Short thesis for the degree of doctor of philosophy (PhD)

Investigation of antiepileptic treatment, adverse drug reactions, co-medication of other medicines acting on central nervous system and their relation to seizure freedom

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1. Introduction

Epilepsy is a complex issue that has an impact on the patients' quality of life. Treating epilepsy means a life-time treatment, so real-life studies are important. Camfield concluded that population-based research with large grouping had a considerable impact on the understanding of epilepsy. Many factors, including comorbidities and their medication, could influence the outcome of antiepileptic treatment. A number of drugs can predict patient adherence. ADRs are commonly experienced with antiepileptic drug (AED) treatment. Most of the ADRs are mild and tolerable, but severe effects have also been reported. 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. 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. 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. 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.

In 1996, the World Health Organization (WHO) launched the methodology defining the daily dose (DDD), a widely used tool in drug utilization studies. Although DDD is an average maintenance dose in adults by definition and a unit used in drug

consumption, notwithstanding, contradictions with prescribed daily dose (PDD) can be observed.

Studies have confirmed that combination therapy is used in the minority of cases; notably, the proportion of combination therapy reported in four studies by Brodie et al., Kořístková et al. and Rochat et al. fell in the range of 15-38.2%. Accordingly, there is another contradiction between clinical practice and DDDs of AEDs assigned for combination therapy in the case of AEDs by WHO.

DDD is used not only as a simple number to compare different periods and/or regions, it is used, e.g., for the estimation of ever-users' prevalence in the equation of population attributable risk (PAR). Further importance of the DDD has been published by Kwan et al. and Brodie et al. who concluded that effective seizure control could be achieved at 50% or 75% of DDD and could be applied to the definition of drug-resistant epilepsy.

2. Aim of the study

East-Hungarian 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.

Our aims were the following:

1. It was our intention to find out what factors might influence PDD.
2. What kind of correlation is between PDD and DDD in case of seizure freedom?
3. We wanted to test the applicability of 75% cut-off of DDD to achieve seizure freedom.

4. Is there any effect of the concomitant medication acting on the central nervous system (CNS) on the outcome of epilepsy treatment?
5. Is the ADR of newer type AEDs favourable than the older type ones?

3. Methods

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. Our epilepsy out-patient unit provides care for patients from 16 years of age.

We excluded those who had no seizures at all or their seizures were related to alcohol dependency.

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.

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, data were entered into the database as follows:

- 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.

Concomitant drugs acting on the CNS were prescribed by a neurologist / epileptologist, psychiatrist or general practitioner.

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.

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.

The data of 1282 patients who had taken AEDs were retrieved from the database and analysed on the basis of gender, age, age at seizure onset, seizure type (generalized and focal), seizure freedom status as an outcome of treatment, and PDD. PDD was calculated on the basis of the proposed dosage regimen of the last follow-up visit. For each patient, DDD% was computed as the percentage of PDD divided by DDD and mean DDD% was calculated in order to compare different groups. The 75% cut-off have been chosen based on Brodie et al.'s suggestion.

The relationship of PDD to DDD was analysed in 894, 286 and 102 epileptic patients on monotherapy, bitherapy and

polytherapy, respectively. The most commonly used AEDs and their role in the outcome of these groups were compared.

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 (SPC) up to a medium dose range, and were further increased up to the maximally tolerated dose in case seizures occurred repeatedly.

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). We followed up the patients' status for many years (until closing the database), to determine whether their seizures truly came under control.

The seizure freedom and current therapy were determined at the last follow-up visit.

On the basis of the above, our database stores individual case safety reports (ICSRs).

We used the criteria of EMA for generating a signal.

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.

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

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.

Another logistic regression model was created in order to analyse what factors characterised 75% DDD cut-off; the dependent variable was equal to or less than 75% of DDD and more than 75% of DDD. The independent variables included gender, age group, age at the onset of seizure, type of seizure, seizure freedom, other CNS related drugs and number of AEDs.

Significant differences were considered if $p<0.05$.

4. Results

4.1. Basic characteristics of patients

Mean age of all registered patients was 48.28 ±18.18 years with no significant difference (male: 49.25±17.9, female: 47.33±18.42 years).

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.

Eight hundred and fifty-six (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.

4.2. 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.

The mean number of AEDs per patient was 1.4.

According to the last follow-up visit 894 (70%) of the patients were on monotherapy, 286 (22%) on bitherapy and 102 (8%) on polytherapy. 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%); (LTG; 118 [13.2%], OXC; 61 patients [6.8%]) and LEV; 35 patients [3.9%]) were the most commonly prescribed ones in this group.

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.

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. 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. Among the seizure free patients 77% of the patients were given monotherapy, 19% received bitherapy and only 4% were on polytherapy.

In the logistic regression model, the number of AEDs and other drugs acting on the CNS had a significant impact on seizure freedom.

Non-adherence was associated with 154 (12%) patients.

4.3. Correlation between prescribed daily dose, seizure freedom and defined daily dose

Comparing the number of prescribed old and new AEDs, a significant increase was observed in the proportion of newer AEDs between the mono- versus bitherapy ($p<0.0001$) and bi- versus polytherapy groups ($p=0.0003$).

The mean DDD% of all prescribed AEDs increased steadily from monotherapy, through bitherapy towards polytherapy (58.54%±24.04, 74.38%±42.89, 93.68%±54.82, respectively).

CBZ and OXC showed similar patterns but CBZ was prescribed in less than 75% of DDD, while OXC was prescribed in all scenarios in more than 75% of DDD.

In the case of VPA, mono- and bitherapy PDDs remained below 75% of DDD but in the group on polytherapy a higher dose did not increase the likelihood of seizure freedom.

Monotherapy

Mean PDDs mostly fell in the range between 50-75% of DDDs.

With the exception of OXC and GBP, the mean DDD% was higher in the group of not seizure free patients. Except for OXC, the vast majority of seizure free patients had taken AED doses in the range of ≤75% of DDDs in monotherapy. Not seizure free patients were treated with higher doses of LTG, and significant differences in means could be seen between seizure free and not seizure free cohorts (p=0.02).

The mean DDD percentage was equal to or less than 75% in most AEDs used in monotherapy in the group of seizure free patients. A significant difference was revealed only among LTG users (p=0.032) in favour of ≤75% of DDD and seizure free patient's group. The mean DDD% exceeded 75% in four cases as follows: clobazam (CLB), OXC, topiramate (TPM) and lacosamide (LCM), 100%, 86.82%, 133.3% and 133.3%, respectively. No preferable AED was confirmed based on general effectiveness (p=0.65) in relation to desired seizure free status.

Bitherapy

The mean PDDs of CBZ, VPA, PRM, CLZ, GBP and VGB were within 50-75% of DDD.

Significantly higher mean DDD% was observed between seizure free and not seizure free cohorts taking LEV; p=0.023). Slightly higher mean DDD% was revealed among seizure free patients on CLB and PRM.

The majority of patients belonged to the group of equal to or less than 75% of DDD (except CLB, OXC, PHT).

Polytherapy

Only PDDs of CBZ, PHT, PRM and CLZ remained under 75% of DDD.

The mean DDD% was higher among not seizure free patients but no significance was confirmed (except CBZ p=0.032 and GBP p=0.045; not seizure free patients taking LEV and TPM had lower values but the differences were not significant).

In polytherapy, the use of more than 75% of DDDs was recorded in the seizure free and not seizure free groups receiving LEV, LTG, OXC and TPM. The mean DDD% was higher among TPM, PRM and LEV users in the seizure free group.

Among the older types of AEDs, both CBZ and VPA had to be given in a significantly higher mean dose in bitherapy than in monotherapy in the seizure free group and in polytherapy in the not seizure free group. Among the newer types, only LEV and LTG had a significantly higher DDD% series pattern between mono-, bi-, and polytherapy in both groups (except LEV in polytherapy in the not seizure free) group.

The mean DDD% of CBZ and GBP in polytherapy was significantly higher in not seizure free patients than in the seizure free group (p=0.032 and 0.045, respectively).

Logistic regression analysis

In this model, gender, age group, type of seizure, seizure freedom and number of AEDs all had a significant impact (all $p<0.05$).

In the logistic regression model, gender served as a significant predictor (p=0.001; Exp(B) [exponentiation of the B coefficient]= 1.456, 95% CI [Confidence Interval]: 1.169-1.813) if it was equal to or less than 75% of DDD among men.

Current age showed significant difference in the model of ≥75% of DDD in the over 65-year-old group (p=0.022; Exp(B)= 1.449, 95% CI: 1.055-1.989).

The odds were higher for focal seizures in more than 75% of DDD group (p=0.002; Exp(B)= 0707, 95% CI: 0.568-0.881) and equal to or less than 75% of DDD in generalized seizure.

There was no higher chance for seizure freedom if more than 75% of DDD was prescribed (p= 0.027, Exp(B)= 0.773, 95% CI: 0.616-0.971).

As a result of increasing the number of AEDs, a higher portion of more than 75% of DDD could be achieved in the logistic regression model.

4.4. Concomitant drugs acting on the CNS

Two hundred and seventy-nine (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.

4.5. 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). There was an unfavourable but not significant trend in the occurrence of ADRs among female patients on bitherapy.

Of 1528 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 423 ADRs were reported due to 326 AEDs by our 247 patients. Most of them were women (217, 66.6%) reports from women and 109 (33.3%) from men.

In the pharmacovigilance report, 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.

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 in accordance with the EMA criteria.

5. Discussion

5.1. Basic characteristics of patients

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 with idiopathic generalised epilepsy too 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.

5.2. Treatment characteristics

In contrast with certain data in the literature, PHT and PB prescriptions were quite uncommon. 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).

A recent study reported 68% overall seizure freedom in generalized and partial seizure which was higher than our finding (50.5%). 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, 35.8% of these patients were seizure free, which is higher than the figure (20.5%) in a study by Stephen LJ et al.

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.).

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.

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.

5.3. Correlation between prescribed daily dose, seizure freedom and defined daily dose

The treatment of epileptic patients is complex. Of course, there are conditions (drug interactions, individual differences in drug metabolism, age, comorbidities, etc.) that emphasise the importance of individual treatment in finding the proper dosage of AED. However, evidence including DDD, clinical trials or TDM is important when choosing the best AED treatment for the patient.

In our study, a new, clinically important, well-defined and feasible approach was tried in order to determine the correlation between PDD and PDD/DDD ratios based on seizure freedom as an outcome of AED treatment. One of our goals was to see whether PDD/DDD could play a role in seizure freedom as an outcome measure in epilepsy; no significant unfavourable impact of the lower ratio of PDD/DDD on the outcome of achieving seizure freedom could be confirmed.

According to our data and similar to publications by others, AEDs – including more newer type ones – are prescribed in monotherapy for more and more patients, but while DDDs of AEDs refer to combination therapy. Therefore, references of monotherapy DDD values are needed for appropriate calculation. The more precisely DDD is quantified the more accurate

calculation of other derived values (e.g. DDD/1000 inhabitants/day, prevalence of drug use, population attributable risk) it would provide, which could also play an important role in decision-making in health care.

A significant increase was observed in the proportion of newer AEDs in our database. Probably these data were obtained with due consideration to the different modes of action of AEDs and their favourable ADRs in bitherapy and polytherapy.

In our outpatient setting, the mean PDDs of AEDs were inconsistent with the DDD. Previous investigations were of the same opinion.

The mean DDD% was equal to or less than 75% for the most commonly prescribed AEDs used in monotherapy in the seizure free group. In contrast with our findings, Hsieh and Huang did not reveal more than 100% of DDD. One of the explanations might be that older AEDs were prescribed more circumspectly due to their well-known ADRs. At the same time, the ADR profiles of new AEDs were considered more beneficial. In case of two newer types of AEDs (LTG and LEV) a significant rise in doses between mono-, bi-, and polytherapy was detected, by other AEDs a wide variety of mean DDD% supposes individual treatment regimen. Still CBZ and VPA are widely prescribed in the clinical practice due to reliable effectiveness and their broad-spectrum. These drugs can be used in low and moderate doses, too.

Our findings suggested that doses equal to or less than 75% of DDD in monotherapy were effective in seizure control and the same quantities were confirmed in bi-, and polytherapy. However, a higher DDD% did not guarantee seizure freedom which emphasises the importance of individual therapy.

It must be remarked that despite the low case numbers of some AEDs (e.g. CLB, CZP, PRM, STM, LCM and TPM) which

were statistically unfit for analysis the majority of the patients on these agents were seizure free. These findings highlighted the importance of carefully choosing drugs carefully, i.e. tailored to the individual e.g. in the treatment of special epileptic syndromes.

Prescribing newer AEDs in bitherapy drug combinations has become an established practice now. This research has revealed the spread of newer type AEDs in epilepsy treatment but they are used not only in combinations, but also in monotherapy among patients on AEDs. The findings of this study suggest that individual therapy in epilepsy must be emphasised but 75% of DDD may also be used as a measure in case of seizure freedom. New-new combinations were given to 38 (12.2%) patients on bitherapy and 133 (46.5%) patients took old-new combinations. In choosing the second and third AEDs it may have played an important role whether or not the specific AED had an enzyme-inducing or enzyme-inhibiting effect on the liver's enzyme system.

A statistically significant, higher DDD% was confirmed between seizure free and not seizure free groups only when LEV was administered.

With logistic regression analysis, gender, age, type of epilepsy and the number of AEDs were found to have had a significant impact on the value of 75% DDD. These were the factors what influenced PDD. These might be limiting factors when making conclusions in studies using DDD.

The present study confirmed that the DDD of prescribed AEDs was equal to or less than 75% of DDD instead of being over 75% among elderly patients. It was in accordance with well-known pharmacokinetic and pharmacodynamic changes in older ages and due to comorbidities and co-medications.

It must be mentioned that, similarly to Kwan et al. and Brodie et al., our findings also emphasise individual therapy and the importance of 75% of DDD.

5.4. Concomitant drugs acting on the CNS

Psychiatric comorbidities are not infrequent in patients with epilepsy. Use of antidepressant and antipsychotic drugs is common in patients receiving enzyme-inducing AEDs. 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. 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.

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.

5.5. 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. Quality of life and adherence to treatment depend on seizure control and the presence of ADRs.

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. 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.

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.

New establishments

1. Using logistic regression model, gender, age, type of epilepsy and number of AED had a significant impact on PDD.
2. The mean PDDs of AEDs were inconsistent with the DDD. No significant inferiority of the lower ratio of PDD/DDD in the outcome of achieving seizure freedom has been confirmed and a higher DDD% did not guarantee seizure freedom.
3. The findings of this study suggest that 75% of DDD may be used as a measure of seizure freedom, but individual therapy in epilepsy must be emphasised.
4. Concomitant drug acting on the CNS influenced seizure freedom unfavourably.
5. The results of PRR analysis of older versus newer AEDs with ADR were unexpected; they revealed no significant superiority of newer AEDs.

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Candidate: László Horváth
Neptun ID: DOFPFA
Doctoral School: Doctoral School of Clinical Medicine

List of publications related to the dissertation

1. **Horváth, L.**, Fekete, K., Márton, S., Fekete, I.: Correlation between prescribed daily dose, seizure freedom and defined daily dose in antiepileptic drug treatment.
   Int. J. Clin. Pharm. 37, 459-467, 2017.
   DOI: http://dx.doi.org/10.1007/s11096-017-0447-1
   IF: 1.339 (2015)
2. **Horváth, L.**, Fekete, K., Márton, S., Fekete, I.: 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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Total IF of journals (all publications): 4,243
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