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Review Article

The pharmacological treatment of epileptic seizures in children and adults: introduction, clinical contexts, psychopharmacological profiles and prospects in the neurogenetic field

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Abstract

Recalling the concept of "epilepsy", already analyzed in a previous publication, this work focuses on the specific study of the best pharmacological treatments for the morbid condition under examination, paying attention to the clinical and prospective aspects of therapy, also in light of recent discoveries in the neuroinflammatory and neurogenetic field.

Keywords: Agraphia; neurobiological; neurogenetic field

Contents of the manuscript:

"Epilepsy" - from the Greek ἐπιληψία, "to be caught, hit by something" - [1], is a neurological condition characterized by recurrent and sudden (at least two twenty-four hours apart) [2], physical manifestations of sudden loss of consciousness and violent convulsive movements of the muscles (the so-called "epileptic seizures") [3-4]. We will, therefore, speak of "epilepsy" only when the cause of the seizure will be primary (and not secondary); in all other cases, in the clinical setting, it is preferable to speak of "epileptic seizure" [5-6]. In ancient times, epilepsy was associated with religious experiences and demonic or divine possession. Known as the "sacred disease", it was widely described in the fifth century BC by Hippocrates of Kos, since epileptic seizures were thought to be a form of attack by demons, or that the visions experienced by patients were messages from the gods; the father of modern medicine himself, however, raised doubts about the divine nature of the phenomenon. However, this belief was more realistic and clinical in the Indian area, where there was already talk of "loss of consciousness". However, in most ancient cultures (and some modern cultures, in Africa and Asia), people with epilepsy were stigmatized, avoided, or even imprisoned, because they were considered dangerous, contagious, or cursed [7]. [8]

Epilepsy is usually treated through the daily intake of drugs, prescribed after the occurrence of a second seizure treated mainly in the hospital setting. During first aid, it is essential to put people with an active tonic-clonic seizure in the lateral safety position to help prevent inhalation of fluids in the lungs. Putting your fingers in your mouth or inserting a tongue depressor is not recommended as it may cause vomiting or cause the rescuer to be bitten. The interventions should aim to avoid trauma, however, precautions for the spine are generally not necessary. If an attack lasts longer than 5 minutes or there are two attacks within an hour without a return to a normal level of consciousness in between, there is a belief that there is a medical emergency known as a "state of illness epileptic". This situation may need medical attention to keep the airway patency protected. The most commonly used drug for a long-term attack is midazolam per os, while diazepam can also be administered rectally. Intravenous lorazepam is preferred in the hospital. If two doses of benzodiazepines are not effective, other drugs such as phenytoin can be used. Seizures that do not respond to initial treatment typically require hospitalization in an intensive care unit and treatment with major medications such as thiopental sodium or propofol. Anticonvulsant drugs are the main treatment for epilepsy and often have to be taken for life. The choice of the active ingredient is based on the type of seizure, on the presence of epilepsy syndrome, on the other drugs prescribed, on the other health problems, and the age and lifestyle of the person. Initially, a single drug is recommended and if this is not effective, or involves serious side effects, you try to change. Taking two drugs at the same time is only recommended if the single does not provide results. In about half, the first prescription is already effective. If the attacks appear well controlled following a particular treatment, it is generally not necessary to regularly check the drug levels in the blood. In the case of drug-resistant epilepsy, resorting to surgery may be an option for individuals with partial epileptic seizures that do not cease to manifest despite the adoption of other treatments. Before evaluating surgical treatment, however, it is necessary to try at least two or three different

drugs. The purpose of surgery is the total control of epileptic seizures. Common procedures include cutting the hippocampus through an anterior temporal lobe resection, removing tumor masses, and removing portions of the neocortex. Some procedures such as callosotomy may be attempted to try to reduce the number of seizures, rather than to cure the condition itself. Following surgery, in many cases, drug therapy can be slowly stopped. Neurostimulation may also be a viable option in those who are not candidates for surgery. Three methods have proven to be effective in those who do not respond to drugs: vagus nerve stimulation, anterior thalamic stimulation, and closed-loop response stimulation. Finally, a ketogenic diet (high-fat content, low carbohydrate content, adequate proteins) seems to decrease the number of attacks by half in about 30-40% of children. [9-18]

2. *The main pharmacological treatments.* [24-25]

In clinical practice, a few simple general rules should be followed to best approach this particular neurological condition:

1) Pharmacological treatment is indicated if all the secondary etiological causes of the epileptic disorder have been removed (for example, in the presence of neoplasms or inflammatory and autoimmune processes) and the symptoms persist.
2) No drug can control all types of seizures and some drugs can worsen seizures if they are not suitable for the specific case.
3) Patients, based on their medical history and clinical data, are subjected to drugs that are likely to give a better picture of their pathological condition.
4) One single drug is not always sufficient and some patients need polypharmacy, especially if epileptic symptoms persist after taking the drug, even if the manifestation of adverse symptoms increases exponentially as the intake of two or more drugs increases.
5) Therapy is aimed at evaluating the most suitable drug(s) for the specific case and the recommended dose.
6) The administration, depending on the specific case, can be oral or intramuscular or intravenous, can be scaled starting from a low dose, and then increasing it within 2-4 weeks (as happens for the suspension and/or interruption of therapy). The initial dose must be adjusted to the patient's tolerance to the drug. Some patients have symptoms of drug toxicity when drug levels in the blood are low; others tolerate high levels without any symptoms. If the seizures continue, the daily dose will be increased by small increments. The appropriate dose of any medication is the minimum dose that stops all seizures and has the least adverse effects, regardless of the level of medication in the blood. Blood levels of medication are only guidelines. Once the response to the medication is known, following the clinical course is more useful than measuring blood levels.
7) Maintenance therapy is calibrated to the patient's needs, laboratory results, and symptoms described, and is subject to periodic monitoring. Once the seizures have been pharmacologically controlled, the therapy should be continued without interruption for at least a prolonged period of two to five years, depending on seizures and familiarity; in the absence of epileptic symptoms of any kind, a 10% suspension of drug therapy every two weeks may be considered.
8) Relapses and new epileptic manifestations are more likely in patients who have had a form of epilepsy since childhood, the need for two or more drugs to contain epileptic symptoms, symptomatic manifestations during anticonvulsant therapy, encephalopathy, abnormal electroencephalographic findings during therapy, relevant structural lesions or neurovascular abnormalities highlighted in imaging studies. In such hypotheses, therapy should be considered throughout the patient's lifetime.

Generally, broad-spectrum anticonvulsants (which are effective in focal onset crises and various types of generalized onset crises) include lamotrigine, levetiracetam, topiramate, valproate, and zonisamide. For generalized partial and tonic-clonic seizures, more recent anticonvulsants (e.g., clobazam, clonazepam, ezogabine, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, zonisamide) are no more effective than established drugs. However, newer medications tend to have fewer adverse effects and are better tolerated. Epileptic spasms (previously, childhood), atonic seizures, and myoclonic seizures are difficult to treat. Valproate or vigabatrin is usually preferred, followed by clonazepam. In epileptic spasms, the use of corticosteroids, for 8-10 weeks, is often effective. The optimal dosage remains controversial; the 20-60 intramuscular hormone adrenocorticotropic hormone can also be used once/day. A ketogenic diet (a diet very rich in fat that induces ketosis) can help, although it is difficult to maintain. For juvenile myoclonic epilepsy, treatment is generally recommended throughout life. Carbamazepine, oxcarbazepine, or gabapentin can however aggravate seizures. Lamotrigine can be used as second-line monotherapy or additional therapy for juvenile myoclonic epilepsy; however, it may aggravate myoclonic seizures in some patients with juvenile myoclonic epilepsy. For febrile seizures, medication is not recommended unless the children have a subsequent seizure in the absence of febrile disease. Many doctors pre-emptively prescribe phenobarbital or other anticonvulsants to children with complicated febrile seizures to prevent the development of non-febrile seizures, but this treatment does not seem effective and, in the long term, phenobarbital reduces learning ability. For seizures due to alcohol withdrawal, drugs are not recommended; on the contrary, treatment of withdrawal syndrome tends to prevent seizures. Treatment usually includes a benzodiazepine.

The different negative effects of anticonvulsants can then influence the choice of drugs for each patient. For example, anticonvulsants that cause weight gain (e.g. valproate) may not be the best option for an overweight patient, and topiramate or zonisamide may not be suitable for patients with a history of kidney stones. Some adverse effects of anticonvulsants can be minimized by gradually increasing the dosage. Overall, recent anticonvulsants have advantages such as better tolerability, better sedation, and fewer drug interactions. All anticonvulsants can cause an allergic scarlatiniform or measles-like rash. Some types of seizures can be aggravated by certain anticonvulsants. For example, pregabalin and lamotrigine may worsen myoclonic seizures; carbamazepine may worsen absence, myoclonic, and atonic seizures. Anti-convulsants are also associated with an increased risk of teratogenicity (in gestation). Fetal antiepileptic syndrome (cleft lips, cleft palate, cardiac abnormalities,

microencephaly, growth retardation, developmental delay, abnormal facies, digital or limb hypoplasia) occurs in 4% of children of epileptic mothers taking anticonvulsants during pregnancy; however, since uncontrolled generalized seizures during pregnancy can lead to fetal harm and death, prolonged pharmacological treatment is generally advisable. Women should be made aware of the risk of anticonvulsants to the fetus, and this should be taken into account: alcohol is more toxic to fetal development than any antiepileptic drug. Taking folic acid supplements before conception helps to reduce the risk of neural tube defects and should be recommended to all women who are of childbearing age and taking anticonvulsants. Many anticonvulsants decrease serum folate and B12 levels, so oral vitamin supplements can prevent this effect. However, the risk of teratogenicity is lower with monotherapy and varies depending on the drug; none is completely safe during pregnancy. The risk with carbamazepine, phenytoin, valproate, and benzodiazepines is relatively high; there is evidence that they have caused congenital malformations (spina bifida, fetal hydantoin syndrome, cleft lip palate, neural tube abnormalities); in particular, the risk of neural tube defects is somewhat higher with valproate than with other commonly used anticonvulsants, while the risk with some of the new drugs (e.g. lamotrigine) seems to be lower.

An analysis of the individual-specific anticonvulsant drugs currently on the market gives the following overview, taking into account that the dosage for adults is based on a weight of 70 kg (unless otherwise specified):

1) Acetazolamide. Acetazolamide is indicated for refractory absences. The dose is identical for adults and children: 4-15 mg/kg orally, 2 times/day (do not exceed 1g/day). Therapeutic levels are 8 to 14 mcg/mL (34 to 59 mcg/mL), while toxic if > 25 mcg/mL (> 106 mcmol/L). Adverse effects of acetazolamide include kidney stones, dehydration, and metabolic acidosis.

2) Carbamazepine. Carbamazepine is indicated for partial seizures, generalized and mixed tonic-clonic attacks, but not for absence, myoclonic or atonic seizures. The dose is 200-600 mg orally 2 times/day (the initial dose is the same for both normal and extended-release tablets), for adults, while for children it should be further distinguished. For children under 6 years of age, the dose is 5 to 10 mg/kg orally 2 times/day (tablets) or 2,5 to 5 mg/kg orally 4 times/day (oral suspension); for children from 6 to 12 years of age, the dose is 100 mg orally twice daily (tablets) or 2,5 mL (50 mg) oral 4 times daily (oral suspension); for children between 12 and 18 years of age, the dose is 200 mg orally twice daily (tablets) or 5 mL (100 mg) oral 4 times daily (oral suspension). Therapeutic levels are 4-12 mcg/mL (17-51 mcmol/L), while toxic levels are > 14 mcg/mL (> 59 mcmol/L). Adverse effects of carbamazepine include diplopia, dizziness, nystagmus, gastrointestinal disorders, dysarthria, lethargy, leukopenia (3000-4000/mcL), severe rash (in 5%). Idiosyncratic adverse effects include granulocytopenia, thrombocytopenia, liver toxicity, and spinal cord aplasia. If subjects are carriers of the HLA-B*1502 allele, particularly Asians, the risk of severe rash (Stevens-Johnson's syndrome or epidermal toxic necrolysis) is higher than the usual frequency of 5%. Thus, before prescribing carbamazepine, physicians must assess HLA, at least in Asians. Blood counts should be routinely monitored during the first year of therapy. Decreases in white blood cell counts and dose-dependent neutropenia (neutrophils < 1000/mcL) are frequent. Sometimes, if the drug cannot be easily replaced with another, decreasing the dose can manage these effects. However, if erythrocytes and white blood cells decrease rapidly, carbamazepine should be discontinued immediately.

3) Clobazam. This active ingredient is indicated for absence seizures; it is also indicated as an adjunctive therapy for tonic or atonic seizures in Lennox-Gastaut syndrome and refractory partial seizures with or without secondary generalization. The dose is 5 mg to 20 mg orally 2 times/day, for adults, and 5 to 10 mg orally 2 times/day (up to 20 mg orally 2 times/day with weight > 30 kg), for children. Therapeutic levels are currently not clearly defined. Side effects of clobazam include drowsiness, sedation, constipation, ataxia, suicidal ideation, drug addiction, irritability, and dysphagia.

4) Clonazepam. Clonazepam is indicated for atypical absence seizures in Lennox-Gastaut syndrome, atonic and myoclonic seizures, epileptic spasms, and possibly for absence seizures refractory to ethosuximide. The dose is initially 0.5 mg orally 3 times/day, up to 5-7 mg orally 3 times/day for maintenance (maximum: 20 mg/day), in adults, and initially 0.01 mg/kg orally 2 to 3 times/day (maximum: 0.05 mg/kg/day), increasing by 0.25-0.5 mg every 3 days until seizures are controlled or adverse events occur (usual maintenance dose: 0.03-0.06 mg/kg orally 3 times/day), in children. Therapeutic levels are 25-30 ng/mL, while toxicity is mentioned if > 80 ng/mL. Adverse effects of clonazepam include drowsiness, ataxia, behavioral abnormalities, and partial or complete tolerance to beneficial effects (usually in 1-6 months); rare serious reactions.

5) Divalproate. Divalproex is a compound consisting of sodium valproate and valproic acid and has the same indications as valproate; i.e. it is indicated for absence seizures (typical and atypical), partial seizures, tonic-clonic seizures, myoclonic seizures, juvenile myoclonic epilepsy, epileptic spasms, and neonatal or febrile convulsions. It is also indicated for tonic or atonic seizures in Lennox-Gastaut syndrome. The dose is the same for both adults and children: 10-15 mg/kg/day orally in doses 3 times/day (e.g. 5 mg 3 times/day), to be slowly increased, for example, from 5 to 10 mg/kg/day (1.67 to 3.33 mg/kg orally 3 times/day) at weekly intervals, especially if other drugs have been used (maximum: 60 mg/kg/day). Children may take delayed-release tablets (slow) once daily. The total daily dose is 8 to 20% higher than normal tablets. Delayed-release valproate may have fewer adverse effects, improving therapeutic adherence. Therapeutic levels are 50-100 mcg/mL (347-693 mcmol/L) before the morning dose, while toxicity is considered if > 150 mcg/mL (> 1041 mcmol/L). Adverse effects of Divalproex include nausea and vomiting, gastrointestinal intolerance, weight gain, reversible alopecia (in 5%), transient sleepiness, transient neutropenia, and tremor. Hyperammonemia encephalopathy may occur idiosyncratically. Fatal liver necrosis rarely occurs, particularly in young children with neurological deficits treated with multiple anticonvulsant drugs. The risk of neural tube defects is somewhat higher with Divalproex than with other commonly used anticonvulsants.

Since liver side effects are possible, patients taking Divalproex should perform liver function tests every 3 months for 1 year; if there is a significant increase in transaminases or ammoniaemia (> 2 times the normal value), the drug should be discontinued. Increases in ammoniaemia, up to 1.5 times the normal upper limit, can be tolerated without danger to the patient.

6) Eslicarbazepine. Eslicarbazepine is indicated for the treatment of partial seizures, as in monotherapy or additional therapy. Unlike carbamazepine and oxcarbazepine, eslicarbazepine is administered once a day, possibly improving adhesion. The effectiveness of eslicarbazepine, carbamazepine, and oxcarbazepine is comparable. The dose is initially, 400 mg orally once/day, increased by 400 mg to 600 mg/day at weekly intervals for a recommended maintenance dose of 800 to 1600 mg once/day. Hexlicarbazepine is not indicated for use in patients < 18 years of age. Side effects of eslicarbazepine include dizziness, diplopia, drowsiness, hyponatremia, suicidal ideation, and dermatological reactions including Stevens-Johnson's syndrome.

7) Ethosuximide. Ethosuccimide is indicated for seizures of absence. The dose is 250 mg orally 2 times/day increasing by 250 mg\ every 4-7 days (maximum: 1500 mg/day), in adults, while in children a specification is required. If the age is between 3 and 6 years, the dose is 250 mg orally once/day (maximum: 20 to 40 mg/kg/day), while if the age is over 6 years, the dose is 250 mg orally twice/day, increasing by 250 mg/day if necessary every 4-7 days (maximum: 1500 mg/day). Therapeutic levels are 40-100 mcg/mL (283-708 mcmol/L), while toxicity is considered if > 100 mcg/mL (> 708 mcmol/L); however, toxic levels have not been well established. Side effects of ethosuximide include nausea, lethargy, dizziness, and headaches. Idiosyncratic adverse reactions include leukopenia or pancytopenia, dermatitis, and systemic lupus erythematosus.

8) Felbamate. Felbamate is indicated for refractory focal onset crises and atypical absences in Lennox-Gastaut syndrome. The dose is initially 400 mg orally 3 times/day (maximum: 3600 mg/day), in adults, and initially 15 mg/kg/day orally (maximum: 45 mg/kg/day), in children. Therapeutic levels are 30-60 mcg/mL (125-250 mcmol/L), while toxic levels are not yet well defined. Side effects of felbamate include headache, fatigue, liver failure, and rarely spinal cord aplasia. Written informed consent is required from the patient.

9) Fosphenytoin. Fosphenytoin is indicated for the epileptic state, such as tonic-clonic seizures and complex partial seizures, but also the prevention of secondary seizures from head trauma and convulsive epileptic state. The dose is 10 to 20 phenytoin equivalents/kg EV or IM 1 time (maximum infusion rate: 150 phenytoin equivalents/min), both for adults and children. The dose of fosphenytoin is given in phenytoin equivalents: 1.5 mg fosphenytoin is equivalent to 1 mg phenytoin. Heart rate and blood pressure should be monitored if the maximum infusion rate is used, but not at a slower rate. Therapeutic levels are 10-20 mcg/mL (40 to 80 mcmol/L) and are considered toxic if > 25 mcg/mL (> 99 mcmol/L). Adverse effects of fosphenytoin include ataxia, dizziness, drowsiness, headache, itching, and paresthesias.

10) Gabapentin. Gabapentin is indicated as adjunctive therapy for partial seizures in patients aged 3 to 12 years and as adjunctive therapy for partial seizures, with or without focal to bilateral tonic-clonic seizures in patients aged ≥ 12 years. The dose is 300 mg orally 3 times/day (maximum: 1200 mg 3 times/day), in adults, while for children a specific dose should be made. If the age is between 3 and 12 years, the dose is 12.5-20 mg/kg orally 2 times/day (maximum: 50 mg/kg 2 times/day), while if the age is over 12 years, the dose is 300 mg orally 3 times/day (maximum: 1200 mg 3 times/day). Toxic and therapeutic levels have not yet been determined. Side effects of gabapentin include drowsiness, dizziness, weight gain, and headache and, in patients 3 to 12 years of age, drowsiness, aggressive behavior, moodiness, and hyperactivity.

11) Lacosamide. Lacosamide is indicated as second-line monotherapy or additional therapy for focal onset epileptic seizures in patients ≥ 17 years of age. The dose is 100 to 200 mg, orally 2 times/day, and is not indicated for patients < 17 years of age. Therapeutic levels are 5 to 10 ug/mL, while toxic levels are not well established. Lacosamide side effects include dizziness, diplopia, and suicidal ideation.

12) Lamotrigine. Lamotrigine is indicated as an additional therapy for partial seizures in patients ≥ 2 years, generalized seizures in Lennox-Gastaut syndrome, and generalized tonic-clonic seizures. In patients ≥ 16 years, lamotrigine is used as monotherapy for partial or secondarily generalized seizures after discontinuation of concomitant use of enzyme-inducing anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital) or valproate. Lamotrigine metabolism is increased by enzyme-inducing antiepileptic drugs and decreased by enzyme-inhibiting antiepileptic drugs (e.g. valproate). Valproate inhibits a broad spectrum of liver enzymes. Lamotrigine can have a particular synergistic effect when used in combination with valproate. The dosage in adults is: a) with enzyme-inducing anticonvulsants and without valproate: 50 mg orally once daily for 2 weeks, followed by 50 mg twice daily for other 2 weeks, then increasing by 100 mg/day every 1-2 weeks to the usual maintenance dose (150-250 mg orally twice daily); b) with valproate and with or without enzyme-inducing anticonvulsants: 25 mg orally every other day for 2 weeks, followed by 25 mg orally 1 v/day for 2 weeks, then increasing by 25-50 mg/day every 1-2 weeks to the usual maintenance dose (from 100 mg orally once daily to 200 mg twice daily). The dosage in patients aged < 16 is: a) with enzyme-inducing anticonvulsants and without valproate: initially 1 mg/kg orally 2 times/day for 2 weeks, followed by 2.5 mg/kg orally 2 times/day for 2 weeks, then 5 mg/kg orally 2 times/day (maximum: 15 mg/kg or 250 mg/day); b) with enzyme-inducing anticonvulsants and valproate: initially 0,1 mg/kg orally twice daily for 2 weeks, followed by 0,2 mg/kg orally twice daily for 2 weeks, then 0,5 mg/kg orally twice daily (maximum: 5 mg/kg or 250 mg/day); (c) with valproate and without enzyme-inducing anticonvulsants: initially 0,1-0,2 mg/kg orally 2 times/day for 2 weeks, followed by 0,1-0,25 mg/kg orally 2 times/day for 2 weeks, then 0,25-0,5 mg/kg orally 2 times/day (maximum: 2 mg/kg or 150 mg/day). No significant correlation between blood levels and pharmacological effect has been

observed. Common adverse effects of lamotrigine include headache, dizziness, drowsiness, insomnia, fatigue, nausea, vomiting, diplopia, ataxia, tremor, menstrual abnormalities, and rash (2 to 3%), which sometimes progress to Stevens-Johnson syndrome (in 1/50-100 children and 1/1000 adults). The risk of skin rash can be reduced by increasing the dosage more slowly, especially if lamotrigine is added to valproate. Lamotrigine can exacerbate myoclonic seizures in adults.

13) Levetiracetam. This medication is indicated as an adjunctive therapy for the following types of seizures: partial seizures in patients ≥ 4 years old, primarily generalized tonic-clonic seizures in patients > 6 years old, myoclonic seizures in patients > 12 years old, and juvenile myoclonic epilepsy. The dose is 500 mg orally 2 times/day (maximum: 2000 mg 2 times/day), in adults, and 250 mg orally 2 times/day (maximum: 1500 mg 2 times/day), in children. No significant correlation between blood levels and pharmacological effect has been observed. Adverse effects of levetiracetam include fatigue, weakness, ataxia, mood, and behavioral changes.

14) Oxcarbazepine. Oxcarbazepine is indicated for partial seizures in patients aged 4-16 years as additional therapy and for partial seizures in adults. The dose is 300 mg orally 2 v/day, increasing by 300 mg 2 v/day at weekly intervals as needed up to 1200 mg orally 2 v/day in adults, and initially from 4 to 15 mg/kg orally 2 v/day, increasing after 2 weeks to 15 mg/kg orally 2 v/day (usual maintenance dose) in children. The therapeutic level is 15 to 25 mcg/mL, while the toxic level has not yet been established with certainty. Adverse effects of oxcarbazepine include: fatigue, nausea, abdominal pain, headache, dizziness, drowsiness, leukopenia, diplopia, and hyponatremia (in 2.5%).

15) Perampanel. The perampanel is indicated as an additional therapy for partial seizures and generalized tonic-clonic seizures in subjects who have epilepsy and are ≥ 12 years old. The dose is initially 2 mg orally once daily, increased by 2 mg once daily at weekly intervals, depending on clinical response and tolerability, until the recommended maintenance dose of 8-12 mg once daily for partial seizures and 8 mg once daily for generalized seizures in the first instance. Perampanel is not indicated for use in children < 12 years of age. Side effects of perampanel include aggressiveness, behavioral and mood changes, suicidal ideation, dizziness, drowsiness and fatigue, irritability, falls, headache, nausea, vomiting, abdominal pain, weight gain, and gait disturbances.

16) Phenobarbital. This medication is indicated for generalized tonic-clinical seizures, partial seizures, epileptic state, and neonatal convulsions. The usual dose administered, in adults and adolescents (15 to 18 years of age), is 200-400 mg per day, elevated up to 500 mg per day for adults. In children 1 to 12 years of age and adolescents up to 15 years of age, the usual dose is 10 mg for each year of age. The dose for the epileptic condition is 15-20 mg/kg intravenously (maximum infusion rate: 60 mg/min or 2 mg/kg/min), for adults, and 10-20 mg/kg intravenously (maximum infusion rate: 100 mg/min or 2 mg/kg/min), for children. Generally, therapeutic levels are 10-40 mcg/mL (43-129 mcmol/L), while they are considered toxic if > 40 mcg/mL (> 151 mcmol/L). Adverse effects of phenobarbital include drowsiness, nystagmus, ataxia, and, in children, learning difficulties, and paradoxical hyperactivity. Idiosyncratic adverse effects include anemia and rash.

17) Phenytoin. This drug is indicated for generalized tonic-clonic secondary seizures, complex partial seizures, and epileptic convulsive state. It is also used to prevent secondary seizures to head trauma. The dosage for all indications, except for the epileptic state, is 4-7 mg/kg orally before bedtime, for adults, and initially, 2.5 mg/kg orally 2 times/day (usual maintenance dose: 2.5-4 mg/kg orally 2 times/day), for children. The dosage for the epileptic condition varies from 6 to 20 mg/kg intravenously, for children and until adulthood. Therapeutic levels are 10-20 mcg/mL (40 to 80 mcmol/L), while toxic if > 25 mcg/mL (> 99 mcmol/L). Adverse effects of phenytoin include megaloblastic anemia, gingival hyperplasia, hirsutism, adenopathy, and osteoporosis. Folic acid supplements (0.5 mg/day) can significantly reduce gingival hyperplasia. At elevated blood levels, phenytoin may cause nystagmus, ataxia, dysarthria, lethargy, irritability, nausea, vomiting, and confusion. Idiosyncratic adverse effects include rash, exfoliative dermatitis, and, rarely, exacerbation of seizures.

18) Pregabalin. Pregabalin is indicated as an additional therapy for partial seizures. The dose is initially 50 mg orally 3 times/day or 75 mg orally 2 times/day increasing to 200 mg orally 3 times/day or 300 mg orally 2 times/day (maximum: 600 mg/day); this active substance is not indicated for use in children < 18 years. No significant correlation between blood levels and pharmacological effect has been observed. Adverse effects of pregabalin include dizziness, drowsiness, ataxia, blurred vision, diplopia, tremors, weight gain. Pregabalin can exacerbate myoclonic seizures.

19) Tiagabine. This medication is indicated as an additional therapy for partial seizures in patients ≥ 12 years. The dose is 4 mg once/day orally, increased from 4 to 8 mg/day at weekly intervals up to 28 mg orally 2 times/day or 14 mg orally 4 times/day (maximum: 56 mg/day, for adults, and 4 mg orally 1 time/day, increased by 4 mg/day if necessary at weekly intervals up to 16 mg orally 2 times/day or 8 mg orally 4 times/day (maximum: 32 mg/day), for adolescents over 12 years of age. No significant correlation between blood levels and pharmacological effect has been observed. Adverse effects of tiagabine include dizziness, feeling empty-headed, confusion, slowing of thought, asthenia, tremor, sedation, nausea, and abdominal pain.

20) Topiramate. Topiramate is indicated for partial seizures in patients ≥ 2 years, for atypical absence seizures and as a second-line monotherapy or additional therapy for primarily generalized tonic-clonic seizures. The dose is 50 mg orally once daily, increasing from 25 to 50 mg/day every 1-2 weeks (maximum: 200 mg twice daily), for adults, and 0.5-1.5 mg/kg oral twice daily (maximum: 25 mg/day), for children 2 to 16 years of age. The therapeutic level is 5-20 mg/mL. Adverse effects of topiramate include: decreased concentration, paresthesia, fatigue, speech dysfunction, confusion, anorexia, weight loss, reduced sweating, metabolic acidosis, nephrolithiasis (1 to 5% of cases) and psychosis (1%).

21) Valproate. This medication is indicated for absence seizures (typical and atypical), partial seizures, tonic-clonic seizures,

myoclonic seizures, juvenile myoclonic epilepsy, infantile spasms, and neonatal or febrile convulsions. It is also indicated for tonic or atonic seizures in Lennox-Gastaut syndrome. Valproate inhibits a broad spectrum of liver enzymes. The dose is identical for adults and children (aged ≥ 10 years) 10-15 mg/kg/day orally in doses 3 times/day (e.g. 5 mg 3 times/day), to be increased slowly, e.g. from 5 to 10 mg/kg/day (1.67 to 3.33 mg/kg 3 times/day) at weekly intervals, especially if other drugs have been used (maximum: 60 mg/kg/day). Therapeutic levels are 50-100 mcg/mL (347-693 mcmol/L) before the morning dose and are considered toxic if > 150 mcg/mL (> 1041 mcmol/L). Adverse effects of valproate include nausea and vomiting, gastrointestinal intolerance, weight gain, reversible alopecia (in 5%), transient sleepiness, transient neutropenia, and tremor. Hyperammonemia encephalopathy may occur idiosyncratically. Fatal liver necrosis rarely occurs, particularly in young children with neurological deficits treated with multiple anticonvulsant drugs. The risk of neural tube defects is somewhat higher with valproate than with other commonly used anticonvulsants. Since it is possible to have adverse liver effects, patients taking valproate should perform liver function tests every 3 months for 1 year; if there is a significant increase in transaminases or ammoniaemia (> 2 times the normal value), taking the drug should be discontinued. Increases in ammoniaemia up to 1.5 times the normal upper limit can be tolerated without danger to the patient.

22) Vigabatrin. Vigabatrin is indicated as an additional therapy for partial seizures; it is also indicated for epileptic spasms. The dose is initially 500 mg orally 2 times/day, increasing by 250 mg 2 times/day each week as needed up to the usual maintenance dose of 1500 mg orally 2 times/day in adults. In children, on the other hand, it is necessary to increase up to 100 mg/kg/day orally in 1 week, then the usual maintenance dose of 100-150 mg/kg/day. No significant correlation between blood levels and pharmacological effect has been observed. Adverse effects of vigabatrin include drowsiness, dizziness, headache, fatigue, and irreversible visual field defects (requires periodic visual field assessments).

23) Zonisamide. Zonisamide is indicated as an adjunctive therapy for partial seizures in patients ≥ 16 years of age; it is also indicated as an alternative or adjunctive therapy for tonic or atonic seizures in Lennox-Gastaut syndrome. The dose is 100 mg orally once daily, increased up to 100 mg/day every 2 weeks (maximum: 300 mg twice daily). Zonisamide is not used in children < 16 years of age. Therapeutic levels are 15 to 40 mcg/mL (for levels > 30 mcg/mL, adverse effects on the central nervous system are likely to increase), while they are considered toxic if > 40 mcg/mL. Adverse effects of zonisamide include sedation, fatigue, dizziness, ataxia, confusion, cognitive impairment (e.g., difficulty finding words), weight loss, loss of appetite, and nausea. Less commonly, zonisamide can cause depression, psychosis, urinary stones, and oligohidrosis.

3. The new orientations and discoveries

Recently, a British study described the presence of an "epileptic network" of 320 genes, called "M30", which is associated with epilepsy. It is thought that the genes in the network are involved in the way brain cells communicate with each other. The results of the study suggest that when this network malfunctions it causes epilepsy: "The relationship between monogenic and polygenic forms of epilepsy is poorly understood and the extent to which the genetic and acquired epilepsies share common pathways is unclear. Here, we use an integrated systems-level analysis of brain gene expression data to identify molecular networks disrupted in epilepsy. (…) We identified a co-expression network of 320 genes (M30), which is significantly enriched for non-synonymous de novo mutations ascertained from patients with monogenic epilepsy and for common variants associated with polygenic epilepsy. The genes in the M30 network are expressed widely in the human brain under tight developmental control and encode physically interacting proteins involved in synaptic processes. The most highly connected proteins within the M30 network were preferentially disrupted by deleterious de novo mutations for monogenic epilepsy, in line with the centrality-lethality hypothesis. Analysis of M30 expression revealed consistent downregulation in the epileptic brain in heterogeneous forms of epilepsy including human temporal lobe epilepsy, a mouse model of acquired temporal lobe epilepsy, and a mouse model of monogenic Dravet (SCN1A) disease. These results suggest functional disruption of M30 via gene mutation or altered expression as a convergent mechanism regulating susceptibility to epilepsy broadly. Using the large collection of drug-induced gene expression data from Connectivity Map, several drugs were predicted to preferentially restore the downregulation of M30 in epilepsy toward health, most notably valproic acid, whose effect on M30 expression was replicated in neurons. (…) Taken together, our results suggest targeting the expression of M30 as a potential new therapeutic strategy in epilepsy". [19]

In the same line, the neurogenetic one, a more recent Italian research has stated that the epileptic crisis is due to a disorder in the passage of ions through the channels of neurons altered by a genetic mutation: "The mutation of genes causes a structural and functional alteration of the neuronal channels and therefore the flow of ions entering and leaving the nerve cells is no longer balanced: the imbalance in electrical regulation determines a hyperexcitability of brain cells and therefore the appearance of an epileptic crisis. It has thus been discovered that neonatal family seizures are linked to a pathology of the potassium channels determined by two different genes located on chromosomes 20 and 8, while epilepsy with nocturnal frontal seizures is due to a disease of the chlorine channels caused by several genes on chromosomes 20 and 15. Also, some generalized epilepsies, which can be accompanied by febrile seizures, are caused by diseases of the sodium channels, due to a gene located on chromosome 2". [20-22]

Recently, another Italian study has focused attention on the neuroinflammatory condition that favors epileptic symptoms: "It has been shown that neuroinflammation plays an important role in the genesis and progression of epilepsy; it is also accompanied by a high degree of localized oxidative stress, which can promote the onset of the epileptic attack. (...) Anti-neuroinflammatory therapy can have different effects depending on whether it is epilepsy caused by brain damage such as head trauma or stroke or central nervous system infections, where there is an important neuroinflammatory component before epileptic episodes or epilepsy with genetic and metabolic causes. In any case, it has been demonstrated that the ultra-micro compound Pealut (palmitoylethanolamide co-ultra micronized with Luteolin) can intervene

on the neuroinflammatory process modulating the action of non-neuronal cells and the effect of oxidative stress thanks to the antioxidant action of luteolin". (...) In the case of drug-resistant epilepsies, i.e. epilepsies in which the neuroinflammatory component may be the cause itself, the molecule may delay the onset of the epileptic episode; in all other cases, Pealut is a pharmacological support to the antiepileptic drug, which often cannot be ignored, facilitating its action no longer hindered by neuroinflammatory cells. The antiepileptic drug will, therefore, work on the activity of the neuron and the supportive drug will reduce the neuroinflammatory process obtaining an improvement in treatment". [23]

4. Conclusions

Epilepsy often has negative effects on social and psychological well-being. These effects may include social isolation, stigmatization or a real state of disability, poor academic performance, and on average lower occupations, but also learning difficulties, attention disturbances, and socialization problems. All aspects that deserve to be adequately addressed with the help of a psychotherapist, supported by the clinical staff. Progress in research is giving encouraging signals and new, less and less invasive, targeted therapies are passing the test of scientific reliability. It is assumed, in the recent future, that attention will be increasingly focused on the well-being of patients and their definitive recovery. The best pharmacological therapy is therefore one which, in addition to taking into account clinical and anamnestic aspects, also takes into account the patient's general well-being and quality of life.s

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