Original Article

Pharmacoepidemiology of Antiepileptic Drugs in Children

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Abstract

With the pharmacotherapy of epilepsy, there is a decrease in the number of seizures or their complete cessation. The aim of the study was to conduct a comparative analysis of the efficacy and safety of antiepileptics traditionally used in medicine (valproate, carbamazepine) and new-generation analogs (topiramate) in the treatment of epilepsy in children and adolescents. The study was conducted in 2014 and 2018, at the Center for Epileptology and Neurology, Moscow (Russian Federation). In 2014, 777 medical records of children registered with epileptologists were studied, in 2018 - 840 medical records of children. The age interval of 3 months is 18 years. Favorable outcomes of epilepsy therapy with different drugs were calculated, with different approaches monotherapy and polytherapy. A favorable outcome meant remission, which lasted more than 1 year and more than 3 years. In 2014 and 2018, monotherapy prevailed among the treatment methods. With monotherapy, valproates are used more often (up to 70%), carbamazepine is used 3.0 times less often ($p \leq 0.01$ relative to valproates). The use of topiramate is 10 times less than the number of valproate therapy ($p \leq 0.0001$), and barbiturates - 15 times ($p \leq 0.0001$). Among the new generation drugs, topiramate was often used, with monotherapy, with symptomatic forms of epilepsy (10.4% in 2014 and 7.9% in 2018, $p \leq 0.05$), as well as with a cryptogenic form (9.6% and 4.4%, respectively, $p \leq 0.05$). The chosen type of therapy can significantly affect the number of side effects. With polytherapy, in 2014, side effects were observed in 44.1% compared with monotherapy (18.1%, at $p \leq 0.01$), in 2018 - 45.1% against 20.9% (at $p \leq 0.01$). Topiramate showed lower efficacy compared with carbamazepine in all years of the study with monotherapy (0.65, at $p \leq 0.04$). The results did not confirm the effectiveness of the new drugs. There was no difference in efficacy and safety between traditional drugs (valproate, carbamazepine) and new generation drugs (topiramate and others). In 2014 and 2018, monotherapy (72.8%) over polytherapy (27.2%) prevailed among the treatment methods for epilepsy. Among the drugs, valproate was predominant (65.8%), and in all identified forms of epilepsy. The new generation of drugs did not show statistically significant advantages compared to traditionally used ones. The method of polytherapy of epilepsy in children gives a twofold increase in the likelihood of side effects ($p \leq 0.01$).

Key words: epilepsy, pharmacotherapy, monotherapy, polytherapy, children, valproate, carbamazepine, topiramate.

Introduction

Epilepsy is one of the most common diseases of the central nervous system (Aliyu et al., 2016). Among children, this disease is widely represented, ranging from 0.2 to 2.1% of the population (Mani, 2013). The average prevalence of epilepsy in children is 1% (Brodie et al., 2012). According to the age distribution of epilepsy, the greatest number of cases are in the elderly (Martinez-Lizana et al., 2017), as well as in children under 10 years of age (Vajda et al., 2018). A person suffering from bouts of epilepsy is characterized by low self-esteem and realization in society as well as at home (González et al., 2015).

The main goal of the treatment of epilepsy is to reduce the number of seizures or to completely stop them, while minimizing possible side effects from the drugs used (Shih et al., 2016). Discontinuation or a lower frequency of epilepsy attacks will significantly improve the patient's quality of life (Legge et al., 2018). Given that this is a rather large group of the population, in which a significant part is made up of children, the problem of the treatment of epilepsy remains relevant today (Slater et al., 2018; Liu et al., 2020). In most

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cases, the prognosis of the disease is favorable for the patient, but in a third of cases, remission is not observed (Blaszczyk et al., 2018). The lack of remission can cause a deterioration in the health of patients, which, in turn, entails a deterioration in the quality of life. In the event of remission, the health status of patients who take or do not take anticonvulsant drugs improves, reaching the average population level of healthy people (Sarhan et al., 2015).

In monetary terms, medical expenses in the EU for epilepsy account for about 0.5% of all medical expenses (Schmidt, 2016). At the same time, the costs of treating epilepsy can vary significantly, depending on how it proceeds, as well as on the observed effect of treatment. For example, the bulk of the costs are associated with inpatient treatment, as well as the purchase of necessary drugs. Per month, for a patient with epilepsy, there are between 50 and 400 euro costs (Schmidt & Schachter, 2014). Minimum amounts are spent by patients who have less severe seizures of epilepsy and who are monitored by general practitioners, for example, general practitioners (Margolis et al., 2014).

Therapy of epileptic seizures is reduced to a long period of use of antiepileptic drugs. The main purpose of antiepileptic drugs (synonyms - anticonvulsants or anticonvulsants) is the prevention of the onset of epileptic seizures in patients. This class of drugs includes drugs such as valproate (valproic acid), lamotrigine, phenobarbital, progabide, carbamazepine, phenytoin. A possible basis for the action of drugs of this class is the inhibition of activating neurons, or the excitation of nerve cells responsible for the slowdown (inhibition) of nerve processes (Villanueva et al., 2012). To achieve a state of remission, when seizures become less or less pronounced, it is necessary to reach the level of effective concentration of drugs in blood plasma (Czornyj et al., 2018). In the case of an incorrectly chosen treatment strategy, for example, with the combined prescription of anticonvulsant drugs, without taking into account their mutual influence, and also when choosing a too low or high concentration of the drug, their effect may be reduced or absent. The consequences of this are the refusal to use the drug, which could be effective with the right dose. On the other hand, an incorrect therapy strategy may lead the doctor to conclude that the patient is resistant to the drug and the resistant form of epilepsy. Such cases of a false diagnosis of epilepsy have the corresponding name - relative pharmacoresistance. According to some reports, this diagnosis is observed in almost half (48%) of inpatients (Aliyu et al., 2016).

There is also a category of patients with absolute pharmacoresistance. These include patients who do not have the therapeutic effect of monotherapy with one of the two main antiepileptics at the maximum permissible doses, or from a combination of two antiepileptics, or from a combination of the main antiepileptic with an antiepileptic from the latest generation (Malek et al., 2017). Valproates, carbamazepine, and topiramate are the main ones (Kwon et al., 2017). The second group, additional drugs in pediatric practice, are succinimides, benzodiazepines, and lamotrigine (Schmidt & Schachter, 2014). One of the reasons for the lack of effect from treatment may be a subjective assessment of their condition by the patient.

Today, in addition to the pharmacotherapy of epilepsy itself, there are other methods of treating seizures, in particular, autogenous training of the patient, as well as techniques associated with the formation of biological feedback (Malek et al., 2017). However, pharmacotherapy is still the most common and most effective method of treating epilepsy, including in children (Kwon et al., 2017).

At the same time, the question of the need for monotherapy of epilepsy with one or another drug, or the effectiveness of their combined action remains quite debatable (Vitturi et al., 2019). Choosing the right pharmacotherapy strategy is one of the most important issues in the treatment of epilepsy among children (Legge et al., 2018). Children are the age group most susceptible to epilepsy, in some regions the incidence can be up to 5% (Vajda et al., 2018). A specificity of a child's organism is changes that constantly occur in it as it grows up. Changes occur at all levels - morphological-anatomical, physiological and biochemical. Such dynamic processes determine a completely different pharmacodynamics and pharmacokinetics of the antiepileptic drugs used compared with adults (Ben-Menachem, 2014). The situation of adequate therapy is further complicated by the fact that many of the children, due to their young age, cannot provide accurate information about the symptoms of epilepsy, as well as about side effects from the drugs used. The greatest specificity is in infancy and neonatal age (Lee, 2014). All of the above factors have determined the relevance of this article on the pharmacoepidemiology of antiepileptic drugs among children.

The purpose of the study was to conduct a comparative analysis of the effectiveness and safety of a number of antiepileptics that are used in the treatment of epilepsy in children and adolescents. The authors hypothesized that the new generation of drugs does not have statistically significant advantages compared to the base ones, as well as the increased risk to patients' health from side effects during treatment with several drugs (polypharmacotherapy).

Material and research methods

Material

The study was conducted in 2014 and 2018 on the basis of the Center for Epileptology and Neurology. A. A. Ghazaryan, Moscow (Russian Federation). In 2014, we examined 777 outpatient cards of children, which were observed at that time by the Center's epileptologists. In 2018, 840 outpatient cards for children were similarly studied. Age and gender distribution are presented in Tab. 1.

It should be noted that in 2018, some of the children from the 2014 sample were not registered with epileptologists, since they reached remission and their antiepileptic drugs were canceled. Some of the children have reached adulthood and

Table 1. Age and gender distribution in patient samples 2014 and 2018

Patients characteristics	2014	2018
Number of male patients	401	459
Number of female patients	376	381
Average age of male patients	9.7±4.8	9.9±4.9
Average age of female patients	10.1±5.2	10.5±5.0

have been attached to other epileptologists who work with adults. Another group is the inclusion of children with newly diagnosed epilepsy. In total, there were 253 patients from the 2014 sample excluded from the 2018 sample.

The age interval in the samples of both years did not have statistically significant differences and ranged from 3 months to 18 years.

Methods

For each patient whose history was analyzed, an individual card was compiled and filled out. Here, the diagnosis was formulated according to the generally accepted International Classification of Epilepsy.

The distribution of patients into groups depending on the therapy used in 2014 is presented in Table. 2.

In 2014, treatment with monotherapy predominated, exceeding the performance of the polytherapy group by 2.6 times. At the same time, the average age and sex ratios in each of the groups did not have significant differences. In 2018, there were no significant differences in the methods used.

Inclusion criteria

The study included children of the specified age range (3 months - 18 years old), registered with an epileptologist.

Exclusion criteria

The study did not include children who did not meet the age range (including those who came of age by 2018), as well as children with other diseases of the central nervous system. Medical cards that did not contain complete and reliable information about the occurrence and course of the disease were also not taken into account.

Table 2. Gender ratio and age indicators in groups with mono- and polytherapy of epilepsy in 2014

Patients characteristics	Monotherapy method	Polytherapy Method
Total number of patients	566	211
Number of male patients	298	106
Number of female patients	268	105
Average age of male patients	10.2±5.2	8.9±4.6
Average age of female patients	10.4±5.5	10.3±5.1
% in each group*	72.8	27.2

*100 % - total number of patients in 2014 (777)

Ethical, moral standards, non-disclosure agreement

An agreement was signed with each of the parents of patients on the anonymity of the processed information. A parallel verbal agreement was concluded with older children. This study respected moral and ethical standards.

Statistical analysis

Statistical calculations were performed using the statistical analysis package Microsoft Excel 2013 (Microsoft Inc.), as well as the program Past v. 3.0 The following values were calculated: the arithmetic mean of each feature±the mean error. The distribution of attributes corresponded to normal, which determined the choice of parametric methods of statistical analysis - a two-sample t-test, the calculation of confidence intervals. Separately, we calculated the favorable therapy outcomes (in the text - FTO) for different types of epilepsy drugs. The outcomes reflected remission, which lasted for a long time, more than 1 year and more than 3 years.

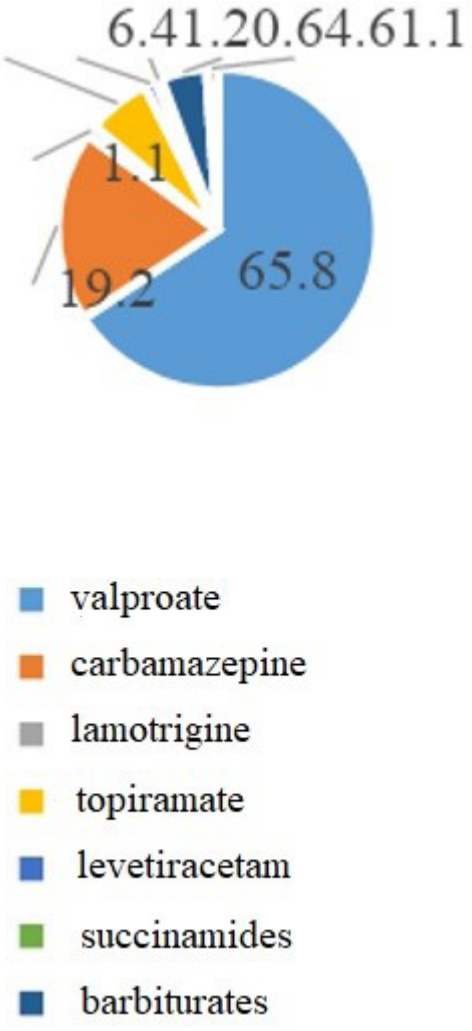

Figure 1. Representation of antiepileptic drugs in monotherapy of children who were registered with an epileptologist in 2014

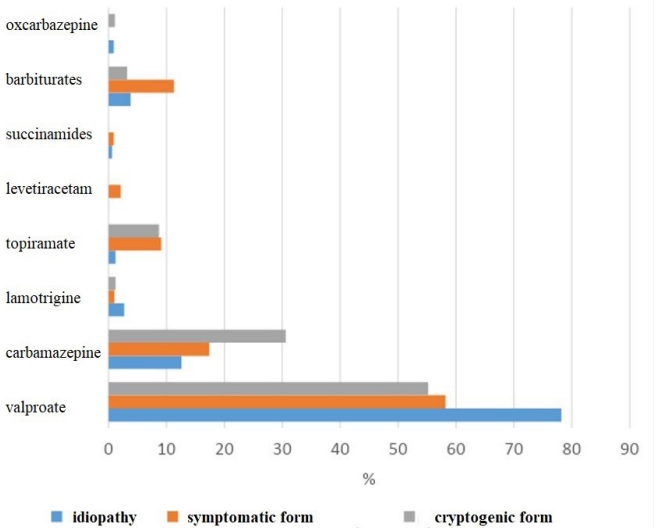

Figure 2. The use of antiepileptics in children with cryptogenic, symptomatic and idiopathic forms of epilepsy.

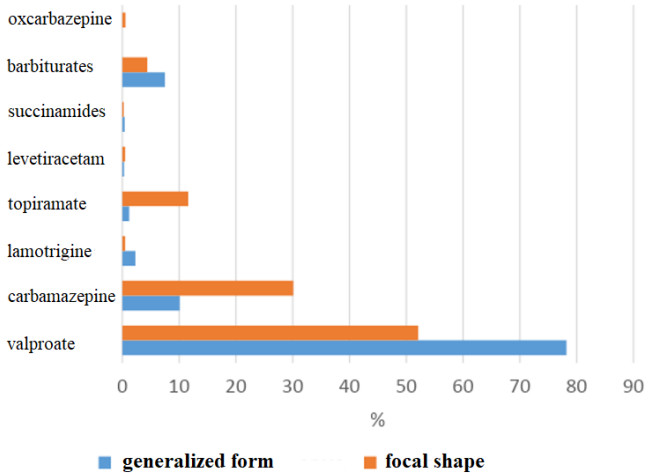

Figure 3. The use of antiepileptics in the treatment of generalized and focal forms of epilepsy in children.

Results

In 2014 and 2018, the predominance of monotherapy treatment methods was recorded. Among the drugs used in monotherapy, valproates predominate (Fig. 1). Carbamazepine is used 3.0 times less often ($p \leq 0.01$ with respect to valproate).

The share of other drugs is even lower than carbamazepine, inferior to the number of valproate therapy cases by 10 times ($p \leq 0.0001$, topiramate), 15 times ($p \leq 0.0001$, barbiturates) or more.

In 2018, there was a change in the applied therapy compared to 2014: valproate was prescribed more (from 65.8 (Fig. 1) to 79.6%, $p \leq 0.05$), while the number of carbamazepine was reduced from 19.2% to 11.7 % in 2018 ($p \leq 0.01$), as well as barbiturates (from 4.6% to 0.7%, at $p \leq 0.01$) and topiramate (from 6.4% to 4.9%, $p \leq 0.05$). At the same time, the number of patients receiving topiramate remained the same in 2018. Levetiracetam (1.4% in 2018, $p \leq 0.05$), as well as ethosuximide (1.1%, $p \leq 0.05$), but less often lamotrigine, were prescribed twice as often. (0.6%, $p \leq 0.05$).

In monotherapy, valproates and carbamazepine were most often used (Fig. 2).

The drugs were used at different frequencies for different forms of epilepsy. So, valproates were most often prescribed for the idiopathic form of epilepsy (Fig. 2, $p \leq 0.05$) compared with the cryptogenic and symptomatic forms, while carbamazepine was prescribed for the cryptogenic form ($p \leq 0.05$). For other drugs, no significant differences were obtained, due to the small number of cases of their appointment.

For drugs belonging to the new generation, quite frequent use of topiramate with monotherapy, with symptomatic forms of epilepsy (10.4% in 2014 and 7.9% in 2018, $p \leq 0.05$), as well as with the cryptogenic form (9.6% and 4.4) %, respectively, $p \leq 0.05$). Finally, with idiopathy, topiramate was used in 1.9% and 1.6% of cases ($p \leq 0.01$ with respect to other forms of epilepsy). The remaining drugs were practically not used, and there was also a decline in the number of cases of prescribing barbiturates, if in 2014 it was 8.7%, then in 2018 it was 2.1% ($p \leq 0.01$).

Valproates were prescribed 1.5 times more often with generalized forms of epilepsy compared with focal ones ($p \leq 0.05$), while carbamazepine was vice versa, 2.5 times more often with focal forms ($p \leq 0.01$, Fig. 3).

We found that the selected type of therapy can significantly affect the number of side effects. Thus, in 2014, 44.1% of such cases were noted during polytherapy compared with monotherapy (18.1%, at $p \leq 0.01$), a repeated analysis conducted in 2018 confirmed this trend: 45.1% against 20.9% (at $p \leq 0.01$). There were no significant differences in the number of cases between the years for monotherapy, as well as for polytherapy.

The number of cases of FTO for remission of at least 1 year in 2014 and 2018 for valproate and carbamazepine preparations did not differ (FTO values of 0.93 and 0.91, respectively). At the same time, carbamazepine was found to be more effective than valproate for remission for more than 3 years (0.60, $p \leq 0.03$, 0.69, $p \leq 0.05$). It was also found that in 2014 valproates showed less effectiveness compared to barbiturates under monotherapy (0.35, at $p \leq 0.03$, 0.44, at $p \leq 0.009$) and for cases of remission of at least 1 year and at least 3 years.

Topiramate showed lower efficacy compared with carbamazepine in all years of the study with monotherapy (0.65, at $p \leq 0.04$). Monotherapy, in the overall results, showed greater efficiency compared to polytherapy, in case of achieving remission of both annual and three-year duration. It should be noted that polytherapy was the only option when monotherapy did not produce the desired effect. Side effects in 2014 with monotherapy were achieved in a significantly smaller number of cases than with polytherapy (FTO 0.39, at $p \leq 0.0001$). The

same trend was noted in 2018 (0.51, at $p \leq 0.0001$). In case of monotherapy, topiramate gave a greater number of side effects compared with carbamazepine (0.33, $p \leq 0.03$), as well as lamotrigine compared with carbamazepine (0.28, $p \leq 0.04$), and, finally, valproate with respect to carbamazepine (2.3, with $p \leq 0.02$).

For 2018, there was a tendency toward a predominance of the number of adverse events when using topiramate compared with valproate (0.55, $p \leq 0.04$), or with carbamazepine (0.34, $p \leq 0.01$).

Discussion

Among the recommendations of the World Health Organization, the advantage in therapy is given to valproate, in the case of a generalized form of epilepsy (Contin et al., 2018). With focal form, carbamazepine is preferred (Sarkis et al., 2018). At the same time, there is no substantiated data on such a choice with respect to valproate for generalized and carbamazepine for focal forms of epilepsy. Our data confirmed these recommendations - carbamazepine was indeed more often prescribed for the focal form of epilepsy.

The number of cases of side effects in the treatment of epilepsy may, according to some reports, reach values of 20-30%. (Kanemura et al., 2018) It is also known that polytherapy is less desirable since it increases the number of side effects (Burns et al., 2019). This is also confirmed by our data. On the other hand, some studies did not find a difference in efficacy as well as safety for patients with the methods of treatment used (Brigo et al., 2013; Lee, 2014).

The specificity of this study lies in the choice of the age group - children. In many other studies on epilepsy and its forms, children and adolescents are not included in the sample due to exclusion from the study due to age mismatch (Chang et al., 2017). Therefore, such data are necessary, given the characteristics of the physiological development of the body in childhood and adolescence (Gladilina et al., 2018).

In our opinion, the true criterion for the effectiveness of a new antiepileptic drug is their comparison with the effectiveness of those already used, and not with placebo.

The question of the effectiveness of the use of new generation drugs (topamax, vigabatrin, and others) remains open (Carmichael et al., 2013; Pulman et al., 2014). The principles of treatment with these drugs do not differ from those of traditional drugs (valproate, carbamazepine). In practice, the opinion is realized that after three attempts to use the drug, which ended with the absence of significant results, the probability of success from using the new drug does not exceed 5-10% (Chang et al., 2017). It is noted that new drugs, such as topiramate, have maximum antiepileptic efficacy (Soffietti et al., 2018). Our data did not confirm this statement, but, on the contrary, confirmed the hypothesis that there are no significant effects between traditional drugs and new generation drugs.

Conclusion

In 2014 and 2018, monotherapy (72.8%) prevailed over polytherapy (27.2%) among the treatment methods for epilepsy. Among the drugs, valproate was predominant (65.8%), and in all identified forms of epilepsy. The new generation of drugs did not show statistically significant advantages compared to traditionally used ones. The method of polytherapy of epilepsy in children gives a twofold increase in the likelihood of side effects ($p \leq 0.01$).

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