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THE BASIC PRINCIPLE OF EPILEPSY TREATMENT

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Abstract: The main principle of epilepsy treatment is the long-term regular use of antiepileptic drugs (AEDs) to reduce the frequency of seizures or their complete reduction in the absence of clinically significant side effects. Important importance is given to the issues of tolerability of antiepileptic therapy and the problem of compliance - the patient's desire to correctly fulfill the recommendations of doctors, the presence of mutual understanding between the doctor and the patient, as well as his relatives and friends.
Keywords: antiepileptic therapy, effectiveness, principles of therapy, safety, quality of life.

Relevance. Timely detection and correction of adverse reactions is an integral part of epilepsy treatment. Currently, special attention is also paid to the quality of life of patients with epilepsy (which includes various spheres of the patient's life: physical and mental health, education, social and psychological functioning). In individual cases, maintaining rare seizures with minimal clinical manifestations and even more frequent seizures that do not pose a threat to the patient may be more appropriate than increasing the number or dose of PEPs, leading to a decrease in the patient's quality of life. The balance between the therapeutic and toxic effects of PEPs is a major issue in the treatment of epilepsy. Drug treatment of epilepsy requires in-depth knowledge of PEPs: the spectrum of therapeutic efficacy and strength of their action; safety, tolerability, as well as their adverse reactions (in particular, severe and life-threatening adverse reactions); features of pharmacokinetics, pharmacodynamics, drug interactions and mechanisms of action; titration rate, the need for laboratory tests on the background of treatment, the specifics of pharmacoeconomics. The present review is devoted to the consideration of modern aspects of epilepsy therapy.

Modern achievements in the field of epileptology in recent decades - the creation of a modern classification of epilepsy; improvement of diagnostic methods, including the widespread use of video-EEG monitoring and the introduction of high-resolution MRI,

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positron emission tomography (PET); as well as the emergence of many new effective antiepileptic drugs (PEP), have led to the fact that epilepsy has entered the category of curable diseases. Approximately 65-70% of patients now achieve remission or a significant reduction in seizure frequency.

The mainstay of epilepsy medication is the long-term (multi-year or lifelong) regular use of PEPs to prevent the onset of epileptic seizures.

It is traditionally believed that the main goal of epilepsy treatment is to achieve complete disappearance of seizures (seizure control) in the absence of clinically significant side effects. However, in approximately 20% of patients, PEPs are not always sufficiently effective. These patients are considered candidates for neurosurgical treatment of epilepsy, as well as for the use of other pharmacologic and nonpharmacologic therapies (vagus nerve stimulation, special diets). In addition, nowadays the ideas about the goals of epilepsy treatment have significantly expanded to include the assessment of the quality of life of patients, which covers various spheres of the patient's life: physical and mental health, education, the possibility of full social and psychological functioning.

A prerequisite for the prescription of any epilepsy treatment method is confidence in the correctness of the diagnosis of epilepsy. According to the literature, ¼ of patients treated for epilepsy are misdiagnosed (these patients do not have true epileptic seizures and have paroxysmal conditions of other etiologies). Thus, the decision to prescribe antiepileptic therapy is an important responsibility for the physician, both from the point of view of confidence in the diagnosis itself and due to the fact that the patient must receive PEPs for many years and sometimes for life, but all PEPs can cause side effects (including serious and reducing the patient's quality of life).

Once the diagnosis of epilepsy is established, the type of seizures and the epileptic syndrome are correctly identified, the next important step for prescribing adequate therapy is the choice of PEP, which depends on the type of seizures, and the duration of antiepileptic therapy is determined mainly by the epileptic syndrome. Drug treatment of epilepsy is recommended to start with monotherapy (single-drug treatment). Approximately 50-70% of patients on the background of treatment with one correctly selected PEP (in monotherapy) in therapeutic dose can achieve complete elimination of seizures (or reduction of their frequency to a minimum) with no (or minimal) side effects. The number of patients who can achieve remission with monotherapy varies considerably depending on the type of seizures and the form of epilepsy. In 30-50% of patients who do not respond to monotherapy, polytherapy has to be used. However, one should not strive to achieve complete freedom from seizures at any cost, especially at the cost of severe treatment-related adverse events (severe drug-related complications of antiepileptic therapy). In some cases, maintaining infrequent seizures with minimal clinical manifestations and even more frequent seizures that are not dangerous to the patient may be more appropriate than increasing the number or dosage of PEPs, leading to a reduction in the patient's quality of life.

Knowledge of adverse reactions of antiepileptic therapy, their timely detection and correction is an essential component of epilepsy treatment. Side effects of PEPs in some cases may reduce the quality of life to a greater extent than the disease itself (epileptic seizures). The balance between the therapeutic effect and side effects of PEPs is a major challenge in the treatment of epilepsy. The main goal of treatment cannot be achieved without a detailed assessment of the frequency and nature of epileptic seizures, the history of the disease, concomitant therapy for other diseases and individual characteristics in each clinical case.

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Patients, relatives or guardians of patients should be provided with detailed information about the goals of epilepsy drug treatment, its efficacy, side effects and duration of therapy. Otherwise, low compliance (non-compliance with medical prescriptions), illusory perceptions of patients about the expected effects of treatment, and lack of trust between doctor and patient are inevitable.

There are several categories of patients with epilepsy that require special attention and therapeutic approach in the treatment of epilepsy: children, elderly patients, women (especially those of childbearing age), and patients with mental retardation.

As mentioned above, epilepsy treatment should start with monotherapy with first-choice PEPs: these drugs are usually the most effective, and the likelihood of side effects is lower. The definition of the first choice drug depends on many factors and their importance varies considerably between monotherapy and polytherapy. The main characteristics of PEPs that influence the choice of the drug include: efficacy in certain types of seizures (specificity of therapeutic action), the spectrum of therapeutic efficacy and strength of therapeutic action; safety, tolerability and the spectrum of adverse reactions (sometimes severe and life-threatening); features of pharmacokinetics, pharmacodynamics, drug interactions and mechanism of action; titration rate (time required to reach the therapeutically effective dose), the need for laboratory tests; and the need for therapeutic effects. In polytherapy, such factors as pharmacokinetics and pharmacodynamics, drug interactions, the mechanism of action of the drug, and the total cost of treatment are of particular importance.

So, the choice of PEP is primarily determined by the type of seizures. Depending on the specificity of the therapeutic action, some PEPs may be highly effective in certain types of seizures and epileptic syndromes and contraindicated in others, as they may cause an increase in frequency or aggravation (aggravation). A typical example is carbamazepine, the drug of first choice for focal seizures, but it should be avoided in idiopathic generalized epilepsy (IGE).

Drugs such as carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine and vigabatrin are ineffective or contraindicated in IGE, but carbamazepine, oxcarbazepine and phenytoin can be used for isolated primary generalized tonic-clonic seizures. For focal seizures (simple or complex), carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, tiagabine, topiramate, valproate, vigabatrin, and zonisamide are effective. Etosuximide is not effective for focal seizures, and the efficacy of clonazepam is not supported by evidence-based medicine. For secondary generalized tonic-clonic seizures, carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, tiagabine, topiramate, valproate, vigabatrin, and zonisamide are effective. Etosuximide is not effective and causes aggravation of secondary generalized seizures, and the efficacy of clonazepam has not been proven. For primary generalized tonic-clonic seizures, carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate, and zonisamide are effective. Gabapentin, tianabine, and gabapentin are not effective; there is insufficient data on the efficacy of clobazam; clonazepam and ethosuximide may cause aggravation (but reliable evidence is lacking).

Aggravation is most common in types of epileptic seizures such as myoclonic seizures and absences. Carbamazepine, oxcarbazepine, gabapentin, tiagabine, and vigabatrin can cause aggravation. Lamotrigine can also cause aggravation of myoclonic seizures, but it is effective in absences. Phenobarbital may be effective in myoclonic seizures and aggravate absences; phenytoin is not effective in myoclonic seizures and worsens the course of absences.

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Clonazepam, ethosuximide, topiramate (no reliable evidence for efficacy in absences), levetiracetam, valproate and zonisamide (no reliable evidence for efficacy in absences) are effective in the treatment of the latter; clobazam has no reliable evidence for efficacy in either type of seizure.

The greater the strength of the therapeutic effect of the drug, the more likely it is that seizure control will be achieved. The optimal and often achievable goal of treatment is complete seizure control (clinical-electroencephalographic remission). A reduction in seizure frequency by more than 50% is taken as a positive effect of therapy, although it cannot be regarded as an optimal therapeutic effect. However, it is often taken as a basis for assessing the effectiveness of treatment in randomized controlled trials.

The spectrum of therapeutic action plays an important role in the treatment of patients in whom it is difficult to accurately classify epileptic seizures as generalized or partial. In such cases, broad-spectrum PEPs that are effective for different types of focal and generalized seizures are recommended. These include, for example, valproate and levetiracetam.

Pharmacokinetics studies the processes that occur with a drug in the human body. Absorption, distribution, metabolism, and excretion are the main pharmacokinetic parameters that determine the pharmacokinetic profile of a drug and have a significant impact on efficacy, adverse reactions, and interactions with other drugs. In the treatment of epilepsy, preference should be given to the choice of PEP with the most favorable pharmacokinetic profile. These include: levetiracetam, vigabatrin and gabapentin. The least favorable pharmacokinetic profile has: thiagabine, zonisamide, phenobarbital, valproates, carbamazepine and phenytoin. The intermediate position in the evaluation of pharmacokinetic parameters is occupied by: topiramate, ethosuximide, oxcarbazepine and lamotrigine.

Most PEPs are metabolized in the liver with the participation of cytochrome P450 (CYP) and uridine diphosphate-glucoronyl-transferase enzymes. Metabolism in the liver is characteristic of carbamazepine, phenobarbital, clobazam, phenytoin, clonazepam, tiagabine, zonisamide, ethosuximide, topiramate, lamotrigine, valproates, and oxcarbazepine. Some PEPs cause induction of liver enzymes - stimulation of production and increase in CYP enzymes. This leads to an increase in the rate of metabolism of drugs metabolized by CYP enzymes, which contributes to a decrease in the plasma concentration of these drugs. Inducers of liver enzymes (cytochrome CYP system) include: carbamazepine (to a lesser extent - oxcarbazepine), phenytoin, phenobarbital and topiramate. The effect of induction, in contrast to inhibition of liver enzymes, persists for several days after withdrawal of the drug that has an inducing effect. Drugs that have active metabolites may be less affected by inducers, but induction of liver enzymes may increase metabolite concentrations and enhance toxic effects without increasing the plasma concentration of the parent drug.

Pharmacodynamics studies the biochemical and physiologic effects of drugs and their mechanisms of action. Drug interactions are pharmacokinetic and pharmacodynamic changes that occur when different drugs are administered simultaneously. Drug interactions are often the cause of reduced treatment efficacy and adverse reactions. Most PEPs can enter into numerous drug interactions, including induction and inhibition of liver enzymes and displacement of other drugs from binding to proteins. Drug interactions can be additive, synergistic, or antagonistic. They may have positive or negative effects or result in a combination of positive and negative effects. In some cases, drug interactions may have positive effects (increased treatment efficacy, decreased risk of adverse events, or a combination of these effects). An example is the combination of lamotrigine and valproate

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(increased therapeutic efficacy combined with increased risk of adverse reactions and teratogenicity). Knowledge of potential drug interactions that may result from induction or inhibition of liver enzymes and careful clinical monitoring can avoid many treatment problems.

Conclusions: thus, for all forms of epilepsy that have been diagnosed recently, regardless of the cause and prognosis of the disease. The term may be applied to any patient of any age with any type of epileptic seizure who first seeks medical attention for paroxysmal disorders that are regarded as epileptic seizures. Recently diagnosed epilepsy is not a diagnostic or therapeutic category. The purpose of using this term is to emphasize that these patients require special attention regarding diagnosis and treatment, which in most cases is necessary. The diagnosis first made at this stage and the treatment first administered can have a significant impact on the patient's entire future life, as well as the lives of family members. Recently diagnosed epilepsy is not synonymous with new-onset epilepsy (seizure debut), and it is not correct to equate the two. In many cases, the debut of epileptic seizures predates the initial health care utilization by many years. Management of patients with newly diagnosed epilepsy requires accurate diagnosis of both seizure type and epileptic syndrome.

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