Epilepsy is a chronic neurologic disorder that affects about 0.7% of the population. Patients with epilepsy suffer from recurrent seizures, which can be focal or generalized in nature. Generalized seizures involve both cerebral hemispheres simultaneously, whereas focal seizures start as a specific focus in the brain, but they may be also secondarily generalized (called ‘focal to bilateral tonic-clonic seizures’). The new classification of seizure types and classification of epilepsies have been announced by the ILAE (International League Against Epilepsy) in 2017. Epilepsy is defined as having 2 or more unprovoked seizures. One seizure does not signify epilepsy (up to 10% of people worldwide have one seizure during their lifetime) (1, 2). However, epilepsy can also be diagnosed after one unprovoked seizure if additional data suggest that the risk of recurrent seizure is high (3).

As the first line of treatment, antiepileptic drugs (AEDs) are routinely used to control seizures.

AEDs treat the symptoms (seizures) but not the cause of epilepsy, there is no drug that inhibits the processes of epileptogenesis (4). There are currently three generations of AEDs (Table 1). The first-generation of AEDs were developed as early as 1912 (phenobarbital) through the 1970s. The first of the second-generation drugs, felbamate, was approved in 1993. The overall aim of developing newer AEDs is better efficacy, more favorable pharmacokinetics and fewer undesirable effects in comparison to the first-generation drugs. However, there are a lot of examples of the limitations of the second-generation anticonvulsant drugs, like Steven-Johnson syndrome with lamotrigine, cognitive impairment with topiramate, kidney stones with zonisamide and topiramate, encephalopathy and non-convulsive status epilepticus with tiagabine, life-threatening aplastic anemia or hepatic failure with felbamate. Moreover, not all of the second-generation drugs have favorable pharmacokinetics. An example might be felbamate, which is an inhibitor of CYP2C19 and CYP1A2, thus inhibiting the metabolism of several others AEDs. On the other hand, among the second-generation drugs, levetiracetam is an example of the drug with high oral availability (almost 100%), linear pharmacokinetics, minimal protein binding (<10%), no metabolism through P450 enzymes, and renal elimination (95% of the dose).
Third-generation anticonvulsant drugs
The third-generation of AEDs begins in 2008 with the approval of lacosamide in Europe and the United States (3). It includes also rufinamide, vigabatrin, retigabine, perampanel, eslicarbazepine acetate, brivaracetam, and stiripentol.

Lacosamide

Lacosamide (R-2-acetamido-N-benzyl-3-methoxypropionamide) a chiral functionalized amino acid molecule is an anticonvulsant drug with a unique mode of action, selectively enhancing slow inactivation of voltage-gated sodium channels (5). It is thought that slow inactivation may involve rearrangement of the inner pore structure of sodium channels, while fast inactivation is mediated by an intracellular peptide loop located between domains III-IV (4). Moreover, lacosamide is the first drug for which an interaction with the collapsin response mediator protein-2 (CRMP-2) has been described. This phosphoprotein, mainly expressed in the nervous system, is involved in neuronal differentiation and axonal growth. It has been reported, that the decrease of CRMP-2 may contribute to the pathomechanisms involved in temporal lobe epilepsy (6). The nature of the interaction between lacosamide and CRMP-2 is not completely known, it may directly bind with CRMP-2 or act by an indirect functional interaction with CRMP-2 (4). Chemically lacosamide is (R)-enantiomer, and it is at least 100 times more potent in seizure models compared to the (S)-enantiomer (Less et al., 2006). Lacosamide was approved as monotherapy or adjunctive therapy in adults (≥ 17 years) with partial-onset (focal) seizures in the United States, and as adjunctive treatment of partial-onset seizures with or without secondary generalization in patients with epilepsy, age 16 and over in the EU (7, 8). Currently, in the EU it is indicated as monotherapy and adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents and children from 4 years of age with epilepsy. Lacosamide is available in oral and intravenous forms with a maximum daily dose of 400 mg, divided twice daily (3). At doses > 400 mg/d, patients with known cardiac conduction disorders, severe heart disease, and parallel PR prolongation therapy should be carefully observed.

The pharmacokinetic properties of lacosamide include almost 100% bioavailability, biding with protein < 15%, a half-life of approximately 13 h, minimal cytochrome P450 interaction and excretion by the kidneys (unchanged about 40% of the dose, the remainder in the form of metabolites). Lacosamide has limited interactions with a range of other AEDs.

Common undesirable effects include dizziness, diplopia, headache, fatigue, nausea, and vomiting. Dizziness was reported in approximately 30% of patients and was the primary reason for discontinuation from clinical trials (9).

The efficacy and safety of adjunctive lacosamide have been demonstrated in randomized placebo-controlled trials that recruited patients with uncontrolled partial seizures (10, 11). Currently this drug, as well as the other second-line drugs, such as levetiracetam, topiramate, or pregabalin have been increasingly used for the treatment of status epilepticus.

Table 1. Anticonvulsant drugs.

<table>
<thead>
<tr>
<th>Specific anticonvulsant drugs</th>
<th>First-generation</th>
<th>Second-generation</th>
<th>Third-generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid</td>
<td>Valproic acid</td>
<td>Felbamate</td>
<td>Lacosamide</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Carbamazepine</td>
<td>Lamotrigine</td>
<td>Rufinamide</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Phenytoin</td>
<td>Tiagabine</td>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Ethosuximide</td>
<td>Topiramat</td>
<td>Ezogabine (retigabine)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Phenobarbital</td>
<td>Levetiracetam</td>
<td>Perampanel</td>
</tr>
<tr>
<td>Primidone</td>
<td>Primidone</td>
<td>Oxcarbazepine</td>
<td>Eslicarbazepine acetate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabapentin</td>
<td>Brivaracetam</td>
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<tr>
<td></td>
<td></td>
<td>Pregabalin</td>
<td>Stiripentol</td>
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<td></td>
<td></td>
<td>Zonisamide</td>
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</tbody>
</table>
ticus in humans (off-label use) (12, 13). Recently, it has been demonstrated in a multicenter open-label trial that lacosamide is efficacious and well-tolerated by the treated patients with uncontrolled partial-onset seizures as first add-on treatment at doses of 300-400 mg/day, which means that it can be added as a first adjunctive drug after a first monotherapy (14). Furthermore, other studies showed, that long-term therapies with lacosamide, both as monotherapy and as adjunctive treatment were efficient, generally well tolerated, with good safety profile (7, 15, 16). It seems to be a valued option for patients with focal epilepsy.

Lacosamide was also evaluated for the treatment of peripheral diabetic neuropathy initially with positive outcomes (17-19), however, recently its limited efficacy in this condition, even at higher doses has been reported (20, 21). Analgesic efficacy of lacosamide has not been adequately proved in any other neuralgia, and it is not licensed for the treatment of any painful conditions.

Rufinamide

Rufinamide (1-[(2,6-difluorophenyl) methyl]-1H-1,2,3-triazole-4 carboxamide) is a triazole derivative structurally unrelated to other AEDs. The mechanism of action of rufinamide is modulation of activity in sodium channels, particularly prolongation of the inactive state, resulting in a decrease of frequency of sustained repetitive firing (22). In the in vitro, studies rufinamide at 1 µmol/L or higher significantly slowed sodium channel recovery from inactivation after a prolonged prepulse in cultured cortical neurons from immature rats. It limited sustained repetitive firing of sodium-dependent action potentials, with an EC50 of 3.8 µmol/L (23).

Rufinamide is approved for adjunctive treatment for children 4 years and older and adults with Lennox-Gastaut syndrome (childhood drug-resistant epilepsy, with intellectual dysfunction and particular EEG abnormalities). In particular, it has shown adequate efficacy against tonic and atomic seizures (24). Rufinamide is available in oral form with a maximum daily dose of 3200 mg, divided twice daily. The pharmacokinetic properties include > 85% bioavailability, time to peak blood levels of 4-6 h, up to 35% protein bound, a half-life of 6-10 h. Rufinamide metabolism does not involve isoenzymes of the cytochrome P450. The main metabolic pathway is hydrolysis of the carboxyl-amidic group with the production of inactive metabolites which are eliminated through renal excretion (70%). Rufinamide levels can be modified by the concomitant administration of other AEDs. Valproic acid increases the plasma concentration of rufinamide up to 70%, whereas phenytoin, phenobarbital, and less carbamazepine can decrease levels by up to 40-50%. The efficacy of rufinamide in the treatment of Lennox-Gastaut syndrome, adult and pediatric focal seizures, and other epilepsy syndromes has been estimated through clinical trials (22, 25-27). Common adverse effects involved somnolence, fatigue, poor appetite, nausea, vomiting, and pyrexia. Rufinamide may induce potential arrhythmogenic risk since it does have a potential to shorten QT interval (28). It appeared to have a favorable cognitive profile (22). The new result from Phase IV study showed a consistent and generally favorable safety/tolerability profile of rufinamide used in routine clinical practice. Herein, the most frequently reported adverse effects were somnolence and decreased appetite (29). Moreover, it has been shown that rufinamide in children aged less than four years seems to be a safe and effective drug for a broad range of seizures and epilepsy syndromes (30).

Vigabatrin

Vigabatrin (vinyl-γ-aminobutyric acid) was designed as an analog of γ-aminobutyric acid (GABA). It is one of the newer anticonvulsant drugs, however, it was already introduced in 1989, but the Food and Drug Administration (FDA) approved this drug for use in the United States in 2009. The mechanism of action is irreversible inhibition of GABA-transaminase (GABA-T), which causes the increase of GABA in CNS and thereby vigabatrin inhibits excitatory processes that facilitate seizure activity (31). Vigabatrin is approved for adjunct treatment in refractory complex partial seizures in patients 10 years and older when all other antiepileptic drugs used in combination treatment are insufficient or poorly tolerated. Vigabatrin is also used in monotherapy as the first-line treatment.
The pharmacokinetic profile of vigabatrin includes > 60% bioavailability, no binding with protein, a half-life of approximately 5-10 h, no metabolism by cytochrome P450 enzyme and excretion by the kidneys. Vigabatrin is a racemic mixture and only S-enantiomers are active.

The most common adverse effects observed during treatment with vigabatrin include tiredness/fatigue, drowsiness, dizziness, depression, and ataxia. Whereas, concentric bilateral visual field deficit is the most serious adverse effect of vigabatrin and occurs in up to 30-45% of patients, and is related to dose and duration of treatment. Moreover, numerous studies have reported magnetic resonance imaging (MRI) signal abnormalities in the basal ganglia and brainstem in children with infantile spasm receiving vigabatrin. Nevertheless, despite these undesirable effects, vigabatrin demonstrated indisputable efficacy through randomized-controlled trials in patients with infantile spasm. Thus, according to the expert statement, the current benefit/risk ratio of vigabatrin as first-line therapy is considered to be positive in infantile spasm, given the severity of this epilepsy and the lack of a safer optional therapy.

Several studies have reported the efficacy of vigabatrin in the treatment of focal seizures in pediatric patients also with tuberous sclerosis complex (TSC) etiology. The results suggest that patients who start vigabatrin treatment at an earlier age may have better seizure outcome. Moreover, a shorter delay to treatment from seizure onset may also improve seizure outcome.

Retigabine (Ezogabine)

Retigabine (N-(2-amino-4-(4-fluorobenzylamino)-phenyl) carboxamid acid) was approved in Europe in 2011 and in the United States in 2010 as an adjunctive treatment of drug-resistant focal seizures with or without secondary generalization in patients aged 18 years or older with epilepsy, where other multiple alternative treatments have proved inadequate or have not been tolerated. However, in June 2017 the production of retigabine has been discontinued. Retigabine is a first-in-class voltage-gated potassium channels opener. It stabilizes neuronal potassium channels Kv7.2-7.5 (KCNQ2-KCNQ5) in the open position, thereby causing hyperpolarization and reduced firing of high-frequency action potentials. It has been reported that KCNQ2/Q3 channel mutations are connected with neonatal epilepsy. An additional mechanism of action involves selective positive modulation of GABA_A receptors, with preference for extrasynaptic receptors. The pharmacokinetic properties of retigabine include ~60% bioavailability, ~80% protein bound, time to peak plasma concentration of 0.5-2 h, a half-life of 6-8 h, and elimination of ~84% of the dose by the kidneys. Retigabine is partly metabolized to a less potent N-acetyl metabolite. It showed little or no potential to inhibit cytochrome P450 isoenzymes. Ezogabine is dosed orally, 3 times daily at a maximum daily dose of 1200 mg.

Several clinical trials have supported the efficacy of retigabine. Adjunctive therapy with this agent was generally well tolerated and reduced the frequency of partial-onset seizures in a dose-dependent manner. However, ezogabine has shown a number of unique adverse effects. As it targets potassium channels in a non-selective way, not only in the central nervous system, also in the smooth muscle of the bladder, it may reduce the contractility of the bladder smooth muscle, resulting in urinary retention and dysuria. Furthermore, the risk of retinal abnormalities, potential vision loss, and blue-grey discoloration, most notably on or near the lips, nails, and skin. In 2013 the FDA approved changes to the drug label (a black boxed warning) on the risks of abnormalities to the retina in the eye, potential vision loss, and skin discoloration that may become permanent. Retigabine may also prolong the QT interval. Additional adverse effects, similar to other anticonvulsant drugs include dizziness, somnolence, confusion, vertigo, fatigue, diplopia, hallucinations, psychotic symptoms, and ataxia.
Perampanel (2-(2-oxo-1-phenyl-5-pyridin-2-yl-1,2-dihydropyridin-3-yl)benzonitrile) is a novel AED approved in 2012 in Europe and the United States. It is a first-in-class selective noncompetitive antagonist at postsynaptic α-AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) glutamate receptors. Through this mechanism of action, perampanel reduces neuronal hyperexcitability and seizure occurrence. Moreover, a competitive AMPA receptor antagonist, selurampanel, is being studied in epilepsy. Competitive and noncompetitive AMPA receptor antagonists have similar profiles of efficacy in animal seizure models although noncompetitive antagonists should have stronger anticonvulsant activity, due to the inability of high glutamate levels, as seen in prolonged seizures, to overcome their blocking action (44). It is approved for adjunctive treatment of partial seizures with or without secondary generalization in adults and adolescents from the age of 12 years. Moreover, perampanel is approved as an adjunctive treatment for primary generalized tonic-clonic seizures in adults and adolescents from the age of 12 years with idiopathic, generalized epilepsy (45). Perampanel is available in an oral form with a maximum dose of 12 mg once daily. The pharmacokinetic properties include ~100% bioavailability, time to peak plasma concentration 0.5-2 h, 95% protein bound, half-life of 48-105 h. Perampanel is extensively metabolized in the liver by CYP3A4 to various inactive metabolites, thus dose adjustments are needed in patients taking anticonvulsant drugs that induce CYP3A4, like carbamazepine, oxcarbazepine, and phenytoin (46). Common undesirable effects associated with perampanel treatment were somnolence, dizziness, headache, fatigue, and irritability which were mild in severity in the majority of patients and more frequent at higher doses (47). Perampanel carries a black box warning for serious or life-threatening adverse effects, including aggression, hostility, irritability, anger, and homicidal ideation, which were the main reason of discontinuation of perampanel treatment (48). Also recently, it has been reported that perampanel was effective and exhibited a satisfactory tolerability profile. In another study, perampanel was fairly effective in children and adolescents with very refractory epilepsy, however, the rate of adverse events leading to discontinuation was considerable in this group (51).

Eslicarbazepine acetate

Eslicarbazepine acetate ((S)-10-acetoxy-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide), like carbamazepine and oxcarbazepine, is a dibenzazepine carboxamide analog, but it differs from them in its molecular structure, which results in differences in metabolism and pharmacology. Eslicarbazepine acetate is a prodrug of the active compound eslicarbazepine (S-licarbazepine), which is the main entity responsible for the pharmacological efficacy (52). Unlike carbamazepine, eslicarbazepine acetate is not metabolized to carbamazepine-10,11 epoxide, the active metabolite mainly responsible for the adverse effects, and is not susceptible to metabolic autoinduction.

The mechanism of action of eslicarbazepine acetate is still being examined. It inhibits voltage-gated sodium channels, especially in rapidly firing neurons. However, it has a much lower affinity for these channels in the resting state compared to carbamazepine and oxcarbazepine (53). On the other hand, metabolite of eslicarbazepine acetate – eslicarbazepine – like lacosamide reduces the availability of voltage-gated sodium channels through enhancement of slow inactivation, but lacosamide demonstrated higher interaction with these channels in the resting state, with fast inactivation gating and shorter time to enter in the slow inactivated state. Moreover, it has been found that eslicarbazepine acetate inhibits T-type voltage-gated calcium channels (Ca,3.2), in contrast to carbamazepine which inhibits P/Q-type calcium channels (Ca,2.1) (54). Eslicarbazepine acetate was approved by the European Medicines Agency (EMA) in 2009 and the US Food and Drug Administration (FDA) in 2013 as adjunctive therapy in adults with refractory
partial-onset seizures with or without secondary generalization (52). Currently, in the EU it is approved as adjunctive therapy in adults, adolescents and children aged above 6 years, with partial-onset seizures with or without secondary generalization and as monotherapy in the treatment of partial-onset seizures, with or without secondary generalization, in adults with newly diagnosed epilepsy. Eslicarbazepine acetate is available only in oral form with a maximum daily dose of 1600 mg. It is a one-daily anticonvulsant drug.

The pharmacokinetics are linear and dose-dependent and include > 80% bioavailability, < 40% protein bound, time to peak plasma concentration of 1-4 h, a half-life of 20-40 h, and elimination mostly by kidneys. Eslicarbazepine acetate is a weak inhibitor of CYP2C19 and a weak inducer of CYP3A4, but only few drug-drug interactions have been noticed (55).

Several studies have reported the efficacy of eslicarbazepine acetate for focal seizures, also when used as monotherapy (52, 56, 57). Most frequently reported adverse effects were dizziness, somno-lence, headache, diplopia, fatigue, and nausea. A case report of an intentional overdose of eslicarbazepine acetate presenting with recurrent seizures, hypoxemia and ventricular dysrhythmias has been reported (58). Eslicarbazepine acetate has also been examined for its utility in the treatment of bipolar disorder, but it is not currently approved for this condition (3).

**Brivaracetam**

Brivaracetam (2S-2-(4R)-2-oxo-4-propylpyrrolidinyl)-butanamide) is a selective, high-affinity ligand of the synaptic vesicle protein 2A (SV2A), which is located in presynaptic membranes of all synaptic vesicles in the central nervous system and regulates the calcium-dependent exocytosis of neurotransmitters into the synaptic cleft. It has a binding affinity approximately 15- to 30-fold higher than levetiracetam, another SV2A ligand, resulting in a dose approximately 10 times lower. Recently, levetiracetam and brivaracetam binding sites have been identified within the transmembrane hydrophilic core of SV2A (59). It has been shown that the expression of SV2A protein is significantly decreased during epileptogenesis suggesting that the progression of epilepsy may be influenced by this protein (44). Brivaracetam, in contrast to levetiracetam, does not interact with high voltage-gated calcium channels and with AMPA receptors.

Brivaracetam was approved in 2016 for adjunctive treatment of focal (partial-onset) seizures with or without secondary generalization in patients from the age of 16 years. Currently, it is approved in the United States also as monotherapy treatment of focal seizures in adults. Dosage forms include oral and intravenous formulations with a maximum daily dose of 400 mg/kg, twice daily (3). Furthermore, brivaracetam, like levetiracetam may find an indication for generalized epilepsies, as well as in progressive myoclonic epilepsies, which is currently being examined and needs further studies (60, 61).

The pharmacokinetic profile of brivaracetam is favorable and linear, with high oral bioavailability, time to peak plasma concentration of 0.25-3 h, very low protein binding, a half-life of approximately 8-9 h. The drug undergoes metabolism into inactive compounds, mainly through the hydrolysis of its acetamide group and to a lesser extent, via hydroxylation involving the cytochrome P450 CYP2C19. Brivaracetam has not shown any significant effect on CYP3A4 activity. Moreover, it does not significantly interact with other antiepileptic drugs and more than 95% of it is excreted through the urine, with an unchanged fraction of 8-11% (60). The only noticeable interaction is a modest increase in carbamazepine-epoxide when brivaracetam is co-administrated with carbamazepine (62, 63).

Efficacy of brivaracetam as an adjunctive treatment in patients with refractory partial seizures have been established in randomized, placebo-controlled clinical trials and meta-analyses. The safety profile of brivaracetam was favorable with mild to moderate undesirable effects that usually do not affect the compliance to the treatment. The most common adverse effects were somnolence, fatigue, dizziness, and rarely irritability (60, 64). As brivaracetam is a close analog of levetiracetam, it would be interesting to know which of them has better efficacy or tolerability for treating patients with refractory partial seizures. It has been recently reported that in patients with uncontrolled seizures add-on therapy with levetiracetam might have a slightly higher efficacy in comparison to brivaracetam. Moreover, treatment with levetirac-
etam was associated with a lower probability of dizziness (65). However, as the authors stated that several potentially confounding factors may have contributed to or attenuated these findings, hence further research is still needed. Additionally, it is worthy to note that in brivaracetam showed antiepileptogenic effects in kindling models in mice and this effect was more pronounced than the one obtained for levetiracetam (66). These evidence indicated than SV2A ligands may exert not only antiseizure activity but also antiepileptogenic or disease-modifying activity (67).

**Stiripentol**

Stiripentol (4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol), is structurally unrelated to the other anticonvulsant drugs. As a result of the presence of a chiral center at C-3, stiripentol is a racemic mixture of two enantiomers (68). Although

<table>
<thead>
<tr>
<th>Anticonvulsant drug</th>
<th>Mechanism of action</th>
<th>Indications (types of seizures/syndromes)</th>
<th>Common side effects</th>
<th>Serious side effects/overdose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacosamide</td>
<td>Slow inactivation of sodium channel/CRMP-2 binding</td>
<td>Focal</td>
<td>Dizziness, headache, diplopia, nausea</td>
<td>Hypotension, PR and QRS prolongation, conduction abnormalities</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Sodium-channel blockade</td>
<td>Focal, Lennox-Gastaut syndrome</td>
<td>Somnolence, dizziness, headache, nausea and vomiting, tremor, anorexia, diplopia, fatigue</td>
<td>Shortened QT interval, hematological abnormalities, life-threatening rash, suicidal ideation</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>↑ GABA via GABA-T</td>
<td>Focal, West syndrome</td>
<td>Fatigue, drowsiness, depression, ataxia</td>
<td>Permanent vision loss, fatal hepatitis, encephalopathy and coma, bradycardia, hypotension, status epilepticus</td>
</tr>
<tr>
<td>Retigabine/ezogabine</td>
<td>↑ K⁺ via potassium channels</td>
<td>Focal</td>
<td>Dizziness, somnolence, confusion, fatigue dysarthria, paresthesia, pigment changes (discoloration) of ocular tissues, blue-grey discoloration of the nails, lips and/or the skin</td>
<td>Potential vision loss, urinary retention, cardiac arrhythmia</td>
</tr>
<tr>
<td>Perampanel</td>
<td>↓ glutamate via AMPA receptor antagonism</td>
<td>Focal, generalized tonic-clonic seizures</td>
<td>Dizziness, somnolence, fatigue, ataxia, irritability</td>
<td>Aggression, psychosis, homicidal/suicidal ideation, stupor</td>
</tr>
<tr>
<td>Eslicarbazepine acetate</td>
<td>Sodium-channel blockade/Slow inactivation of sodium channel</td>
<td>Focal</td>
<td>Dizziness, somnolence, diplopia, headache, nausea and vomiting, ataxia, fatigue, insomnia</td>
<td>Hyponatremia, cerebellar syndrome, life-threatening rash, PR prolongation</td>
</tr>
<tr>
<td>Brivaracetam</td>
<td>Binds SV2A</td>
<td>Focal</td>
<td>Dizziness, somnolence, headache, fatigue</td>
<td>Severe somnolence</td>
</tr>
<tr>
<td>Stiripentol</td>
<td>↑ GABA via GABA A receptor</td>
<td>Dravet syndrome</td>
<td>Drowsiness, ataxia, insomnia, nausea, loss of appetite, weight loss, hypotonia, dystonia</td>
<td>Neutropenia, thrombocytopenia</td>
</tr>
</tbody>
</table>

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; CRMP-2, collapsing response mediator protein-2; GABA, gamma-aminobutyric acid; GABA-T, GABA-transaminase; SV2A, synaptic vesicle 2A. * References in the text
its mechanism of action has not been fully elucidated, evidence suggests an action of stiripentol on the neurotransmission mediated by γ-aminobutyric acid (GABA). More specifically, stiripentol potentiates GABAergic neurotransmission by acting directly on the GABA<sub>A</sub> receptors as a positive allosteric modulator (69). Another postulated mechanism of action may be inhibition of lactate dehydrogenase (LDH), an enzyme that is best known as a marker of disease and tissue injury (70). Recently, neuroprotective properties of stiripentol, by reducing sodium- and calcium-mediated neurotoxicity have been also reported (71). Stiripentol was originally approved in Europe in 2001 as an orphan drug for the treatment of Dravet’s syndrome (72). Currently, it is approved for use in combination with clobazam and valproate as adjunctive treatment of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate (36). The dose of stiripentol is calculated on a mg/kg body weight basis and divided into 2 or 3 doses.

The pharmacokinetic properties of stiripentol include oral bioavailability = 90%, 99% protein bound, time to peak plasma concentration of about 1-2 h, a half-life of 4.5-13 h, and elimination by the kidneys. Because of its inhibition of several cytochrome P450 enzymes, with high activity at human CYP1A2, CYP3A4 and CYP2C19, it has extensive pharmacokinetic interactions, including phenobarbital, clobazam, carbamazepine, phenytoin and valproate (73).

Results from clinical trials indicate that stiripentol is significantly better than placebo with regards to greater reduction in seizure frequency and severity in the majority of cases (74-76). Common adverse events have been related to a significant increase in plasma concentrations of valproate and clobazam after the addition of stiripentol. They include drowsiness, ataxia, nausea, abdominal pain and reduced appetite with weight loss. Also, neutropenia was occasionally observed (77).

Furthermore, the efficacy of stiripentol as add-on treatment for patients with focal refractory epilepsy, as well as for the treatment of super-refractory status epilepticus have also been evaluated in clinical trials (78, 79).

Selected compounds under clinical investigation
Ganaxolone
Ganaxolone (3α-hydroxy-3β-methyl-5α-pregn-20-one) is a synthetic analog of allopregnanolone. Like endogenous neurosteroids, it acts as a positive allosteric modulator of GABA<sub>A</sub> receptors, but without activation of progesterone receptors (80, 81). This agent exerts its inhibitory effect on neuronal excitability in two ways: rapid phasic inhibition via synaptic GABA<sub>A</sub> receptors activation and persistent or tonic inhibition through activation of extrasynaptic GABA<sub>A</sub> receptors. Both these actions occur at sites on the receptor complex that are distinct from those for benzodiazepines or barbiturates (44). At the moment, ganaxolone is being developed as an adjunctive therapy for the treatment of refractory focal seizures in adults. In the Phase II study ganaxolone given 1500 mg/day in adults with uncontrolled partial-onset seizures despite taking up to three concomitant antiepileptic drugs (AEDs) reduced seizures frequency and was generally safe and well tolerated. Observed common adverse events were mild to moderate in severity and included dizziness, fatigue, and somnolence (82). Moreover, the benefit from the use of ganaxolone had been also examined in patients with infantile spasms and continuing seizures. Ganaxolone was able to reduce spasm frequency and was found to be well tolerated with a good pharmacokinetic profile (83, 84). Recently, it has been suggested by Yawno et al. that ganaxolone may be an ideal antiseizure drug for the treatment of neonatal seizures because of its efficacy with a high safety profile and minimal or no adverse effects on the neonatal brain (81).

Cannabidiol
Cannabidiol is a phytocannabinoid compound derived from the cannabis plant. In contrast to tetrahydrocannabinol, it does not appear to have psychoactive effects. The mechanism of action is unknown, as cannabidiol has a very low affinity for the endocannabinoid receptors CB1 and CB2. A number of proposed mechanisms of anticonvulsant action of cannabidiol have been investigated and include antagonism at G-coupled protein receptor protein 55 (GPR55), blocking voltage-gated calcium (T-type) and sodium channels, an agonist effect at TRP channels, specifically in the TRPV1 channel, modulation of adenosine (A1 and A2) receptors, voltage-dependent anion-selective channel protein 1 (VDAC1), and tumour necrosis factor alpha (TNFα), among others (85). Cannabidiol is a potent inhibitor of CYP3A4, CYP2C19, and CYP2C9, which can increase concentrations of several other antiepileptic drugs (86). The results from an open-label trial, in patients (aged 1-30 years) with severe, intractable, childhood-onset, treatment-resistant epilepsy have indicated that cannabidiol might reduce seizure frequency. Most common adverse
effects include somnolence, decreased appetite, diarrhea, fatigue, convulsions, appetite changes, and status epilepticus, which was the most common serious adverse event (87). Recently, it has been reported in Phase III clinical trial in children with the Dravet syndrome, that a liquid formulation of purified cannabidiol showed a greater reduction in the median frequency of convulsive seizures per month compared to placebo treatment. Adverse events in the cannabidiol group included diarrhea, vomiting, fatigue, pyrexia, somnolence, and abnormal results on liver function tests (88). Currently, cannabidiol has an orphan drug designation for Dravet syndrome, infantile spasm, Lennox-Gastaut syndrome, and tuberous sclerosis complex (87).

Selurampanel

Selurampanel (N-[7-isopropyl-6-(2-methylpyrazol-3-yl)-2,4-dioxo-1H-quinazolin-3-yl]methanesulfonamide) is a competitive antagonist of the AMPA and kainate glutamate receptors. The dose-dependent antiseizure effect of selurampanel has been obtained in patients with photosensitive epilepsy (90). In the Phase II trial selurampanel (100 and 150 mg) was tested as add-on therapy to 1–3 antiepileptic drugs in patients with partial-onset seizures. Results showed no statistically significant dose–response relationship in selurampanel groups, however, reductions in the total partial seizure frequency over placebo were noted. Dizziness, somnolence, and fatigue were the most common adverse events (91).

Everolimus

Everolimus (40-O-(2-hydroxyethyl)-rapamycin) is a selective inhibitor of the mammalian/mechanistic target of rapamycin (mTOR) pathway. The mTOR signaling pathway regulates cell growth, differentiation, proliferation, and metabolism. However, hyperactivity of the mTOR pathway is associated with cellular alterations, including abnormal differentiation, proliferation, and growth. It has been found that inhibition of the mTOR pathway may prevent epilepsy (92). Everolimus had been developed as an antitumor drug and then approved for the treatment of several types of cancer (93). More recently, it has been approved to treat pediatric and adult patients with tuberous sclerosis complex (TSC), which is associated with epilepsy. Seizures are the most common neurological symptom of tuberous sclerosis complex, occurring in 80% to 90% of affected patients and are often refractory to antiepileptic treatment (93, 94). It has been reported that mTOR dysregulation has been involved in several genetic and acquired models of epileptogenesis. In preclinical studies, mTOR inhibitors showed not only an antiseizure activity but also an antiepileptogenic potential. The clinical reports support the promising potential of everolimus in treating epilepsy in patients with TSC. In the phase III, randomized, double-blind, placebo-controlled study, eligible patients aged 2-65 years with tuberous sclerosis complex and treatment-resistant seizures (≥ 16 in an 8-week baseline phase) receiving one to three concomitant antiepileptic drugs, everolimus treatment significantly reduced seizure frequency with a tolerable safety profile compared with placebo (95). Adverse effects associated with the mTOR inhibitors include infections of the upper respiratory tract, aphthous ulcers, fatigue, rash, mucositis, anorexia, gastrointestinal disorders, arthralgias, thrombocytopenia, and effects on lipid metabolism (96).

Moreover, other compounds with different mechanisms of action are currently in phases I-III of clinical development, namely adenosine, allopregnanolone, bumetanide, cannabidivarin, 2-deoxy-D-glucose, fenfluramine, huperzine A, minocycline, SAGE-217, and valnoctamide. Furthermore, numerous compounds or classes of compounds are investigated in preclinical studies, including bumetanide derivatives, sec-butyrylpropylacetamide, FV-082, 1OP-2198, NAX 810-2, and SAGE-689, among others (97).

Some limitations in pharmacotherapy of epilepsy

Although the administration of antiepileptic drugs allows freedom from seizures in approximately 75% of patients with epilepsy, the occurrence of adverse drug effects is still responsible for poor compliance as well as the discontinuation of the therapy in up to 25% of patients before having reached the effective dose amount. Moreover, patients who take a combination of AEDs are exposed to increased risk of drug-drug interactions (55).

Psychiatric undesirable effects and suicidal ideation/behavior after exposure to AEDs

It is worth to be highlighted that epilepsy, especially drug-resistant epilepsy, is associated with psychiatric comorbidities including depression, psychoses and anxiety disorders. About 30% of patients with newly diagnosed epilepsy and 50% of those with drug-resistant epilepsy are considered to be affected (98). The consequence of this is the fact that suicide prevalence in patients with epilepsy is approximately 2 times higher than that in the general population, occurring at a rate of about 12%.
Moreover, suicide attempts occur in 5-30% of patients with epilepsy compared to 1-7% in general population (99).

On the other hand, epilepsy treatment with anticonvulsant drugs can negatively affect mood, behavior and cognition. Recently, it has been reported in a retrospective study that one or more neuropsychiatric undesirable effects, including depression, aggression, irritable mood, anxiety, mood instability, paranoid ideation, delusions, hallucinations, and thought disorders, led to discontinuation of the anticonvulsant drug in 1.9-16.7% of patients. However, patients with pre-treatment psychiatric conditions were statistically more likely to discontinue the treatment with the new anticonvulsant drug compared to patients who had no previous psychiatric history (98). It has been demonstrated that levetiracetam, perampanel, and topiramate seem to be associated with increased rates of irritability, hostility, and/or aggression, particularly in patients with psychiatric symptoms (100). As mentioned above, perampanel carries a black box warning for serious or life-threatening psychiatric undesirable effects. No specific risk of aggression-related behavior has been reported in adult patients treated with carbamazepine, eslicarbazepine acetate, gabapentin, lamotrigine, oxcarbazepine, and retigabine. Similarly, children and adolescents who are treated with levetiracetam, perampanel (especially at higher doses), and topiramate, but also those taking gabapentin, sodium valproate, and zonisamide should be monitored closely for possible aggressive behaviors (100).

Anticonvulsant drugs should also undergo screening for suicidality during clinical studies and post-marketing surveillance. Since 2008, after the FDA issued an alert on an increased risk of suicide ideation and behavior in people with epilepsy treated with AEDs, a number of studies on this issue have been published (101). Among the first-generation drugs, phenobarbital has the highest risk of suicidality (even up to 47%) and the rate is dose-related. Thus treatment with this drug should be avoided in patients with depression or cognitive dysfunction (99). Furthermore, it has been reported that some first- and second-generation AEDs, including topiramate, zonisamide, levetiracetam, tiagabine, and felbamate may increase a risk of depression and suicidal ideation. Less risks (<1%) for depression have been associated with phenytoin, valproate, carbamazepine, oxcarbazepine, gabapentin, pregabalin, and lamotrigine (102).

Amongst the third-generation, anticonvulsant drugs, suicidal ideation and behavior have been noted for rufinamide, retigabine, perampanel, vigabatrin, brivaracetam, and lacosamide (37, 40, 47, 48, 103, 104). In the case of lacosamide, clinical trials did not report a statistically significant increase in depression and suicidal ideation (3). However, there has been case report of sudden episode of depression and suicidal ideation associated with the new onset therapy with lacosamide (105). Two cases of suicidal ideation when rufinamide was used in the treatment of refractory bipolar disorder have been reported (106). Yates et al. have noted a serious suicidal ideation and suicide attempt in one patient with epilepsy receiving levetiracetam who switched to brivaracetam (107). Huber and Schmid have reported that in patients with highly drug-resistant epilepsy and cognitive impairment, perampanel showed the highest rate of psychiatric adverse effects amongst anticonvulsant drugs, such as irritability, aggression, increased sensitivity, and suicidal ideation/behavior, which occurred in 30% of the patients and were the main reason to discontinue the drug (49). The experts emphasized that psychiatric adverse effects ranging from mild depression to aggression and suicidal attempts should be especially monitored in patients treated with perampanel and a history of psychiatric disorders (108).

Summing up, experts from ILAE stressed that suicidality in epilepsy is a multifactorial problem, and although treatment with some AEDs can be associated with suicidal ideation and behavior, the actual risk is very low. Moreover, the risk of stopping or even refusing to start AEDs is significantly worse and can result in serious harm including death of patient. Nevertheless, patients starting treatment with AEDs or switching from one to another drug should be advised to pay attention to any changes in mood and suicidal ideation (101).

Drug-resistant epilepsy

About 30% of epilepsy patients suffer from uncontrolled seizures despite pharmacotherapy, including the third-generation of anticonvulsant drugs. The International League Against Epilepsy Task Force proposed that “drug-resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”. Brodie et al. have reported that out of a total group of 1098 patients with newly diagnosed epilepsy only 49.5% of them remained seizure-free (i.e., not experiencing seizures for at least 1 year) on their first AED, while only 13.3, 3.7, 1.0, 0.4, 0.2, and 0.2% of the cohort became seizure-free on the second, third, fourth,
fifth, sixth or even seventh regimen (either as monotherapy or in combination), respectively (109). It is important to better understand these mechanisms, as refractory epilepsy is especially associated with increased morbidity and mortality, as well as cognitive problems, serious psychosocial consequences, and restricted quality of life. Recently, a review which summarizes various theories that have been proposed to clarify the mechanism(s) underlying refractory epilepsy has been reported by Tang et al. (110). Based on existing evidence the pharmacoresistance in epilepsy is a multifactorial phenomenon and can include mechanisms such as:

- the transporter hypothesis (overexpression of ABC transporters (especially P-glycoprotein) at the blood-brain barrier, the multidrug resistance-associated proteins – MRP or breast cancer resistance proteins – BCRP ),
- the target hypothesis (changes in voltage-gated ion channels and receptors, which resulted in diminished drug sensitivity),
- the gene variant hypothesis (variations in genes associated with AED pharmacokinetics and pharmacodynamics cause inseparable pharmacoresistance),
- the intrinsic severity hypothesis (common neurobiological factors which contribute to both epilepsy severity and pharmacoresistance),
- the neural network hypothesis (seizure-induced degeneration and remodelling of the neural network suppress the endogenous antiseizure system and inhibit AEDs from accessing neuronal targets),
- the pharmacokinetic hypothesis (abnormalities in AED plasma concentration range; overexpression of efflux transporters in peripheral organs such as intestine, liver or kidney; increased P-glycoprotein overexpression),

Authors summarised that each of these refractory mechanisms has its own strengths and weaknesses and none of these theories alone sufficiently explains pharmacoresistance in epilepsy.

Summary

Over the past few years, various anticonvulsant drugs with new mechanisms of action were introduced. The third-generation anticonvulsant drugs have some therapeutic advantages relative to the first- and the second-generation AEDs. The better part of these AEDs, except for perampanel and eslicarbazepine acetate, is that they are not metabolized via cytochrome P450 enzymes thus resulting in less drug-drug interactions. Most of the adverse effects caused by third-generation drugs are dose-depend-

ent. However, all anticonvulsant drugs should be screened for suicidal ideation or behavior. Moreover, despite the availability of these new drugs with favorable properties and new modes of action a significant proportion of patients still continue to experience seizures and the problem of refractory epilepsy still exists. Lastly, the anticonvulsant drugs work only symptomatically, currently there is no drug that inhibits the processes of epileptogenesis. However, a better understanding of the underlying mechanisms leading to epilepsy has permitted to find new therapeutic strategies. A new drug for seizure control is always welcome.

Therefore, numerous preclinical and clinical studies are still needed to be performed.

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