



Review

Third-generation antiepileptic drugs: mechanisms of action, pharmacokinetics and interactions

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Abstract:

This review briefly summarizes the information on the molecular mechanisms of action, pharmacokinetic profiles and drug interactions of novel (third-generation) antiepileptic drugs, including brivaracetam, carabersat, carisbamate, DP-valproic acid, eslicarbazepine, fluorofelbamate, fosphenytoin, ganaxolone, lacosamide, losigamone, pregabalin, remacemide, retigabine, rufinamide, safinamide, seletracetam, soretolide, stiripentol, talampanel, and valrocecide. These novel antiepileptic drugs undergo intensive clinical investigations to assess their efficacy and usefulness in the treatment of patients with refractory epilepsy.

Key words:

antiepileptic drugs, brivaracetam, carabersat, carisbamate, DP-valproic acid, drug interactions, eslicarbazepine, fluorofelbamate, fosphenytoin, ganaxolone, lacosamide, losigamone, pharmacokinetics, pregabalin, remacemide, retigabine, rufinamide, safinamide, seletracetam, soretolide, stiripentol, talampanel, valrocecide

Abbreviations: 4-AP – 4-aminopyridine, AED – antiepileptic drug, AMPA – α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, BIC – bicuculline, BRI – brivaracetam, CBM – carisbamate, CRB – carabersat, DMD – desmethyl-diazepam, DP-VPA – DP-valproic acid, ESL – eslicarbazepine, FFBM – fluorofelbamate, FPHT – fosphenytoin, GABA – γ -aminobutyric acid, GAERS – genetic absence epilepsy rat from Strasbourg, GNX – ganaxolone, LCM – lacosamide, LSG – losigamone, MES – maximal electroshock-induced seizures, NMDA – N-methyl-D-aspartic acid, PGB – pregabalin, PIC – picrotoxin, PTZ – pentetrazole, RMC – remacemide, RTG – retigabine, RUF – rufinamide, SAF – safinamide, SEL – seletracetam, SRT – soretolide, STP – stiripentol, SV2A – synaptic vesicle protein 2A, TLP – talampanel, UDP – uridine diphosphate, VLR – valrocecide

Third-generation (novel and potential) antiepileptic drugs

Despite the scientific progress in understanding the pathophysiological processes related to seizure initia-

tion, amplification and propagation in the brain, and despite the large number of first- and second-generation antiepileptic drugs (AEDs) available on the pharmaceutical market, there are still approximately 30% of epilepsy patients that are inadequately treated with the current frontline antiepileptic drugs (AEDs) [22]. For these patients, the most appropriate therapeutic option is presumably the combined administration of two or more AEDs or the application of novel (third-generation) AEDs [18–22]. Pharmaceutical companies have recently created and licensed approximately 20 novel AEDs, which belong to the third-generation category. At present, three different techniques are used to search for novel AEDs [22, 95, 127]. The first method is based on chemical and/or structural modifications of currently available AEDs. This is to obtain more efficacious drugs that will suppress seizures and/or drugs that have minimal or no adverse effects (i.e., less neurotoxic) compared to available maternal

AEDs. The second method is based on the initial screening of many chemical substances in search for compounds with anticonvulsant properties in both *in vivo* and *in vitro* experimental models of epilepsy. This technique allows the fortuitous discovery of compounds that possess antiseizure action in acute and chronic models of epilepsy. The third method used in the creation of novel AEDs is associated with pathophysiological processes that underlie seizure activity in the brain. Some compounds that selectively inhibit excitatory amino acid neurotransmission and/or enhance inhibitory neurotransmission in the brain may be useful as potentially effective AEDs. In other words, AEDs are selected in response to how they modify neurotransmission in the brain. Based on this technique, some drugs that selectively potentiate the γ -aminobutyric acid (GABA_A) receptor-mediated response or inhibit excitatory neurotransmission, such as N-methyl-D-aspartic acid (NMDA) or α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptor antagonists, have been created. In some cases, two or three techniques are simultaneously used in searching for novel AEDs that provide epileptic patients with successful treatment options [18–22, 95, 127].

The third-generation AEDs consist of 20 novel drugs, including brivaracetam (BRI), carabersat (CRB), carisbamate (CBM), DP-valproic acid (DP-VPA), eslicarbazepine acetate (ESL), fluorofelbamate (FFBM), fosphenytoin (FPHT), ganaxolon (GNX), lacosamide (LCM), losigamone (LSG), pregabalin (PGB), remacemide hydrochloride (RMC), retigabine (RTG), rufinamide (RUF), safinamide (SAF), seletracetam (SEL), soretolide (SRT), stiripentol (STP), talampanel (TLP) and valroceamide (VLR).

The aim of this review is to summarize our knowledge on the molecular mechanisms of action, activity profile in animal seizure models, pharmacokinetic profiles, drug interactions and the current clinical status of third-generation AEDs.

Brivaracetam (BRI) {(2S)-2-[(4R)-2-oxo-4-propylpyrrolidinyl]-butanamide}

Mechanism of action

Brivaracetam is a synaptic vesicle protein 2A (SV2A) ligand and is structurally related to levetiracetam

[127, 149]. The SV2A assists with the coordination of synaptic vesicle exocytosis and neurotransmitter release, especially for excitatory amino acids [100, 149]. Brivaracetam has inhibitory effects on voltage-dependent sodium currents [20].

Activity profile in animal seizure models

Like levetiracetam, BRI does not show anticonvulsant activity in acute seizure models (i.e., maximal electroshock-induced seizure (MES) and pentetrazole (PTZ)-induced seizure tests in rodents) [149]. It protects against secondarily generalized motor seizures in corneally kindled mice and against clonic convulsions in audiogenic-susceptible mice. The drug suppresses seizures in amygdala kindled rats and spike-wave discharges in the genetic absence epilepsy rat from Strasbourg (GAERS) [100]. Brivaracetam reduces the duration of active seizures in an animal model of acute, partially drug-resistant self-sustaining status epilepticus induced by perforant path stimulation in rats [149].

Pharmacokinetics

Brivaracetam is rapidly and almost completely absorbed after oral administration over approximately 2 h [128]. Less than 20% of the drug is bound to plasma proteins [132]. The elimination half-life of BRI is approximately 7–8 h [128]. It is eliminated by hepatic metabolism and its renal clearance is low. The metabolic pathways of BRI include hydrolysis of the acetamide group and liver microsomal cytochrome CYP2C8-mediated hydroxylation [133]. More than 95% of a dose is recovered in the urine within 72 h [132, 133, 149]. The total body clearance of BRI was reduced by 24–35% and the plasma half-life of BRI was prolonged from 14.2 to 17.4 h in patients with hepatic function impairment [20].

Drug interactions

Brivaracetam decreases plasma concentrations of carbamazepine and phenytoin [149]. It increases plasma concentrations of carbamazepine-10,11-epoxide [20]. A moderate reduction of the estrogen and progestin components of low-dose oral contraceptives was observed after BRI administration, without any impact on suppression of ovulation [20, 149].

Ongoing clinical trials

Brivaracetam is currently undergoing an intensive clinical assessment in adult patients with partial-onset seizures and as an add-on treatment in adolescents and adults (16–65 years) with refractory partial-onset seizures. It is also being tested in patients with photosensitive epilepsy [156]. Brivaracetam is examined in trials evaluating the pharmacokinetic profile of the drug in children (1 month–16 years) with epilepsy and during conversion to monotherapy in adult patients with partial-onset seizures [156].

Carabersat (CRB) [*trans*-(+)-6-acetyl-(4S)-(4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-(3R)-ol hemihydrate]

Mechanism of action

Carabersat does not bind to ion channels, purinergic, aminergic, opioid and other peptidergic receptors [19, 95]. It selectively interacts with its own binding site, which is not yet elucidated [19, 95]. Carabersat has no effect on sodium channels, GABAergic or glutamate pathways [19].

Activity profile in animal seizure models

Carabersat is effective against MES-induced seizures and *sc* PTZ-induced clonic seizures in rodents. The drug appears to slow the development of amygdala kindled seizures in rats [19].

Pharmacokinetics

The half-life of CRB is 24 h and its oral bioavailability is enhanced by food [19]. The drug is predominantly cleared by hepatic metabolism [19]. The pharmacokinetic profile of CRB in humans has not been clarified [19].

Ongoing clinical trials

At present, this AED is not under clinical trial evaluation.

Carisbamate (CBM) (formerly RWJ-333369) (S-2-O-carbamoyl-1-*o*-chlorophenyl-ethanol)

Mechanism of action

Molecular actions of CBM that contribute to its anti-epileptic activity have not been elucidated and remain under investigation [20, 21, 46, 66, 107].

Activity profile in animal seizure models

Carisbamate suppresses MES, PTZ, bicuculline (BIC), and picrotoxin (PIC)-induced seizures [66]. The drug reduces seizure severity in corneal kindled rats and in the hippocampal kindling model of partial epilepsy [66]. In GAERS rats, the drug suppresses the duration of spike-wave discharges [66]. Carisbamate reduces the frequency of spontaneous seizures in the kainic acid model of temporal lobe epilepsy [107]. The drug prevents the development of spontaneous recurrent seizures in the lithium/pilocarpine model of status epilepticus in rats [66, 107].

Pharmacokinetics

Carisbamate is rapidly and almost completely absorbed from the gut with a bioavailability of approximately 95% and with a peak plasma concentration achieved within 1–3 h [97]. Plasma protein binding of CBM is approximately 44% [157]. Total recovery in urine is approximately 94% with only about 2% as unchanged drug [96]. Carisbamate is extensively metabolized through O-glucuronidation (44% of the dose is recovered in the urine as S-glucuronide), and hydrolysis of the carbamate ester is followed by oxidation of the aliphatic side chain (resulting in chloromandelic acid, chlorobenzoic acid and chlorophenylglycine comprising 36% of the dose) [96, 88]. Chiral inversion to form the R-enantiomer followed by O-glucuronidation (11%) and hydroxylation of the aromatic ring followed by sulfation (5%) are minor routes of metabolism [97, 157]. The half-life of CBM is approximately 12 h [20, 21].

Drug interactions

Carisbamate reduces valproic acid and lamotrigine concentrations by 20% [36]. Carbamazepine reduces the concentrations of CBM by 36%, whereas lamo-

trigine and valproic acid have no impact on CBM concentrations [35, 36]. Concomitant administration of oral contraceptives reduces the concentrations of CBM by 20–30% [20, 21].

Ongoing clinical trials

Carisbamate is currently undergoing clinical evaluation of the long-term effectiveness, safety and tolerability of the drug as an add-on therapy in patients with partial onset seizures [156]. Furthermore, CBM is tested in patients with postherpetic neuralgia, diabetic peripheral neuropathy, and in prevention of migraines [156].

DP-valproic acid (DP-VPA) (phosphatidylcholine esteric conjugate of valproic acid)

Mechanism of action

DP-valproic acid is a phosphatidylcholine esteric conjugate of valproic acid, comprised of the drug attached to the sn-2 position of the lecithin [41]. The cleavage of DP-VPA and local release of valproic acid occurs selectively in response to paroxysmal neuronal activity by the enzyme phospholipase A2. The activity of phospholipase A2 is increased in neurons associated with epileptiform activity prior to seizures [18, 41].

Activity profile in animal seizure models

DP-valproic acid is active in the *sc* PTZ-induced clonic seizure test in mice [18]. The drug suppresses seizures induced by PIC in mice and rats. This drug protects audiogenic seizure-prone Frings mice against clonic and tonic seizures [18]. In contrast, the drug does not suppress spike-wave discharges in the GAERS rats [18].

Pharmacokinetics

DP-valproic acid is slowly absorbed after oral administration. Bioavailability of the drug is low, suggesting incomplete absorption mechanisms [41]. Food or bile significantly improve absorption. This drug is minimally metabolized by the liver [41] and is excreted

unchanged in the urine (39–57%), in the expired air (19–26%) and, in a small proportion, in feces [18].

Drug interactions

DP-valproic acid does not compete with valproic acid, carbamazepine, phenytoin for their plasma protein binding sites [18]. The drug itself does not cause the induction of carbamazepine metabolism [18]. Phenobarbital has no effect on plasma DP-VPA concentrations [18].

Ongoing clinical trials

At present, this AED is not under clinical trial evaluation.

Eslicarbazepine acetate (ESL) [(S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide]

Mechanism of action

Eslicarbazepine acetate only forms (S)-licarbazepine, which blocks voltage-gated sodium channels [6, 7, 112]. It inhibits sodium channel-dependent release of neurotransmitters with similar potency to carbamazepine and oxcarbazepine [13]. Eslicarbazepine acetate does not bind to receptors for benzodiazepine, GABA or glutamate [6, 7]. This drug competitively interacts with site 2 of the inactivated state of voltage-gated sodium channels [112], stabilizes the inactive form of the sodium channel and sustains repetitive neuronal firing [4, 112].

Activity profile in animal seizure models

Eslicarbazepine acetate is effective in the MES test and the amygdala kindling model in rodents [13]. It is also effective against seizures induced by PTZ, BIC, PIC and 4-aminopyridine (4-AP) [4].

Pharmacokinetics

Following oral administration, ESL is rapidly and extensively reduced in the liver to the major metabolite S-licarbazepine by liver esterases [58, 94]. Minor metabolites of ESL are R-licarbazepine and oxcarbazepine

pine, formed by non-microsomal cytochrome P450-mediated metabolism [2, 3, 94]. Approximately 95% of ESL appears in plasma as (S)-licarbazepine and only 5% undergoes chiral conversion to (R)-licarbazepine [5]. Eslicarbazepine acetate is not metabolized to carbamazepine-10,11-epoxide and is not susceptible to auto-induction. Approximately 30% of ESL binds to plasma proteins [20]. The half-life of ESL after single dose application is 8–17 h, while with repeated application, the half-life of ESL is 20–24 h [2, 3]. The total amount of ESL recovered in the urine is 40% within 24 h post-administration [93].

Drug interactions

Eslicarbazepine acetate has no effect on the activity of numerous cytochrome P450 isoenzymes, UDP-glucuronosyltransferase and epoxide hydrolases in human microsomes [2, 3]. It does not affect plasma concentrations of carbamazepine, lamotrigine, levetiracetam, topiramate, phenobarbital, or diazepam [54]. Conversely, warfarin, diazepam, digoxin, phenytoin and tolbutamide do not alter plasma concentrations of ESL [20]. It moderately inhibits (by 38%) CYP2C9-mediated 4-hydroxylation of tolbutamide and enhances (by 39%) UDP-glucuronosyltransferase 1A1-mediated ethinylestradiol glucuronidation [20].

Ongoing clinical trials

Eslicarbazepine acetate is currently being evaluated in patients with moderate hepatic impairment to determine its pharmacokinetics and metabolism after a single dose of the drug [156]. Furthermore, the drug is undergoing evaluation in clinical trials examining the safety, tolerability and efficacy of ESL in the treatment of patients with manic episodes of bipolar disorder [156].

Fluorofelbamate (FFBM) (2-phenyl-2-fluoro-1,3-propanediol dicarbamate)

Mechanism of action

Substitution of a hydrogen for a fluorine atom at the 2-position of the propanediol moiety of felbamate to form FFBM prevents the formation of the reactive toxic metabolite of felbamate known as atropaldehyde

[20, 21, 126]. Fluorofelbamate does not enhance GABA receptor-mediated responses. It decreases responses to NMDA and kainate receptor activation [103] and reduces voltage-dependent sodium currents [21]. The mechanisms of action of FFBM are similar to those observed for felbamate [20, 21, 126].

Activity profile in animal seizure models

Fluorofelbamate is effective against MES-induced seizures, 6 Hz psychomotor seizures and PIC induced clonic seizures in rats and mice [20, 126]. The drug blocks sound-induced seizures in the audiogenic seizure-prone Frings mice [21]. Fluorofelbamate reduces generalized seizures in the hippocampal kindling rat model of focal seizures and attenuates seizures in an animal model of acute, partially drug-resistant self-sustaining status epilepticus induced by perforant path stimulation in rats [103]. In contrast, the drug is ineffective against BIC and PTZ-induced seizures [20, 126].

Pharmacokinetics

Fluorofelbamate utilizes different metabolic pathways than felbamate and does not form reactive intermediates (atropaldehyde) in human liver preparations [113]. Bioavailability of FFBM is between 82–100%. The peak plasma concentration is reached within 2–6 h [21]. Urinary excretion is the primary route of elimination and is nine-fold higher than the fecal route [113].

Ongoing clinical trials

At present, this AED is not under clinical trial evaluation.

Fosphenytoin (FPHT) (disodium phosphate ester of 5,5-diphenylhydantoin)

Mechanism of action

Fosphenytoin is a prodrug of phenytoin and its primary cellular mechanisms of action are similar to the mechanisms of phenytoin on the modulation of voltage-dependent sodium channels [18, 19, 27].

Activity profile in animal seizure models

Fosphenytoin is effective in the MES test in mice and rats, similar to the effectiveness of the parent compound [19, 27].

Pharmacokinetics

Fosphenytoin, administered both *intravenously* or *intramuscularly*, is rapidly and completely converted to phenytoin in the heart, lungs, liver, spleen, kidneys, small intestine, and other organs of the human body [28, 43, 81, 152]. The plasma binding of FPHT is 95–99% [64, 82]. The mean FPHT conversion half-life is 8.5 min in children receiving comparable doses of phenytoin [122, 150]. Plasma FPHT and phenytoin concentration-time profiles are similar in adult patients [152]. This drug displaces phenytoin from its plasma binding sites [82, 108, 150].

Ongoing clinical trials

Clinical trials provide evaluation of the efficacy of FPHT in the treatment of patients with non-convulsive status epilepticus as well as in patients with recurrent malignant glioma [156].

Ganaxolone (GNX) (3 α -hydroxy-3 β -methyl-5 α -pregnan-20-one)

Mechanism of action

Ganaxolone is a 3 β -methylated synthetic analogue of the endogenous neurosteroid allopregnanolone and is a potent positive modulator of GABA_A receptors containing the α_1 , α_2 , α_3 , β_2 , and γ_{2L} subunits [32, 105]. Neuroactive steroids activate all GABA_A receptor isoforms, including those composed of α_4 and α_6 subunits [1, 32, 106]. Receptors that lack γ_2 and contain δ -subunits are especially sensitive to neurosteroids [127]. Ganaxolone increases chloride channel permeability within the GABA_A-benzodiazepine receptor-chloride ionophore complex [32, 106, 127].

Activity profile in animal seizure models

Ganaxolone is effective against *sc* PTZ and BIC-induced clonic seizures in mice and rats [127]. It sup-

presses seizures in the 6 Hz model in mice and corneal and amygdala kindling in rats [32, 127]. The drug has anticonvulsant activity against fluorothyl-induced seizures in immature rats and suppresses seizures induced by aminophylline in mice [106].

Pharmacokinetics

Ganaxolone is rapidly absorbed from the gut with the time to peak maximum concentration of 1.5–2 h after administration [84, 124]. It has a linear and dose-proportional pharmacokinetic profile and 99% of the drug is bound to plasma proteins [84, 104]. Ganaxolone is metabolized by microsomal cytochrome CYP3A4 isoenzyme to 16-OH-GNX [20]. Most of the orally administered drug is excreted *via* the fecal route. Approximately 20% is excreted *via* the renal route [117]. The plasma half-life of GNX is about 20 h [84]. Both high-fat and high-carbohydrate meals slightly delay absorption of GNX [20]. The peak plasma concentrations of GNX associated with high-fat meals is three times higher than with high-carbohydrate meal [20, 104, 106].

Drug interactions

Ganaxolone does not modify the plasma protein binding of valproic acid [104, 105]. In *in vitro* drug-drug interaction studies, GNX does not have significant interactions with other antiepileptic drugs. Moreover, phenobarbital, phenytoin and carbamazepine have no impact on the GNX interaction profile in children [80, 105, 117].

Ongoing clinical trials

Ganaxolone is undergoing clinical evaluation in children with infantile spasms and adult patients with uncontrolled partial-onset seizures [156].

Lacosamide (LCM) (formerly harkoseride) [(R)-2-acetamido-N-benzyl-3-methoxypropionamide]

Mechanism of action

Lacosamide is a functionalized amino acid because it is an optical antipode of the naturally occurring amino

acid L-serine [39, 40, 87]. It does not affect voltage-activated calcium channels (L-, N-, P/Q-, T-type) or voltage-activated potassium channels [51, 56]. It also does not modulate delayed-rectifier or A-type potassium currents [56, 86]. The drug does not mimic the effects as an allosteric modulator of GABA_A receptor currents [51, 56]. Lacosamide selectively enhances sodium channel slow inactivation with no effect on fast inactivation [57]. The drug displays affinity for the glycine strychnine-insensitive recognition site of the NMDA receptor complex [56], and allosterically blocks NMDA receptors with a specific action on receptors containing the NR2B subunit [20, 138].

Activity profile in animal seizure models

Lacosamide is active in the MES test in mice and rats [18]. The drug is also effective in the rat hippocampal kindling model of partial seizures and protects the Frings mice against sound-induced seizures [18, 138]. It is effective in animal models of status epilepticus, including perforant path stimulation, cobalt/homocysteine thiolactone and lithium/pilocarpine status epilepticus models in rats [51, 138]. The drug suppresses psychomotor seizures in the 6 Hz model and attenuates the development of amygdala kindling in rats [51]. Lacosamide is ineffective in the threshold PTZ test [19].

Pharmacokinetics

Lacosamide is rapidly and completely absorbed from the gut with a negligible liver first-pass effect and has an oral bioavailability of approximately 100% [51]. The peak plasma concentration of LCM occurs approximately 0.5–4 h after administration [20, 25]. The half-life of LCM is about 12–13 h. The drug is less than 15% protein bound [20]. Approximately 95% of the oral LCM dose is excreted in the urine either as unchanged drug (30–40%) or as O-desmethyl-LCM metabolite (30%) [14, 20]. Less than 1% of LCM is recovered in feces. The drug inhibits microsomal cytochrome CYP2C19 isoenzyme at concentrations greater than therapeutic plasma concentrations [20].

Drug interactions

Lacosamide does not affect the plasma concentrations of carbamazepine, phenytoin, levetiracetam, lamotrigine, topiramate, or valproic acid in epileptic patients

[14, 25]. It does not affect pharmacokinetics of metformin, digoxin, or oral contraceptives (ethinylestradiol and levonorgestrel) [20].

Ongoing clinical trials

Lacosamide is being evaluated in clinical trials as an adjunctive therapy in patients with partial seizures with or without secondary generalization, in painful distal diabetic neuropathy and chronic refractory neuropathic pain [156]. Additionally, LCM is considered for monotherapy for partial-onset seizures and in patients in migraine prophylaxis or with fibromyalgia syndrome [156].

Losigamone (LSG) {(±)-5(R,S)-α(S,R)-5-[(2-chlorophenyl)hydroxymethyl]-4-methoxy-2(5H)-furanone}

Mechanism of action

The S(+)-enantiomer (AO 242; (+)-5(R)-α(S)-5-[(2-chlorophenyl)hydroxymethyl]-4-methoxy-2(5H)-furanone) is more pharmacologically potent than R(-)-enantiomer (AO 294; (-)-5(S)-α(R)-5-[(2-chlorophenyl)hydroxymethyl]-4-methoxy-2(5H)-furanone) [78]. Losigamone presynaptically affects sodium channels by reducing the frequency of spontaneous and stimulus-induced epileptiform discharges in hippocampal slices [67]. It enhances chloride uptake in the absence of GABA and potentiates the effects of GABA [48]. Losigamone does not bind to the GABA_A-benzodiazepine receptor-chloride ionophore complex [48]. It suppresses NMDA-induced depolarization, but not that induced by AMPA [52]. Losigamone reduces potassium-evoked release of glutamate and aspartate from cortical slices [137].

Activity profile in animal seizure models

Losigamone is effective against MES-induced seizures and *sc* PTZ-induced clonic seizures in rodents [48]. It suppresses convulsions induced by BIC, nicotine, PIC and 4-AP [48]. The drug is also effective against audiogenic seizures in GAERS rats [48, 78].

Pharmacokinetics

Losigamone is rapidly absorbed from the gastrointestinal tract, with a peak plasma concentration observed within 2–3 h after administration [23, 114]. Losigamone is approximately 60% bound to plasma proteins. The half-life of LSG is 4–7 h. The oral clearance of the R(–)-enantiomer is 10-fold higher than that of S(+)-enantiomer [114]. The half-life of R(–)-enantiomer is 2.2 h, whereas it is 4.8 h for S(+)-enantiomer [145]. Approximately 15% of the orally administered LSG dose is excreted in the urine as a glucuronide conjugate. Losigamone undergoes oxidative biotransformation, forming five principal metabolites in humans (M1–M5) [145]. Metabolism of LSG is stereoselective, with M1 produced from S(+)-enantiomer and M3, M4, and M5 formed from R(–)-enantiomer [145]. Microsomal cytochrome CYP2A6 isoenzyme is involved in the metabolism of both enantiomers [145].

Drug interactions

Phenytoin and carbamazepine reduce plasma LSG concentrations [11, 12]. Valproic acid and lamotrigine do not affect LSG pharmacokinetics [11]. Losigamone does not affect plasma concentrations of carbamazepine, phenytoin, carbamazepine-10,11-epoxide, lamotrigine, antipyrine or caffeine [12]. It slightly reduces plasma valproic acid concentrations [145], but does not affect the pharmacokinetics of the oral contraceptive drugs containing ethinylestradiol and levonorgestrel [47].

Ongoing clinical trials

At present, this AED is not under clinical trial evaluation.

Pregabalin (PGB) [(S)-(+)-3-isobutyl-GABA]

Mechanism of action

Pregabalin is a specific ligand of the $\alpha_2\delta$ type 1 and 2 subunits of voltage-gated calcium channels, which attenuates depolarization-induced calcium influx at nerve terminals [143]. Pregabalin decreases calcium inward currents, and reduces glutamate, norepinephrine

and substance P content in the brain [49, 50]. The drug does not interact with NMDA receptors [55]. Although PGB is structurally related to GABA, it does not interact with either GABA_A or GABA_B receptors [15] and is not an inhibitor of GABA uptake or degradation [15, 18, 21].

Activity profile in animal seizure models

Pregabalin is effective against MES-induced seizures in mice and rats [18]. The drug is also effective in preventing threshold clonic seizures induced by PTZ [18]. Pregabalin partially suppresses threshold seizures induced by BIC and PIC, but not by strychnine [18–20]. It protects against audiogenic seizures in DBA/2 mice and prevents seizures in hippocampal kindled rats. In contrast, the drug does not reduce the incidence of spontaneous absence seizures in GAERS rats [15, 21]. Pregabalin protects and delays the occurrence of spontaneous seizures in the lithium-pilocarpine rat model of temporal lobe epilepsy [15].

Pharmacokinetics

Pregabalin is rapidly absorbed from the gut with a bioavailability of approximately 90%. The peak plasma concentration of PGB is achieved approximately 1 h after administration [17]. Pregabalin is not bound to plasma proteins [61]. The drug undergoes minimal metabolism (< 2%) and its half-life ranges between 5.8–6.3 h. Approximately 98% of the drug is eliminated as unchanged drug by renal excretion [21].

Drug interactions

Pregabalin does not affect the plasma concentrations of concomitantly administered antiepileptic drugs, nor do other antiepileptic drugs influence PGB concentrations [29]. It is devoid of enzyme inducing or inhibiting activity [18, 21]. The drug does not affect pharmacokinetics of oral contraceptives [15, 18, 21].

Ongoing clinical trials

Pregabalin is being evaluated in patients with partial-onset seizures as an add-on therapy and the drug is being compared to gabapentin or levetiracetam as an adjunctive therapy in patients with partial seizures [156]. It is also being tested as a monotherapy or an add-on therapy in both adult and pediatric patients

with refractory partial seizures as well as in patients with sleep problems or essential tremor [156]. Additionally, a comparison study has evaluated the efficacy of PGB in comparison to a ketogenic diet in patients with drug resistant epilepsy [156].

Remacemide hydrochloride (RMC) [(±)-2-amino-N-(1-methyl-1,2-diphenylethyl)- acetamide monohydrochloride]

Mechanism of action

Remacemide and its principal active desglycinyll metabolite are low-affinity non-competitive antagonists of NMDA receptors [120, 141]. It inhibits sustained repetitive firing in cultured neurons by blocking voltage-activated sodium channels [151]. The (S)-enantiomer of RMC is more potent than the (R)-enantiomer [44, 102].

Activity profile in animal seizure models

Remacemide and its principal active metabolite are effective in the MES test in mice and rats as well as in the hippocampal kindling model [18, 44]. Remacemide is also effective against NMDA, kainic acid and 4-AP induced seizures [19, 44, 151]. The drug suppresses audiogenic seizures in DBA/2 mice. Remacemide suppresses spike-wave discharges in the WAG/Rij rats and in the GAERS rats [44]. In contrast, RMC affords little or essentially no effect against PTZ, BIC, PIC or strychnine-induced seizures [18, 19]. The drug does not prevent corneal kindled seizures in rats [44].

Pharmacokinetics

Remacemide is rapidly absorbed from the gut and the peak plasma concentration is achieved within 1 h, whereas the desglycinyll metabolite takes 2–3 h [73]. Remacemide is 75% plasma protein bound, whereas its desglycinyll metabolite is 90% bound to plasma proteins [111]. The half-life of RMC is 3–4 h and desglycinyll metabolite is 12–15 h [111]. Remacemide inhibits microsomal cytochrome CYP3A4 and CYP2C9 isoenzymes [18, 135].

Drug interactions

Enzyme-inducing drugs (e.g., carbamazepine, phenytoin and phenobarbital) reduce the concentrations of RMC and the desglycinyll metabolite [33, 75, 102, 125]. Valproic acid has no effect on RMC pharmacokinetics [85]. Remacemide increases plasma concentrations of carbamazepine and phenytoin [33, 75, 102, 125].

Ongoing clinical trials

At present, this AED is not under clinical trial evaluation.

Retigabine (RTG) {N-[2-amino-4-(4-fluoro- benzylamino)-phenyl]-carbamic acid ethyl ester}

Mechanism of action

Retigabine activates potassium currents and thus reduces the excitability of neurons [98]. The drug is specific for the M-type potassium current, which is carried by KCNQ (Kv7)-type potassium channels [142, 155]. It shifts the activation of the KCNQ M-current to more hyperpolarized membrane potentials [142]. Retigabine acts on four neuronal KCNQ subunits (KCNQ 2–5), having no effect on the cardiac potassium channel KCNQ 1 subunit. It enhances GABA-activated chloride current responses and positively modulates GABA_A receptors containing β_2 or β_3 subunits [98, 130]. The effects of RTG on GABA_A receptors occur independent of the benzodiazepine site [79, 148]. Retigabine weakly blocks sodium and calcium channels and also stimulates synthesis of GABA [9, 109].

Activity profile in animal seizure models

Retigabine is effective against MES-induced seizures and *sc* PTZ-induced clonic seizures in mice and rats. The drug suppresses PIC, penicillin, kainic acid and NMDA-induced seizures but not against BIC or strychnine induced seizures [79, 121, 129, 130]. Retigabine is effective against audiogenic seizures in genetically epilepsy-prone (GEPR) rats [79] and DBA/2 mice [129]. It suppresses focal and secondarily-generalized seizures in amygdala kindled rats, hippocampal kindled rats, and corneally kindled mice [144].

The drug suppresses seizures in the cobalt/homocysteine thiolactone model of status epilepticus [121].

Pharmacokinetics

Retigabine is rapidly absorbed from the gut with an absolute bioavailability of 50–60% (not affected by food). The peak plasma concentration is achieved within 1.5 h after administration [63]. Retigabine is approximately 80% bound to plasma proteins and the elimination half-life of the drug is 8–11 h [63]. RTG undergoes biotransformation by N-glucuronidation and N-acetylation that results in the formation of 2 inactive N-glucuronides and an N-acetyl derivative that demonstrates minimal pharmacological activity [71]. The majority of drug and metabolites are renally excreted. Retigabine is not metabolized *via* microsomal cytochrome P450 isoenzymes [21, 70]. After drug intake, a considerable fraction of RTG is initially converted to the inactive N-glucuronides with a subsequent gradual release of free parent drug from N-glucuronide pool [20, 21, 74].

Drug interactions

Retigabine does not affect plasma concentrations of concomitantly administered carbamazepine, phenytoin, valproic acid, topiramate and phenobarbital [62]. It increases the metabolism of lamotrigine [72], but does not alter the pharmacokinetics or metabolism of oral contraceptives containing ethinylestradiol and norgestrel [21, 74]. Phenytoin and carbamazepine increase the clearance of RTG. In contrast, valproic acid and topiramate do not affect the pharmacokinetics of RTG [21].

Ongoing clinical trials

Retigabine is being examined in patients with partial refractory seizures and patients with postherpetic neuralgia [156].

Rufinamide (RUF) {1-[(2,6-difluorophenyl)methyl]-1H-1,2,3-triazole 4-carboxamide}

Mechanism of action

Rufinamide prolongs the inactive state of voltage-dependent sodium channels and limits sustained repetitive firing of sodium-dependent action potentials

in neurons [10, 18, 20, 154]. It does not interact with GABA, adenosine, NMDA or AMPA/kainate binding sites [10, 45].

Activity profile in animal seizure models

Rufinamide is effective against MES-induced seizures and *sc* PTZ-induced clonic seizures in mice and rats [10]. The drug suppresses BIC and PIC-induced seizures in mice [45, 154]. It also delays the development of kindling in cats [10].

Pharmacokinetics

After oral administration, the bioavailability of RUF is approximately 85% and its peak plasma concentration is reached within 5–6 h [10, 18, 20]. Rufinamide is 23–34% bound to plasma proteins. The half-life ranges between 8–12 h. Rufinamide is extensively metabolized in the liver, with only traces being recovered unchanged in the urine (2%) and feces (2%) [18, 20, 115]. It is metabolized *via* hydrolysis of the carboxamide group (78%) and by oxidative cleavage at the benzylic carbon atom (7%). This metabolic route is not dependent on the microsomal cytochrome P450 isoenzyme [18, 20]. Both metabolites are excreted in the urine (~85%) [115]. Rufinamide does not act as an inhibitor of the microsomal cytochrome P450 isoenzymes, however, RUF is a weak activator of the CYP3A4 isoenzyme [20, 115].

Drug interactions

Valproic acid and lamotrigine decrease, whereas phenytoin, phenobarbital and primidone increase the clearance of RUF [18, 20, 115]. In children, valproic acid administration leads to elevated concentrations of RUF by up to 70%. In contrast, carbamazepine, clonazepam, vigabatrin, and oxcarbazepine do not affect RUF oral clearance [20]. Similarly, RUF has no impact on plasma concentrations of carbamazepine, phenobarbital, primidone, oxcarbazepine, clonazepam or clobazam [110, 115]. Rufinamide decreases plasma concentrations of ethinylestradiol and norethindrone from oral contraceptives [20]. It has no effect on the pharmacokinetics of olanzapine, but decreases plasma concentrations of triazolam [18, 20].

Ongoing clinical trials

Rufinamide is undergoing evaluation in patients with refractory partial seizures, generalized anxiety disorder and during the assessment of the efficacy of the drug in comparison to ketogenic diet in patients with drug resistant epilepsy [156].

Safinamide (SAF) {(S)-(+)-2-4-[(3-fluorobenzyloxy)benzylamino]propanamide methanesulfonate salt}

Mechanism of action

Safinamide binds to the batrachotoxin-sensitive site 2 of the voltage-sensitive sodium channels [21]. It suppresses sustained repetitive firing by blocking sodium channels [59, 60]. Safinamide also blocks N- and L-type calcium channels and inhibits glutamate and aspartate release from synaptic terminals [19, 21]. It displays affinity for norepinephrine and dopamine uptake sites as well as σ_2 binding sites [21, 59, 60, 131]. The drug has no affinity for norepinephrine, dopamine, serotonin, glutamate or GABA receptors [31, 59, 60]. Safinamide is a highly selective and reversible monoamine oxidase type B (MAO-B) inhibitor, increasing neostriatal dopamine concentrations [24, 139]. It also reduces the free radical formation [99].

Activity profile in animal seizure models

Safinamide is effective in the MES test in mice and rats [59]. The drug is effective against BIC, PIC, strychnine, 3-mercaptopropionic acid induced seizures [59]. It suppresses seizures in amygdala kindled rats and protects against convulsions in the model of multifocal status epilepticus induced by systemic administration of kainic acid in rats [59, 60].

Pharmacokinetics

Peak plasma concentrations of SAF is achieved in 2 h after a single oral dose [42]. After repeated administration, peak plasma concentrations of SAF occur at 5–6 h [21]. It is 89% bound to plasma proteins [21, 99]. Approximately 70% of SAF is metabolized to

a major inactive metabolite, which is conjugated to a second metabolite. The half-life of SAF is 21–23 h [99].

Drug interactions

Enzyme-inducing antiepileptic drugs (such as phenobarbital and carbamazepine) decrease plasma SAF concentration by approximately 30% and shorten the half-life of SAF [99]. Safinamide has no inducing or inhibiting activity on various microsomal cytochrome P450 isoenzymes *in vitro* [99]. It does not affect plasma concentrations of carbamazepine, phenobarbital, valproic acid or lamotrigine [21, 60, 99].

Ongoing clinical trials

Safinamide is currently being examined in patients with early idiopathic Parkinson's disease as an add-on therapy with a single dopamine agonist or levodopa [156].

Seletracetam (SEL) [derivative of (S)- α -ethyl-2-oxo-pyrrolidine acetamide]

Mechanism of action

Seletracetam is a structural analogue of levetiracetam that selectively, stereospecifically and with high affinity (10-fold greater than levetiracetam) binds to the synaptic vesicle protein 2A (SV2A) [119, 127]. The SV2A protein assists with the coordination of synaptic vesicle exocytosis and neurotransmitter release [119, 127]. Seletracetam does not have any effect on nor does it bind to other CNS receptors, uptake systems or ion channel proteins, except for a selectivity towards the glycine receptors [20, 21]. It reduces high-voltage-activated calcium currents, but the drug does not modulate the low-voltage activated T-type calcium currents [16]. Seletracetam has no effect on voltage-dependent sodium or potassium currents [16].

Activity profile in animal seizure models

Seletracetam, like levetiracetam, does not show anti-convulsant activity in acute seizure models (i.e., MES and PTZ tests in rodents) [16]. In contrast, SEL protects against secondarily generalized motor seizures in corneally kindled mice and hippocampal kindled

rats [16]. The drug is effective against clonic convulsions in audiogenic seizure-prone mice and spike-wave discharges in the GAERS rats [16, 119].

Pharmacokinetics

Seletracetam is rapidly and nearly completely absorbed from the gut with an oral bioavailability of approximately 92%; it is 10% bound to plasma proteins [16, 20]. The peak to plasma concentration is reached within 1 h after administration. Seletracetam is metabolized and excreted as unchanged drug (25%) and as an inactive carboxylic acid metabolite (53%) in urine [20]. The major metabolic pathway consists of the hydrolysis of the acetamide group to form the carboxylic acid metabolite [20, 140]. The plasma half-life of SEL is approximately 8 h. Metabolite concentrations are approximately ten-fold lower than those of the parent compound [16].

Drug interactions

There is a low potential for interaction of SEL with other drugs or of other drugs with SEL. To date, no drug-drug interactions have been documented [16, 20, 127].

Ongoing clinical trials

Seletracetam is currently being clinically tested in adult patients from 18 to 65 years with partial-onset seizures and those currently taking levetiracetam [156].

Soretolide (SRT) [2,6-dimethyl-N-(5-methyl-3-isoxazolyl) benzamide]

Mechanism of action

Soretolide does not interact with glutamate or GABA receptors nor does it affect sodium or calcium channels. The mechanism of action of SRT is unknown [116].

Activity profile in animal seizure models

Soretolide is effective in the MES test in rodents [116]. The drug and its active metabolite are ineffective in protecting against PTZ, BIC and PIC-induced

clonic seizures and in blocking generalized seizures in the hippocampal kindling rat model [116].

Pharmacokinetics

Soretolide is absorbed rapidly from the gut with a peak plasma concentration achieved within 90 min. It is approximately 75% bound to plasma proteins. The half-life of the drug is 3–9 h [116]. Soretolide undergoes extensive oxidative metabolism by hydroxylation of the 5-methyl group of the isoxazole moiety forming the active metabolite, which is twice as potent as the parent compound [101, 116]. The hydroxylation is mediated by the microsomal cytochrome CYP1A2 and CYP2C19 isoenzymes. The peak concentration of the hydroxylated active metabolite is reached within 3 h and its half-life is 5–14 h [101, 116]. The active metabolite is transformed to the carboxylic acid [101, 116].

Drug interactions

Soretolide and its active hydroxylated metabolite inhibit the metabolism of phenytoin [116].

Ongoing clinical trials

At present, this AED is not under clinical trial evaluation.

Stiripentol (STP) [4,4-dimethyl-1-(3,4-methylenedioxyphenyl)-1-penten-3-ol]

Mechanism of action

Stiripentol possesses a chiral center at C-3 and therefore, the drug is a racemic mixture of two enantiomers: R(+)-STP and S(-)-STP [134]. Stiripentol inhibits the synaptosomal uptake of GABA [118], increases both the release of GABA and the duration of the activation of GABA_A receptors [37, 123] through a direct allosteric modulation of the GABA_A receptors containing α_3 and β subunits [65].

Activity profile in animal seizure models

Stiripentol is effective against MES, PTZ, BIC and strychnine-induced seizures in rodents [118].

Pharmacokinetics

Stiripentol is rapidly absorbed from the gut with a peak plasma concentration achieved within approximately 1.5 h after administration [8, 89]. Due to its insolubility in water and hepatic first-pass effect, however, the bioavailability of STP is relatively low. It is 99% bound to plasma proteins [89–91]. The drug shows non-linear (Michaelis-Menten) pharmacokinetics with a decrease in clearance with increasing STP dosage [90]. Approximately 18% of the STP dose is recovered in feces and 73% in the urine over 12 h [89–91]. There are five different metabolic pathways of STP: 1) conjugation with glucuronic acid, 2) oxidative cleavage of the methylenedioxy ring system, 3) O-methylation of catechol metabolites, 4) hydroxylation of the *t*-butyl group, and 5) conversion of the allyl alcohol side-chain to the isomeric 3-pentanone structure [8, 20, 21]. Overall, 13 metabolites are detected in humans. The most important pathway of STP transformation, however, is the opening of the methylenedioxy ring to generate catechol derivatives [21, 158]. Stiripentol inhibits microsomal cytochrome CYP3A4, CYP1A2 and CYP2C19 isoenzymes [146].

Drug interactions

Stiripentol increases plasma concentrations of phenytoin, carbamazepine, phenobarbital, valproic acid and desmethyl-clobazam [37, 90, 91, 147]. It decreases carbamazepine-10,11-epoxide formation [147] and inhibits the hydroxylation of desmethyl-clobazam through microsomal cytochrome CYP2C19 isoenzyme [37, 68, 147]. Combining STP with anti-vitamin K medications is prohibited in children [38].

Ongoing clinical trials

At present, this AED is not under clinical trial evaluation.

Talampanel (TLP) [7-acetyl-5-(4-amino-phenyl)-8,9-dihydro-8-methyl-7H-1,3-dioxolo(4,5H)-2,3-benzodiazepine]

Mechanism of action

Talampanel blocks AMPA receptors in a stereoselective and non-competitive fashion *via* an allosteric site

on the AMPA receptor channel complex [92]. Talampanel weakly inhibits kainate receptors [92, 136], and is the active (R)-enantiomer of GYKI 53405 [76].

Activity profile in animal seizure models

Talampanel is effective in the MES and PTZ tests in rodents [19, 21, 76]. The drug protects against amygdala kindled seizures in rats and suppresses chemically kindled seizures in mice [20, 76]. It is also effective in a mouse model of phenytoin-resistant status epilepticus [20, 76].

Pharmacokinetics

Talampanel is well absorbed from the gut and its plasma protein binding ranges from 67–88% [83]. It reaches peak plasma concentration approximately 2.5 h after administration and the elimination half-life is 4 h [30]. The half-life of TLP is 6–8 h after chronic administration [19]. Talampanel is metabolized to several metabolites, including 7-O-methyl catechol, 4'-N-acetyl and O- or N-glucuronidated compounds [19, 21, 53]. The N-acetyl metabolite of TLP produced by hepatic N-acetyl-transferase 2 exerts moderate pharmacological activity *in vivo* [76]. The drug is an irreversible inhibitor of microsomal cytochrome CYP3A4 isoenzyme [19].

Drug interactions

Talampanel increases the plasma concentration of carbamazepine. Enzyme-inducing antiepileptic drugs (phenytoin and carbamazepine) reduce plasma TLP concentration [83]. Talampanel has no effect on plasma lovastatin concentrations [19]. Chronic administration of valproic acid does not affect the pharmacokinetic parameters of either TLP or its N-acetyl metabolite [34].

Ongoing clinical trials

Talampanel is currently being examined in patients with amyotrophic lateral sclerosis, adults with partial seizures, patients with recurrent glioma or advanced Parkinson's disease [156].

Valrocecimide (VLR) (N-valproyl glycineamide)

Mechanism of action

Valrocecimide is an N-valproyl derivative of GABA and glycine [22]. The mechanism of action of the drug is currently unknown [21, 22, 77].

Activity profile in animal seizure models

Valrocecimide is effective against MES-induced seizures and *sc* PTZ-induced clonic seizures in mice and rats [77]. The drug is also effective in the corneal and hippocampal kindling models in rats [20]. Valrocecimide suppresses audiogenic seizures in the Frings mouse model and in the lethargic mouse model [19, 21]. It protects the animals against BIC and PIC-induced clonic seizures and 6 Hz psychomotor seizures in mice [21, 22, 77]. It also suppresses focal seizures in corneally kindled rats [22, 77].

Pharmacokinetics

Valrocecimide is absorbed rapidly from the gut and its bioavailability is approximately 88% [19, 21, 22]. The half-life of VLR ranges between 6.4–9.4 h [69]. After oral dose, about 10–20% of VLR is excreted unchanged in the urine and 40% of the dose is excreted as valproyl glycine [22, 26, 153]. The renal clearance of unchanged drug and valproyl glycine account for 57–75% of the oral clearance [26]. The fraction of VLR metabolized to valproic acid is 4–6% [153]. Valrocecimide and valproyl glycine do not inhibit microsomal cytochrome P450 isoenzymes and epoxide hydrolase in liver microsomes [18–22].

Drug interactions

Valrocecimide metabolism is increased by enzyme-inducing co-medication such as carbamazepine or phenytoin [19]. Valrocecimide reduces the midazolam concentration [20, 21].

Ongoing clinical trials

At present, this AED is not under clinical trial evaluation.

Conclusions

The development of novel and potential (third-generation) AEDs has been possible due to our enhanced understanding of the pathophysiological mechanisms of epileptogenesis and neuronal hyperexcitability. These AEDs have multiple diverse molecular mechanisms of action and thus may offer a novel and advantageous approach to the treatment of epilepsy, especially in patients with refractory seizures. Moreover, third-generation AEDs may offer better tolerability, milder adverse effects, less drug or hormonal interactions and improved pharmacokinetic characteristics compared to the first- and second-generation AEDs. Currently, however, there are very limited data available to make definitive conclusions as to the likely role of these AEDs in the management of refractory epilepsy. It should be mentioned that only clinical trials provide us with complete information on the efficacy, safety and tolerability of the third-generation AEDs. Additional clinical studies are therefore required in order to verify the efficacy of the AEDs in specific forms of epilepsy. Conversely, some of the third-generation AEDs can be readily applied not only in patients with epilepsy, but also in patients with neuropathic pain, migraines or Parkinson's disease. Considering these facts, the third-generation AEDs may be advantageous for patients with refractory epilepsy.

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