, the second choice of AEDs was for enzyme inducers or inhibitors. Nowadays, in routine clinical practice first line AEDs should be used depending on the type of epilepsy but prior to prescribing of enzyme inducer AED, physicians should always consider interactions with co-medications (e.g. antidepressants, antipsychotics, cytostatics, antiretrovirals, statins, anticoagulants, oral contraceptives, immunosuppressant, analgesics, antihypertensives, etc.) [21].

Our data may confirm Brodie's opinion that physicians should consider starting treatment with, or even switching patients to non–enzyme-inducing AEDs in order to avoid complications, particularly if the epilepsy is not fully controlled [26].

In our database, non-adherence to treatment in patients with epilepsy was better (12%) than in the report by Jones et al. in a cross-sectional study (59%) but we did not use special questionnaire scores comparing the patients with well and poorly controlled epilepsy [8].

4.3 Adverse drug reaction (ADR) and pharmacovigilance evaluation of AEDs

Chronic use of AEDs may be associated with several adverse events with systemic effect and affecting the CNS. Furthermore, enzyme-inducing AEDs may contribute to the development of comorbidities. Modern AEDs that lack this property have similar efficacy in common epilepsies [21]. Quality of life and adherence to treatment depend on seizure control and the presence of ADRs [8].

The incidence of self-reported ADRs was 16.2%, approximately half as much (36.5%) as the incidence rate in an Italian study; these patients had drug-refractory epilepsy and only less than a quarter of them received monotherapy [11]. We found that women reported ADRs more frequently than men did. It was especially unexpected among patients on monotherapy; the difference was significant. Female dominance (64%) concerning ADR rates could be attributed to genetic polymorphism [27].

In the database, we found that most of the patients were on older AEDs such as CBZ, VPA and PHT, and on LTG, LEV and OXC belong to newer AEDs. Although newer AEDs were considered more beneficial owing to the fewer ADRs they caused; except for LEV, our data suggested the same profile as that of the older ones.

The results of PRR analysis of older versus newer AEDs with ADR were unexpected, they revealed no significant superiority of newer AEDs. The underlying cause of overreported ADRs regarding newer AEDs may have been associated with greater awareness to the newly marketed drugs and these drugs were introduced as add-on therapy. If a newly introduced drug was prescribed, patients' education was much more thorough and the new drug was strictly monitored.

Using PRR and χ^2, SDR showed the association between drug-event pairs in the database. No unknown or new ADR was detected in our database. Only eight ADRs fulfilled the EMA criteria to report signal detection. Three out of eight were newer AEDs. Due to the relatively low number of cases, only the most common symptoms met the definition of SDR.

4.4 Concomitant drugs acting on the CNS

Psychiatric comorbidities are not infrequent in patients with epilepsy [28, 29]. Use of antidepressant and antipsychotic drugs is common in patients receiving enzyme-inducing AEDs [30]. We analysed and compared all the patients who took at least one medicine acting on the CNS with those who did not; there was a significant difference between the two groups.

In our logistic regression model, we found that the number of AEDs and other drugs acting on the CNS affected seizure freedom and had a significant impact. Increase in the number of AEDs and the presence of other drugs acting on the CNS reduced the chance of seizure freedom significantly.

The explanation of these results may be that these interactions are very complex and combine pharmacokinetic and pharmacodynamic processes [21, 31, 32, 33]. Although variations in the extent of induction may differ between CYPs, there must be common cellular signalling

mechanisms, nuclear receptors (glucocorticoid and oestrogen) may also participate in the induction of certain drugs; however, the transcription factors appear to be broadly involved in enzyme induction [34, 35].

AED doses were built up very carefully, probably that is why our patients had relatively fewer ADRs and interactions between AED(s) and concomitant drugs acting on the CNS.

In clinical studies, researchers have demonstrated that the magnitude of induction of various CYP isoenzymes appears to be at least partially dependent upon the dose of the enzyme-inducing drug [36].

We are aware, that our study has several limitations. First, our study is an observational study and not a randomized, controlled trial, therefore selection bias could have affected the results. Second, treatment options and definitions changed a lot during this 20-year-time period. Nevertheless, the advantage is prospective data collection and detailed information on all subjects can be regarded as an important advance in this field. Further strength of our study may be the real-life data sets leading to a better understanding of real-life clinical settings and the outcome of routine epilepsy treatment.

5. Conclusion

Based on our findings, we can conclude that careful drug selection for epileptic patients must be highlighted in order to improve the outcome of treatment, reduce ADRs and improve patient compliance, especially in female patients. The number of AEDs and other CNS related drugs can influence seizure freedom.

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Conflict of interest statement

None of the authors has any conflict of interest related to this study. 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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