International Journal of Risk & Safety in Medicine 24 (2012) 179–185
DOI 10.3233/JRS-2012-0565
IOS Press


# Pharmacoepidemiology of antiepileptic drugs in children: Comparative analysis of efficacy and safety

Rimma G. Gamirova[a,b], Rosa M. Shaimardanova[a] and Lilia E. Ziganshina[b,*]
[a]*Kazan Children's Municipal Hospital, Kazan, Republic of Tatarstan, Russian Federation*
[b]*Department of Basic and Clinical Pharmacology, Kazan Federal University, Kazan, Republic of Tatarstan, Russian Federation*



**Abstract.** Pharmacoepidemiology analysis of efficacy and safety of antiepileptics was carried out in children (3 months–18 years old) registered with municipal children's epilepsy services: 548 children in 2005, 718 – In 2007 and 32 – In 2011. We used remission lasting for 1 year or longer, and 3 years or longer as primary effectiveness outcomes, and total number of people with adverse effects as a safety outcome. We found no advantages of newer antiepileptics over the older ones in terms of either efficacy or safety. Long-term follow up (more than 3 years) showed higher treatment response rate in patients with childhood versus juvenile absence epilepsy.

Keywords: Pharmacoepidemiology of antiepileptics, efficacy, safety

## 1. Background

Current situation with drug development, advances in pharmacology and healthcare require rational use of drugs and financial resources [1]. Therefore rational antiepileptic therapy should result in fair balance between seizure control and severity of adverse drug reactions for every patient [2]. The realistic, pragmatic understanding of the true clinical efficacy and safety of therapy with anti-epileptic drugs as opposed to ideal indexes derived from clinical trials, which in the vast majority are short-term observations, could be obtained with the help of pharmacoepidemiology methods [3].

The objective of the study was to compare the efficacy and safety of various antiepileptic drugs (AED) used in the treatment of childhood and juvenile epilepsy.

## 2. Materials and methods

The research was carried out at the Epileptology center of the city of Kazan. We analyzed 548 patient cards (248 girls and 300 boys) in 2005 and 718 patient cards (316 girls and 402 boys) in 2007 (Table 1)

*Address for correspondence: Lilia E. Ziganshina, Department of Basic and Clinical Pharmacology, Kazan Federal University, Kazan, Republic of Tatarstan, Russian Federation. E-mail: lezign@gmail.com.

Table 1
Patients' characteristics involved in the study in 2005 and 2007

| | | 2005 | 2007 |
|---|---|---|---|
| Total number, *N* | | 548 | 718 |
| | Boys | 300 | 402 |
| | Girls | 248 | 316 |
| Mean age, | Boys | $10.0 \pm 5.1$ | $9.4 \pm 5.0$ |
| Years, M ± m | Girls | $10.4 \pm 5.0$ | $9.9 \pm 4.8$ |



and carried out a separate analysis of 32 patients with childhood and juvenile absence epilepsy followed during 2007–2011. We used remission lasting for one year or longer, and remission lasting for three years or longer as outcome measures of efficacy of anti-epileptic drug treatment. We used total number of people with adverse effects as a safety outcome measure.

Patients with Childhood (8 boys and 12 girls, mean age – $11 \pm 0.4$ years) and Juvenile (3 males and 9 females, mean age – $16 \pm 0.7$ years) absence epilepsy (CAE and JAE) were followed for more than 10 years in outpatient epilepsy clinic in 2001–2011. We used remission lasting for 3 years or longer as an outcome measure. For all outcome measures we calculated Risk Ratio (with Review Manager 5.2).

The number of children and adolescents who were registered with the Centre in 2007 changed partially due to three reasons: 1 – withdrawal of some of them from the registry on achievement of remission and cancellation of AED treatment, 2 – move into the "adult" group with time, and 3 – enrollment of patients with newly diagnosed epilepsy. The age of children varied from 2 months to 18 years. Each patient case was manually filled on the specially designed individual registration form (electronic and hard copy), which covered all information on the patient case, available from the official medical chart (Form 112/y "Istoriya razvitiya rebenka", approved by the Order of the Ministry of Health of the Soviet Union on 4th October 1980, No 1030).

In all included cases the diagnosis was formulated in accordance with ICD-10 and the International classification of epilepsy, epileptic syndromes and similar disorders (New Delhi, 1989) on the basis of patients' history, neurologic investigation, EEG data, results of video-EEG monitoring and of the neuro-visualization investigations (MRI and CT scans), as required by the acting standard treatment protocols for epilepsy (Ministerial Order N174 dated 28th February 2005, Ministry of Health and Social Development of the Russian Federation).

Pharmacotherapy of all included in the study cases of childhood and juvenile epilepsy was carried out with antiepileptic medicines in doses recommended by the acting standard treatment protocols, tailored to diagnosed form of epilepsy or epileptic syndrome, type of seizures, age, and disease severity, and calculated per kilogram of body weight.

The daily dose range for anti-epileptics used in studied cases was as follows:

Valproic acid – 20–50 mg/kg
Carbamazepine – 10–25 mg/kg
Phenobarbitone – 1–6 mg/kg
Topiramate – 1–5 mg/kg
Lamotrigine – 1–4.5 mg/kg
Oxcarbazepine – 20–30 mg/kg

Levetiracetam – 25–40 mg/kg
Succinimides – 15–21 mg/kg

The daily dose was divided into 2 or 3 doses. Retard forms were taken (introduced) 2 times a day, regular formulations – 3 times a day.

The standard treatment protocols recommended monitoring for plasma levels of phenobarbitone, carbamazepine, valproates and phenytoin. However due to the lack of laboratory facilities therapeutic drug monitoring was not carried out to all patients included in the study, hence we do not present the data available for single patients which did not have any bearing on the dosing regimen.

We did not perform adjustment for confounding variables such as age, dose or therapeutic drug level etc., on the assumption that the results of the non-adjusted analysis would provide more practice-oriented results and on the understanding that the standard treatment protocols were followed in all included cases and the dosing regimens were within the recommended dose ranges.

The risk/benefit ratios (RR) of the measured outcomes and 95% confidence intervals (95% CI) were calculated with the use of the software package RevMan 5.2. Statistics also were implemented with the help of SPSS and statistics module of Excel MS Office XP.



## 3. Results and discussion

Monotherapy was mostly used for the treatment of both childhood and juvenile epilepsy in the year 2005 (Table 2). In 2007 the proportion of monotherapy cases was 82%.

### *3.1. Monotherapy of epilepsy with different anti-epileptic drugs*

Valproates and carbamazepine were the preferred antiepileptics for monotherapy of epilepsy in 2005.

There was an increase in the use of valproates in 2007 compared to 2005 ($64 \pm 6\%$ of all monotherapy cases in 2005 and $76 \pm 4\%$ – in 2007). At the same time there was reduction in percentage of monotherapy cases using carbamazepine ($21 \pm 8\% \longrightarrow 13 \pm 7.5\%$), barbiturates ($5.5\% \longrightarrow 1.4\%$), and topiramate ($7\% \longrightarrow 5.5\%$) while the absolute number of patients receiving topiramate remained the same. We observed some increase in percentage of cases using levetiracetam ($0.7\% \longrightarrow 1.2\%$) and ethosuximide ($0.5\% \longrightarrow 1.2\%$). Lamotrigine was used rarely ($1.4\% \longrightarrow 0.9\%$).

Table 2
Proportions of mono- and polytherapy cases in treatment of childhood epilepsy in 2005 (%)

| | | Monotherapy | Polytherapy |
|---|---|---|---|
| Absolute patient number, *N* | | 440 | 108 |
| | Boys | 247 | 54 |
| | Girls | 193 | 54 |
| Mean | Boys | $10.6 \pm 4.9$ | $7.8 \pm 5.0$ |
| Age, years | Girls | $10.9 \pm 4.8$ | $10.1 \pm 5.6$ |
| Proportion, % | | 80 | 20 |

### 3.2. Monotherapy of various forms of epilepsy

Valproates and carbamazepine were used predominantly as monotherapy of idiopathic, symptomatic, and cryptogenic forms of epilepsy in children and adolescents both in 2005 and 2007.

Among the medicines of the so-called "new generation" in 2005 and 2007 physicians often used topiramate, mostly in symptomatic (11% and 9%) and cryptogenic forms (10% and 6%). In patients with idiopathic epilepsy topiramate was used only in 2% of cases both in 2005 and 2007. Oxcabazepine and benzodiazepines were almost never used, and lamotrigine was prescribed rarely. We observed the tendency of reduction in use of barbiturates in 2007 as compared to 2005 in all forms of epilepsy, particularly in symptomatic forms (10% $\longrightarrow$ 3%) (Tables 3, 4 and 5).

WHO and the International anti-epileptic League recommend valproates as the first choice for treating generalized forms of epilepsy, carbamazepine – for focal ones, though the evidence of the advantages of valporates for generalized forms, and carbamazepines for focal ones from numerous randomized clinical trials (RCTs) is not fully convincing [4].



Table 3
Antiepileptics used in monotherapy of children with epilepsy, registered at the municipal Centre in 2005 (%)

| | Total absolute number, *N* | Boys | Mean age, years/ boys | Girls | Mean age, years/girls | % |
|---|---|---|---|---|---|---|
| Valproates | 280 | 145 | $10.3 \pm 5.1$ | 135 | $10.6 \pm 4.9$ | $64 \pm 6$ |
| Carbamazepine | 92 | 63 | $12.1 \pm 4.0$ | 29 | $11.5 \pm 3.9$ | $20 \pm 8$ |
| Lamotrigine | 6 | 1 | 14 | 5 | $13.2 \pm 3.6$ | 1.4 |
| Topiramate | 32 | 19 | $8.9 \pm 4.8$ | 13 | $9.8 \pm 4.6$ | 7.3 |
| Levetiracetam | 3 | 1 | 4 | 2 | 1 | 0.7 |
| Succinimides | 2 | 1 | 15 | 1 | 5 | 0.5 |
| Barbiturates | 24 | 16 | $8.8 \pm 5.4$ | 8 | 9 | 5.5 |
| Oxcarbazepine | 1 | 1 | 16 | 0 | 0 | 0.2 |
| Total | 440 | 247 | $10.6 \pm 5.0$ | 193 | $10.6 \pm 4.8$ | 100 |

Table 4
Use of antiepileptics in children and adolescents with idiopathic, symptomatic, or cryptogenic forms of epilepsy in 2005 (%)

| | Abs. number, *N*, idiopatic | % | Abs. number, *N*, symptomatic | % | Abs number, *N*, cryptogenic | % |
|---|---|---|---|---|---|---|
| Valproates | 131 | $77 \pm 7$ | 76 | $57 \pm 11$ | 73 | $54 \pm 11$ |
| Carbamazepine | 24 | $14 \pm 14$ | 25 | $19 \pm 15$ | 43 | $32 \pm 14$ |
| Lamotrigine | 4 | 2 | 1 | 0.8 | 1 | 0.7 |
| Topiramate | 3 | 2 | 15 | 11 | 14 | 10 |
| Levetiracetam | 0 | 0 | 3 | 2 | 0 | 0 |
| Succinimides | 1 | 0.6 | 1 | 0.8 | 0 | 0 |
| Barbiturates | 7 | 4 | 13 | 10 | 4 | 3 |
| Oxcarbazepine | 0 | 0 | 0 | 0 | 1 | 0.7 |
| Total | 170 | 100 | 134 | 100 | 136 | 100 |

Table 5
Antiepileptics used for children and adolescents with generalized and focal forms of epilepsy in 2005 (%)

| | Abs. number, *N* generalized forms | % | Abs. number, *N* focal forms | % |
|---|---|---|---|---|
| Valproates | 149 | 80 ± 6 | 131 | 52 ± 9 |
| Carbamazepine | 18 | 10 | 74 | 29 ± 10 |
| Lamotrigine | 4 | 2 | 2 | 0.8 |
| Topiramate | 2 | 1 | 30 | 12 |
| Levetiracetam | 1 | 0.5 | 2 | 0.8 |
| Succinimides | 1 | 0.5 | 1 | 0.4 |
| Barbiturates | 11 | 6 | 13 | 5 |
| Oxcarbazepine | 0 | 0 | 1 | 0.4 |
| Total | 186 | 100 | 254 | 100 |



### *3.3. Adverse effects of antiepileptics used in mono- and polytherapy of epilepsy in children*

The frequency of adverse effects of anti-epileptic therapy, according to some authors, is as high as 25% [5]. Polytherapy increases the risk of development of adverse effects of anti-epileptics [5]. A number of studies found no difference in efficacy or safety of different therapeutic tactics [6, 7]. In 2005 we noted a higher frequency of adverse effects with polytherapy regimens compared to monotherapy: 43% *versus* 17%. Analysis repeated two years later confirmed this: 44% *versus* 22%

### *3.4. Analysis of efficacy and safety of antiepileptic drugs*

Pharmacoepidemiology studies (PhES) unlike RCTs allow inclusion and analysis of different patient groups (in particular, children and adolescents) [8, 9], which often are excluded from clinical trials, and pharmacoepidemiology studies allow following up on development of known and unknown long-term adverse events and quantifying them.

It is important to emphasize that with continuously growing number of new anti-epileptics only comparison of their effects with the existing ones could provide genuine understanding of their effectiveness, and not comparisons with placebo [10]. Moreover it remains a challenge to get any comparative estimates of long-term efficacy of anti-epileptics.

We calculated risk ratios (RR) for comparisons of effects of various anti-epileptics in children and adolescents, using favorable outcomes: remission for 1 year or longer and remission lasting for 3 years or longer; and the total number of patients with adverse effects as a safety outcome.

There was no difference between valproates and carbamazepine in the outcome "remission for 1 year or longer" – both in 2005 and 2007 (RR 0.93; 95% CI [0.74; 1.75], $N = 372$ and RR 0.90; 95% CI [0.75, 1.09], N 526). However, carbamazepine was superior to valproates in maintaining remission for 3 years or longer: RR 0.61; 95% CI [0.38; 0.98] $P = 0.04$ in 2005, $N = 372$ and RR 0.67; 95% CI [0.45, 1.01] $P = 0.05$ in 2007, $N = 526$).

Valproates in monotherapy were less effective than Phenobarbital for both outcomes: "remission for 1 year or longer" – RR 0.33; 95% CI [0.13, 0.85] $P = 0.02$, $N = 304$; and "remission for 3 years or longer" – RR 0.42 95% CI [0.22, 0.79], $P = 0.007$, $N = 304$.

Comparison of polytherapy and monotherapy showed advantages of monoherapy in achieving and maintaining remission both for 1 year (RR 5.68, 95% CI [1.82, 17.72], $P = 0.003$, $N = 548$) and for 3 years or longer (RR 2.06, 95% CI [1.55, 2.73], $P = 0.02$, $N = 718$). Yet it should be kept in mind that doctors used polytherapy in cases when monotherapy was ineffective.

Monotherpay was associated with significantly lower risk of developing adverse effects than polytherapy both in 2005 (RR 0.4; 95% CI [0.30; 0.54], $P < 0.00001$ $N = 548$), and in 2007 (RR 0.50; 95% CI [0.40; 0.65], $P < 0.00001$, $N = 718$).

In 2005 adverse effects were less frequent with carbamazepine monotherapy than topiramate (RR 0.35; 95% CI [0.14; 0.85], $P = 0.02$, $N = 124$), or than lamotrigine monotherapy (RR 0.26; 95% CI [0.07, 0.97], $P = 0.04$, $N = 98$). Valproate monotherapy was associated with more adverse effects than carbamazepine monotherapy (RR 2.22; 95% CI [1.10; 4.48], $P = 0.03$, $N = 372$). There was a tendency to more frequent emergence of adverse effects when using lamotrigine than phenobarbital (RR 4.00 95% CI [0.70; 22.88], $P = 0.12$, $N = 30$).

In 2007 adverse effects were less frequent with topiramate monotherapy than valproate monotherapy (RR 0.6; 95% CI [0.37; 0.96], $P = 0.03$, $N = 480$) or with carbamazepine monotherapy than topiramate (RR 0.31; 95% CI [0.14; 0.66], $P = 0.002$, $N = 110$); or with carbamazepine monotherapy than lamotrigine monotherapy (RR 0.29; 95% CI [0.08; 0.99] $P = 0.05$, $N = 83$). Valproate monotherapy was associated with more adverse effects than carbamazepine monotherapy (RR 1.93; 95% CI [1.02; 3.66], $P = 0.04$, $N = 526$).

In a separate analysis we followed patients with childhood (8 boys and 12 girls, mean age – $11 \pm 0.4$ years) and juvenile (3 males and 9 females, mean age – $16 \pm 0.7$ years) absence epilepsy for longer than 3 years in outpatient setting through the years 2001–2011. Monotherapy was used in 17/20 (85%) of childhood cases with valproic acid (average daily dose – $29 \pm 1$ mg/kg/day). Monotherapy was used in 75% of juvenile cases primarily with valproic acid. Remission lasting for longer than 6 months was observed in 17/20 (85%) of patients with childhood absence epilepsy and 11/12 (92%) of patients with juvenile absence epilepsy. Remission lasting longer than 1 year was achieved in 17/20 (85%) of patients with childhood and in 9/12 (75%) of patients with juvenile absence epilepsy. Remission for longer than 3 years was achieved in 13/20 (65%) of patients with childhood absence epilepsy and only in 2/12 (17%) of patients with juvenile form. RR for remission lasting longer than 3 years for childhood versus juvenile absence epilepsy was 3.90; 95% CI [1.06 to 14.39], $P < 0.05$.



## 4. Conclusions

1. Monotherapy was the preferred treatment option for childhood epilepsy in 2005 and 2007 with valproates as the most frequently prescribed agents for all forms of epilepsy in children and adolescents.
2. Newer anti-epileptics showed no advantage over the older ones neither in efficacy nor in safety.
3. Poly-pharmacotherapy of epilepsy in children and adolescents is associated with a doubled risk of adverse effects.
4. Long-term follow up (more than 3 years) shows higher treatment response rate in patients with childhood versus juvenile absence epilepsy.

## References

[1] Orme M, Sjöqvist F, Birkett D, et al. Clinical pharmacology in research, teaching and health care. Basic Clinical Pharmacology Toxicology. 2010;107(1):531-59.
[2] Elger CE, Schmidt D. Modern management of epilepsy: A practical approach. Epilepsy & Behavior. 2008;12:501-39.
[3] Strom BL, Kimmel SE, editors. Textbook of Pharmacoepidemiology. West Sussex. England: John Wiley and Sons, Ltd; 2006. p. 498.
[4] Marson AG, Williamson PR, Hutton JL, et al. Carbamazepine versus valproate monotherapy for epilepsy. Cochrane Database of Systematic Reviews. 2000; Issue 3. Art. No.: CD001030. DOI: 10.1002/14651858.CD001030.
[5] Voronkova K, Petruchin A, Pylaeva O, Cholin A. Rational anti-epileptic pharmacotherapy. Doctors guidance. Moscow: Binom; 2008. p. 191.
[6] Beghi E, Gatti G, Tonini C, et al. Adjunctive therapy versus alternative monotherapy in patients with partial epilepsy failing on a single drug: A multicentre, randomised pragmatic trial. Epilepsy Res. 2003;57:1-13.
[7] Deckers CL, Hekster YA, Keyser A, van Lier HJ, Meinardi H, Renier WO. Monotherapy versus polytherapy for epilepsy: A multicenter double-blind randomized study. Epilepsia. 2001;42:1387-94.
[8] Ziganshina L, Abakumova T, Vedernikova O, et al. Pharmacoepidemiology and individualization of pharmacotherapy – new technologies of improving the use of drugs. Kazan Medical Journal. 2005;86(2):97-101.
[9] Glauser AT, Dulac O. Preliminary efficacy of levetiracetam in children. Epileptic Disorders. 2003;5:45-50.
[10] Muller M, Marson AG, Williamson PR. Oxcarbazepine versus phenytoin monotherapy for epilepsy. Cochrane Database of Systematic Reviews. 2006; Issue 2. Art. No.: CD003615. DOI: 10.1002/14651858.CD003615.pub2.