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Pharmacological Management of Epilepsy

Recent Advances and Future Prospects

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Abstract

There is still a need for new antiepileptic drugs (AEDs) as the clinical efficacy, tolerability, toxicity or pharmacokinetic properties of existing AEDs may not be satisfactory. One new AED has recently been approved (rufinamide in 2007) and six others are in late-stage development (phase III and onwards) [brivaracetam, carisbamate, eslicarbazepine, lacosamide, retigabine and stiripentol]. The purpose of this review is to provide updated data on proposed mechanisms of action, efficacy and tolerability on these new AEDs, and to discuss the rationale for their development and possible advantages compared with existing treatment, based on recent publications and MEDLINE searches.

Rufinamide, brivaracetam and stiripentol have been given the status of orphan drugs. Rufinamide was approved in Europe in 2007 for the use in Lennox-Gastaut syndrome. Brivaracetam has gained orphan status for development in progressive and symptomatic myoclonic seizures in Europe and the US, respectively. Stiripentol has gained orphan status in children with Dravet's syndrome and pharmaco-resistant epilepsy. All of these drugs demonstrate efficacy as adjunctive therapy in partial seizures. Three of the drugs are derivatives of existing AEDs: brivaracetam is a derivative of levetiracetam with improved affinity for the target molecule; carisbamate is a derivative of felbamate with improved tolerability; and eslicarbazepine is a derivative of carbamazepine with less interaction potential and no auto-induction. Lacosamide, retigabine, rufinamide and stiripentol are new compounds, unrelated to other AEDs.

Further investigation and development of new broad-spectrum drugs is important for improved treatment of patients with epilepsy and other neurological and psychiatric disorders.

There is still a need for new antiepileptic drugs (AEDs), as the clinical efficacy, tolerability, toxicity or pharmacokinetic properties of existing AEDs may not be satisfactory.[1] Any new compounds have to fulfil these requirements for satisfactory efficacy, tolerability and pharmacokinetic properties to become a successful second-generation of AEDs.[2] AEDs consist of a heterogenous group of drugs with different properties, and their mechanisms of action are not completely understood. Most AEDs probably have more than one mechanism of

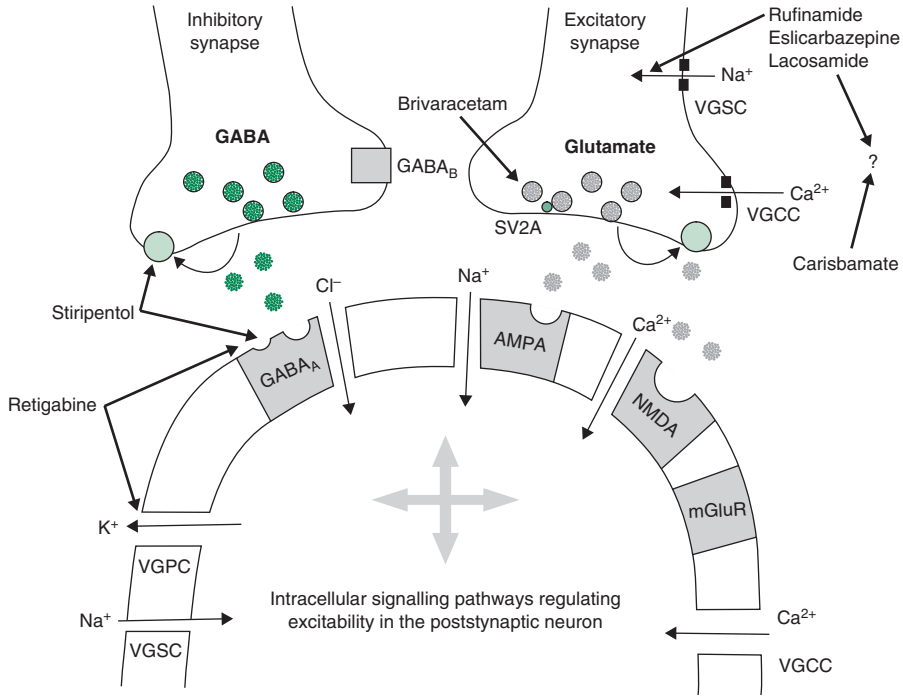

Fig. 1. Proposed mechanisms of action for new antiepileptic drugs (AEDs) that have recently been approved or are in late-stage development. Proposed molecular targets for these new AEDs are shown, with dark arrows pointing to the $GABA_A$ receptor, GABA reuptake, the synaptic vesicle protein 2A (SV2A), intracellular signalling proteins, and voltage-gated sodium channels (VGSC) and voltage-gated potassium channels (VGPC). The mechanism of action of carisbamate is still not known. **AMPA** = α-amino-3-hydroyx-5-methyl-4-isoxazolepropionic acid; **mGluR** = metabotropic glutamate receptor; **VGCC** = voltage-gated calcium channel.

action that may contribute to the various therapeutic effects.[3,4]

The proposed mechanisms of action of AEDs are in the synapses by the main inhibitory neurotransmitter GABA and the main excitatory neurotransmitter glutamate, with their main targets for pharmacological action illustrated in figure 1. The main pharmacodynamic mechanisms responsible for the clinical efficacy of AEDs include increased GABAergic or decreased glutamatergic neurotransmission, inhibition of voltage-gated ion channels or modifications of intracellular signalling pathways.[5,6] A common result of pharmacological intervention with these drugs is a decrease in neuronal excitability.

Several AEDs have recently been marketed or are in development. One new AED has recently been approved (rufinamide in 2007) and six others are in late-stage development (phase III and onwards) [brivaracetam, carisbamate, eslicarbazepine, lacosamide, retigabine and stiripentol] (table I). The purpose of this review is to update the pharmacology, efficacy and tolerability of these AEDs, and to discuss the rationale for their development and possible advantages compared with existing treatment.

1. Search Strategy and Selection Criteria

The present review is based on recently published articles and searches in MEDLINE via PubMed (October 2007 to July 2008). Relevant peer-reviewed articles in recognized international journals in English, from the earliest relevant data (1997–2008), were included in the review. Primary sources were preferred, but review articles of specif-

ic importance were also included. Relevant published case reports were included and also abstracts when a complete published article was not available. Unpublished or non-English material and articles of limited relevance, out-of-date results or inappropriate choice of methodology were excluded. The content in the present review was limited to AEDs that have recently been approved or drugs in late-stage development (phase III and onwards). The following search terms were used: 'retigabine', 'rufinamide', 'lacosamide', 'carisbamate', 'eslicarbazepine', 'brivaracetam' and 'stiripentol', in combinations with 'pharmacology', 'efficacy', 'tolerability', 'orphan drug' and 'phase III'.

2. Pharmacological Management of Epilepsy with Newer Antiepileptic Drugs

The documentation on preclinical and clinical studies regarding the AEDs that have recently been approved or are in late-stage development are presented and reviewed in alphabetical order in sections 2.1–2.7. The chemical structures of these compounds are shown in figure 2.

2.1 Brivaracetam

Two promising novel drug derivatives of levetiracetam are in development, brivaracetam (ucb 34714) and seletracetam (ucb 44212), and brivaracetam has been selected for further clinical development. Brivaracetam has been substituted in the 4-position in the 2-pyrrolidinone ring with one additional chiral centre, giving two stereoisomers, and stereoselectivity in the binding of these molecules seems likely to occur with a potentiated bind affinity.[7,8] The rationale for the development of brivaracetam was to improve the affinity for the target protein. Brivaracetam optimizes the unique mechanism of action of levetiracetam and may further improve medical management of epilepsy.[9-12]

2.1.1 Pharmacology

Brivaracetam is a derivative of levetiracetam. Levetiracetam is a unique broad-spectrum AED that did not show any effect in the commonly used epilepsy models, but was effective in a genetic absence epilepsy model (GAERS).[7,8,13] However, brivaracetam has recently demonstrated a broader anticonvulsant profile by protecting against electrically- and chemically-induced seizures.[9] A novel binding site for levetiracetam, the synaptic vesicle protein 2A (SV2A), was identified in the presynaptic neuron.[10] Brivaracetam could possibly have a broader therapeutic spectrum than the original drug because it also inhibits voltage-gated sodium channels.[12,14,15] Brivaracetam is a reversible and selective ligand for SV2A (inhibition constant [pKi] = 7.1) and displays a 25-fold higher affinity than levetiracetam (pKi = 6.1) for the target molecule SV2A.[16,17] It is still unclear how the drugs interact with the target protein SV2A, but they may be

Table I. Antiepileptic drugs (AEDs) that have recently been approved or are in late-stage development

New AED	Status	Characteristics
Brivaracetam	Phase III ongoing Orphan drug status (Europe and US): progressive myoclonic seizures (Unverricht-Lundborg)	Derivative of levetiracetam, increased selectivity for synaptic vesicle protein 2A
Carisbamate	Phase III ongoing Adjunctive therapy in partial seizures	Derivative of felbamate, increased tolerability
Eslicarbazepine acetate	Phase III ongoing Adjunctive therapy in partial seizures	Derivative of carbamazepine, increased tolerability, no auto-induction
Lacosamide	Phase III ongoing Adjunctive therapy in partial seizures	New AED: new proposed mechanisms of action, well tolerated in polytherapy
Retigabine	Phase III ongoing Adjunctive therapy in partial seizures	New AED: activates neuronal potassium channels
Rufinamide	Approved in Europe Orphan drug status: Lennox-Gastaut syndrome	New AED: sodium channel antagonist
Stiripentol	Orphan drug status: Dravet's syndrome	AED that has been in development for several years Potent cytochrome P450 inhibitor

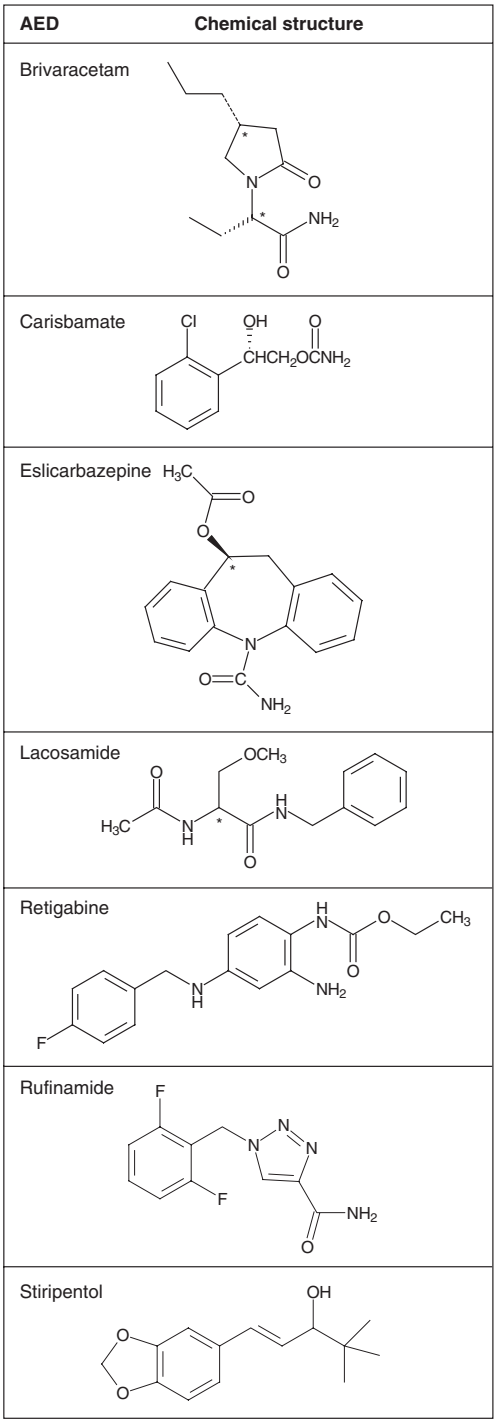

Fig. 2. Chemical structure of antiepileptic drugs (AEDs) that have recently been approved or are in late-stage development.

essential for exocytosis of neurotransmitter from the presynaptic neuron into the synaptic cleft, and may prevent exocytosis of glutamate because there is a correlation between binding affinity and potency in suppressing tonic seizures in audiogenic sensitive mice.[10] Brivaracetam suppresses evoked epileptiform responses *in vitro* in rat hippocampal slices.[17] It is more potent than levetiracetam in protecting against secondarily generalized motor seizures in a corneal-kindled mouse model, in amygdala-kindled rats and in the genetic GAERS model.[8,18,19] Furthermore, brivaracetam, like levetiracetam, showed marked synergy with diazepam in a model for status epilepticus influencing GABAergic activity by increasing chloride currents.[19-21]

Brivaracetam is rapidly and almost completely absorbed after oral administration, as seen in 12 healthy male volunteers given brivaracetam 200, 400 or 800 mg/day for 14 days. [22] It possesses linear metabolic kinetics, the elimination half-life ($t_{1/2}$) is 7–8 hours, the volume of distribution (Vd) is similar to total body water (0.6 L/kg), the primary route of elimination is metabolism to inactive metabolites, the renal clearance of brivaracetam is low (0.06 mL/min/kg) and it is weakly bound to plasma proteins (≤20%).[22] A recent study with ^{14}C-brivaracetam in six healthy male volunteers demonstrated that maximum concentration (C_{max}) was reached within 1.5 hours after intake of brivaracetam and 90% of the radioactivity was found in the plasma, suggesting a modest first-pass effect. The metabolism was identified as non-cytochrome P450 (CYP)-dependent hydrolysis and hydroxylation, and the excretion was renal.[23] Brivaracetam (400 mg/day) seems to interact moderately with carbamazepine, phenytoin and oral contraceptives (C_{max} and area under the concentration-time curve [AUC] of these drugs remaining within the confidence interval of 80–125%), but such a high dose of brivaracetam is likely to be several-fold above a therapeutically relevant dose range.[8] In patients with partial epilepsy receiving concomitant AEDs, no dose adjustments of any commonly used AEDs is needed when brivaracetam 5–150 mg/day is added.[24] The pharmacokinetic properties of the drug were unaltered in

elderly and in renally-impaired patients.[8] Population pharmacokinetics in patients with partial epilepsy demonstrated that most inter-individual variability in kinetics in an ethnically diverse population could be accounted for by variation in bodyweight and concomitant use of enzyme-inducing AEDs, and that brivaracetam has a highly predictable required dosage in individual patients.[25]

2.1.2 Efficacy

The efficacy of a single dose of brivaracetam (10, 20, 40 or 80 mg) was investigated in a study including 19 patients with photosensitive epilepsy versus placebo, showing reductions or abolition of the response in all evaluable patients. Even at the lowest dose of 10 mg, three of four patients who responded had a complete abolition of the photoparoxysmal EEG discharges.[8,12,26] Patients receiving brivaracetam 80 mg had a longer lasting response than those receiving other doses (median 59.5 hours), and it was concluded that the drug is effective in patients with photosensitive epilepsy at doses much lower than tested in interaction and tolerability tests, and that they may be clinically irrelevant.[12,26] However, it remains uncertain if the photoparoxysmal response model is suitable for generalized photosensitive epilepsy.

Two dose-ranging studies are currently ongoing in patients with refractory partial onset epilepsy,[27,28] with brivaracetam as adjunctive treatment compared with placebo. In addition, two pivotal studies in patients with Unverricht-Lundborg disease (progressive myoclonic seizures) are under preparation.[8] In one efficacy and tolerability study of brivaracetam 50 and 150 mg/day as adjunctive treatment in adults with refractory partial-onset epilepsy, a clear differentiation in seizure reduction was shown compared with placebo, and 40% of the patients were responders (n = 157) [defined as those with a ≥50% seizure reduction].[27] In the other study, brivaracetam 5, 20 and 50 mg/day was investigated: 50 mg/day appeared to be the most effective dose, with a responder rate of 56% and seizure freedom rate of 7.7%.[28] A dose- and exposure-response modelling of brivaracetam showed that 20 mg/day is expected to decrease seizure frequency by 50% of the maximum possible change compared with baseline.[29]

2.1.3 Tolerability

Brivaracetam has low short- and long-term toxicity in animal models and in phase I studies.[8] Long-term toxicity was investigated in rats, rabbits, dogs and monkeys, assessing the non-observed adverse effect level for 26 weeks, and the drug showed no effects on fertility, pregnancy or early embryonic development in rats or rabbits in doses up to 600 and 120 mg/kg/day, respectively.[8,12] Genotoxicity was investigated in a panel of studies and, taken together, they suggested that brivaracetam is neither mutagenic nor clastogenic. In addition, carcinogenicity studies are ongoing.[12]

In healthy volunteers and patients, single doses of brivaracetam up to 1000 mg and repeated doses of 800 mg twice daily were well tolerated. The adverse effects were mostly CNS-related and transient with mild to moderate intensity, without any alterations in vital signs, physical or clinical laboratory examinations.[11,23] Safety and tolerability of brivaracetam 5, 20 or 50 mg/day as adjunctive treatment were evaluated in 259 patients (aged 16–65 years) with refractory partial-onset seizures on one to two AEDs, demonstrating a favourable safety and tolerability profile with no major differences found for adverse events (mostly gastrointestinal or CNS related), laboratory parameters or vital signs.[30]

2.2 Carisbamate

Carisbamate (RWJ-33369) is a derivative of felbamate, (S)-2-*O*-carbamoyl-1-*O*-chlorophenyl-ethanol. Felbamate was widely used for partial and generalized seizures, but serious adverse reactions, such as aplastic anaemia and hepatotoxicity due to the formation of a toxic metabolite, atropaldehyde, were discovered and hampered its use in predisposed patients. Therefore, new derivatives of this compound, such as carisbamate, are designed to avoid toxic metabolites.

2.2.1 Pharmacology

Carisbamate is a novel neuromodulator; however, its mechanisms of action remain to be elucidat-

ed and are still under investigation. The compound has been tested in several preclinical models (mice, rats and rabbits), and exhibited potent and broad activity. It also has a favourable profile in epilepsy models (both partial and generalized), such as corneal kindling, hippocampus kindling, the genetic GAERS model, genetic audiogenic generalized seizures and chemically-induced seizures.[8,31-33] In addition, it has been proposed that carisbamate exhibits disease-modifying effects, at least in the lithium-pilocarpine model, as demonstrated by a reduction in neuron loss and dose-dependent delay or prevention of recurrent seizures in a rodent model of status epilepticus.[34] *In vitro* studies demonstrated that carisbamate prevented the development of epileptiform activity and seizures following status epilepticus in hippocampal neuronal cultures, as measured by whole-cell current clamp recordings.[35]

Carisbamate is completely absorbed and extensively metabolized, as studied in eight healthy male volunteers following an oral dose of ^{14}C-labeled carisbamate 500 mg.[36] Plasma, urine and faeces were collected 1 week after the drug administration, and the main metabolism pathways were O-glucuronidation (44%) and hydrolysis followed by oxidation, and only 1.7% of the dose was excreted unchanged in the urine.[36] The time to maximum concentration (t_{max}) is achieved 1–3 hours after oral intake and the protein binding is 44%.[8] In two studies involving 48 healthy male volunteers (aged 18–40 years), one open-label study and one double-blind, randomized, crossover study, carisbamate was given in single or repeated doses from 100 to 750 mg. The drug had linear kinetics, absorption was not altered by the intake of food, the $t_{1/2}$ was 10.6–12.8 hours and renal clearance 0.042–0.094 L/h. Total body clearance (CL/F) was 3.4–4.2 L/h.[37] These results also showed that the drug was extensively metabolized, as the oral clearance (CL/F of 4% of the hepatic blood flow) as a measure of hepatic clearance was low, and it is therefore not subject to first-pass metabolism following oral administration.[37] No apparent differences in pharmacokinetic parameters were observed following administration of an immediate release formulation of carisbamate 250 and 500 mg twice daily in elderly (eight subjects aged 65–74 years and eight subjects aged >75 years) and non-elderly adults (eight subjects aged 18–55 years), confirming the linearity of its kinetics.[38]

The potential kinetic interactions between carisbamate and valproate or lamotrigine were recently evaluated in two open-label sequential studies in 24 healthy volunteers aged 18–60 years.[39] It was demonstrated that there was no clinically relevant interactions in the studies, and that carisbamate was safe to use and well tolerated.[39] The dose of carisbamate that was chosen was 500 mg/day for 5 days, then 1000 mg/day for 5–14 days, followed by a combination with lamotrigine or valproate for 14 days. The studies showed that there were no significant changes in the C_{max} or AUC values of carisbamate.[39] Modest reductions (15–20%) in the same parameters were measured for lamotrigine and valproate, but were not regarded as clinically significant.[39] Carbamazepine induced the metabolism of carisbamate, as seen by a decrease in the C_{max} and AUC values of carisbamate by 37% and 30%, respectively, and the mean half-life was reduced by 30%.[40] The plasma concentration of carisbamate was reduced by 20–30% by oral contraceptives, possibly as a result of the induction of glucoronidation.[8] This study[40] was designed like the other kinetic studies,[39] with 24 healthy volunteers receiving carisbamate 500 mg/day for 5 days and then 1000 mg/day for 5 days, and the study lasted for 8 weeks in total.[40]

2.2.2 Efficacy

A randomized, placebo-controlled, double-blind phase IIb study investigated daily doses of 100, 300, 800 and 1600mg of carisbamate in 537 patients with partial seizures for 16 weeks. Preliminary results indicate that the drug is efficacious in dosages from 300–1600 mg/day, and a daily dosage of 300 mg provided the optimal balance of efficacy and tolerability.[8,41] Over 80% of the patients in the randomized trial continued in an open-label extension study with the longest exposure to patients for over 2 years. Based on these results, carisbamate is enter-

ing phase III trials for adjunctive use in partial onset epilepsy.[8,42]

2.2.3 Toxicity and Tolerability

Carisbamate has demonstrated anticonvulsant efficacy at doses below those that give rise to CNS toxicity, as seen in the rotarod test in rodents and the protective index (median toxic dose/median effective dose [TD_{50}/ED_{50}] <15).[8] Repeated-dose toxicity tests were conducted in adult rats for up to 6 months and adult dogs for up to 12 months in doses far above clinical exposure, and no organ toxicity was observed.[8,42] Carisbamate tested negative for genetic toxicity in the bacterial reverse mutation test, the *in vitro* human lymphocyte chromosomal aberration assay and the *in vivo* oral mouse bone marrow assay.[42]

In patients, the tolerability was equivalent to placebo in the lower dosage range in the phase IIb study of Bialer et al.[8] At 300 mg/day, carisbamate was well tolerated and adverse events were lower than placebo.[42] The most common adverse events were dose dependent (mainly over 1000 mg/day), mild and transient, and included headache, dizziness, somnolence and nausea.[8,37,41,42] Administration of carisbamate 250 and 500 mg twice daily in elderly and non-elderly patients as described by Levy et al.[38] also confirmed that the drug was well tolerated and safe to use.

2.3 Eslicarbazepine

Eslicarbazepine acetate (BIA2-093), S-9-(−)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide, was designed for improved efficacy and safety. It is a derivative of carbamazepine and oxcarbazepine, being a prodrug of the main active metabolite (S)-licarbazepine (eslicarbazepine), one of the enantiomers of the monohydroxy derivative of oxcarbazepine.[8] A modification at the 10,11-position results in a metabolism that does not undergo auto-induction.[8]

2.3.1 Pharmacology

Eslicarbazepine is an inhibitor or voltage-gated sodium channels, and acts in a similar way to carbamazepine and oxcarbazepine, as demonstrated in an experimental study comparing inhibition of release of the neurotransmitters or neuromodulators glutamate, GABA, aspartate and dopamine in striatal slices from the rat.[43,44] Eslicarbazepine stabilizes the voltage-gated sodium channel in the inactive phase because it has the highest affinity for the resting state and prevents its return to the active state, and thereby inhibits repetitive firing, seizure genesis and spreading.[33,43,44] Eslicarbazepine acetate given orally to rats in doses of 3–30 mg/kg demonstrated potent anticonvulsant activity against latruncluin A-induced seizures and, furthermore, prevented the induced increase of the extracellular levels of glutamate and aspartate, while the levels of GABA remained unchanged.[45] Eslicarbazepine acetate has demonstrated efficacy in several seizure models, including the maximal electroshock test (MES), kindling models and several chemoconvulsants (picrotoxin, metrazole, bicuculine and 4-aminopyridine).[7]

Eslicarbazepine acetate is rapidly and almost completely converted to the active metabolite eslicarbazepine, which is responsible for the pharmacological action. Protein binding is about 30%, and C_{max} and t_{max} are attained 1–4 hours post dose.[44] Single- and multiple-dose experiments in healthy volunteers have shown that eslicarbazepine acetate in doses of 20–2400 mg/day was extensively metabolized with a $t_{1/2}$ in the order of 20–24 hours and is consistent with first-order kinetics.[44] *In vitro* experiments have shown that eslicarbazepine has no relevant effect on the activity of major CYP enzymes, uridine diphosphate glucuronosyltransferases (UGTs) or hydroxylases, but leads to an inhibition of about 40% of CYP2C1-mediated hydroxylation of tolbutamide and a similar activation of UGT1A1-mediated glucoronidation of ethinylestradiol.[44] A clinical study with eslicarbazepine acetate 1200 mg/day confirmed that the plasma concentrations of oral contraceptives, both ethinylestradiol and levonorgestrel, were reduced, and AUC decreased by 32% and 24%, respectively.[44]

The potential interaction between eslicarbazepine acetate 1200 mg and lamotrigine 150 mg

was studied in 32 healthy male volunteers following repeated administration, but no changes in C_{max} or AUC for either drug were observed.[46] Eslicarbazepine is primarily excreted renally, and thus its clearance is dependent on renal function, and dosage adjustments may therefore be necessary in patients with renal failure, but not in patients with mild (Child-Pugh category B, score 5–6) to moderate (score 7–9) hepatic failure.[47,48] This was demonstrated in two separate studies with eight healthy volunteers and eight patients in each of the following five groups mild, moderate, severe and end-stage renal impairment, and moderate hepatic failure, respectively.[47,48] AUC increased when renal function decreased by approximately 30%, 50% and 70%, respectively in mild, moderate and severe renal impairment, while the CL/F and renal clearance of eslicarbazepine was not affected by moderate hepatic impairment.[47,48]

2.3.2 Efficacy

A randomized, placebo-controlled, multicentre trial of 143 patients (aged 18–65 years) with refractory partial seizures studied the efficacy of eslicarbazepine acetate (400–1200mg/day for 12 weeks) was studied in and showed that these dosages were effective as add-on therapy (with one to two other AEDs): 54% versus 28% for eslicarbazepine acetate 400 mg compared with placebo, and 58% versus 38% for eslicarbazepine acetate 800 mg compared with placebo in weeks 5–8. A total of 24% of the patients became seizure-free.[44,49] Results from three ongoing phase III studies are expected to be available shortly and they will better define the place for eslicarbazepine in the treatment of epilepsy.[44] In addition, studies in children with epilepsy and monotherapy studies in adults are planned.[44]

2.3.3 Toxicity and Tolerability

Preclinical toxicity studies have shown that in cultured hippocampal neurons from rat, eslicarbazepine acetate was less neurotoxic than both carbamazepine and oxcarbazepine, and it caused less neurological impairment following intraperitoneal administration in the rat than the two other drugs, and it has therefore a higher protective index.[50,51] More than 1200 patients have been exposed to eslicarbazepine acetate in doses up to 2400 mg/day, and the longest exposure has been 20 months.[44] No difference in tolerability has been reported between adults and elderly patients, and no abnormal vital signs were seen in clinical laboratory tests in patients receiving eslicarbazepine acetate.[44] The study by Elger et al.[49] demonstrated that eslicarbazepine acetate was well tolerated. The most commonly reported adverse effects were headache, dizziness and nausea, and no serious drug-related events were reported.

2.4 Lacosamide

Lacosamide (SPM 927; formerly known as harkoseride [ADD 2304037]), R-2-acetamido-N-benzyl-3-methoxypropionamide with one chiral centre, was one in a series of functionalized amino acids that were tested for anticonvulsant properties and it is structurally unlike other AEDs.[52]

2.4.1 Pharmacology

The mechanisms of action of lacosamide are still under investigation because it did not bind to a number of receptors, enzymes, transporters or ion channels tested. However, recently, it was shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels without affecting the fast inactivation current and thus reduces pathophysiological activity in patch-clamp electrophysiology studies.[53] This mechanism is different to other sodium channel blockers because they show no effect on slow inactivation currents.[52] Recent affinity experiments with lacosamide in rat hippocampal cultures demonstrated that a putative molecular target for lacosamide was collapsin response mediator protein 2, which is involved in neuronal differentiation and control of axonal outgrowth.[53] No other AED is known to interact with this target molecule. Lacosamide protects against seizures in several animal models, including the MES, 6 Hz refractory seizure model, hippocampal kindling, sound-induced seizures and amygdala kindling.[8,53,54] In the 6 Hz seizure model in mice, lacosamide exhibited a synergistic anticonvulsant effect in combination with the AEDs topiramate,

gabapentin, lamotrigine, levetiracetam and carbamazepine, which was less profound with valproate and phenytoin, and no enhanced adverse effects were observed in the rotarod test.[55] This study demonstrated the importance of the development of new drugs with a rational basis for polytherapy because 30% of patients with epilepsy use more than one AED.[55]

Lacosamide is rapidly and completely absorbed with negligible first-pass effect. Radio-labelling kinetic studies in humans showed that 95% of the oral dose was excreted in urine, where 40% was unchanged drug and the same amount converted to the active O-desmethyl metabolite. There is no indication that lacosamide affects CYP isoenzymes, even if it inhibited CYP2C19 at concentrations 15-fold higher than therapeutic concentrations. In addition, no differences have been observed in subjects with inhibited CYP2C19, or poor or extensive metabolizers.[52] Food did not affect the absorption of lacosamide (C_{max} and AUC values).[8] The t_{max} is reached 0.5–4 hours following oral administration, the $t_{1/2}$ is approximately 13 hours and <15% is bound to plasma proteins.[8,52] Pharmacokinetic, metabolic and tolerability profiles are comparable following intravenous and oral administration.[8] Lacosamide (400 mg/day for up to 10 days) did not affect the pharmacokinetics of carbamazepine (400 mg/day for 22 days), valproate (600 mg/day for 13 days) or vice versa, and neither levonorgestrel nor ethinylestradiol were affected by lacosamide, as studied in healthy volunteers.[8,56,57] In randomized controlled studies in patients, the plasma concentrations of other commonly used AEDs, including carbamazepine, lamotrigine, levetiracetam, phenytoin, topiramate and valproate, did not seem to be altered by lacosamide.[52]

2.4.2 Efficacy

In one randomized controlled trial by Ben-Menachem et al.,[58] 418 subjects receiving one or two AEDs were given placebo or lacosamide 200, 400 or 600 mg/day for 12 weeks, and the median seizure reduction was 10%, 26%, 39% and 40%, respectively, where the two last values were statistically significant versus placebo. The 50% reduction in seizure frequency in these two groups was about 40%.[58] Lacosamide (400 and 600 mg/day) demonstrated efficacy in a randomized, placebo-controlled study of 405 patients with partial-onset seizures, with a 50% responder rate of 40% and a 37% reduction in seizure frequency.[56] In another study with 370 patients with partial-onset seizures receiving lacosamide (400, 600 or 800 mg/day) as adjunctive therapy, 284, 224 and 140 patients had more than 1, 2 and 3 years of exposure to the drug, respectively, and 46% of them in total had >50% responder rate to the treatment.[57] A recent randomized controlled trial compared the intravenous formulation used as replacement therapy (60- or 30-minute infusions twice daily) with oral lacosamide, and showed similar efficacy and tolerability.[59]

2.4.3 Toxicity and Tolerability

Lacosamide was tested in all stages of reproduction by oral administration of 200 mg/kg/day in rabbits and 25 mg/kg/day in rats, and no adverse effects were observed on male or female reproductive function or teratogenicity.[8,60] Furthermore, juvenile toxicity was investigated in rats (up to 180 mg/kg/day) and dogs (up to 25 mg/kg/day) for 8 weeks. As there was no indication of age-related toxicity, it was concluded that lacosamide has a favourable profile in preclinical, reproductive, developmental and juvenile toxicity studies.[60] In the clinical trial by Ben-Menachem et al.,[58] lacosamide, 400 and 600 mg/day, was generally well tolerated. The most common adverse effects (>10%) were dizziness, nausea, diplopia and blurred vision, vomiting, headache, tremor and somnolence.[8,58] In the long-term study of efficacy and tolerability by Rosenfeld et al.,[57] lacosamide was generally well tolerated and no changes in clinical laboratory tests were seen, except a small increase in ECG median PR interval (5–9 ms) across all subjects. A total of 11% of the patients discontinued because of adverse events; dizziness was the most common, occurring in 1.6%.[57]

2.5 Retigabine

Retigabine has been developed to affect a new target in the synapse, the voltage-gated potassium

channel. A direct effect on the cellular excitability may be an efficient way of reducing the action potentials and epileptogenic activity, and ongoing underlying pathophysiological processes.[4,6]

2.5.1 Pharmacology

Retigabine has displayed anticonvulsant activity in a range of animal models for epilepsy, including generalized seizures (chemically-induced and genetic seizures), partial seizures (kindling models, MES) and status epilepticus, and retigabine has also been shown to have neuroprotective effects.[61,62] Retigabine is among a new class of AEDs that selectively and potently open voltage-gated KCNQ2/3 and KCNQ3/5 potassium channels, which are involved in the control of neuronal excitability.[63-65] Retigabine may also affect disease mutant channels, which is interesting because genes for the KCNQ2/3 channels have been identified to code for a dominant autosomal neonatal epilepsy.[66,67]

Retigabine and its acetyl metabolite possess linear kinetics in doses up to 1200 mg/day, the oral bioavailability is 60%, C_{max} is reached 1.6 hours following oral administration, the mean $t_{1/2}$ is 8 hours and the protein binding is <80%.[8,68] The drug is metabolized via N-glucuronidation and N-acetylation to metabolites without significant activity and is independent of CYP isoenzyme activity, and the drug and metabolites are mainly renally excreted.[68] Retigabine does not affect its own metabolism.[69] No differences in the pharmacokinetic properties related to age (aged 18–81 years) or sex have been observed.[68,69] Retigabine (up to 1200 mg/day) does not affect plasma concentrations of commonly used AEDs, such as carbamazepine, valproate, phenytoin, phenobarbital and topiramate, while the enzyme-inducing AEDs carbamazepine and phenytoin increase the CL/F of retigabine to some extent.[8,70] A study in healthy volunteers demonstrated that lamotrigine clearance increased about 20% when administered with retigabine (400–600 mg/day), which was not regarded clinically significant.[71]

2.5.2 Efficacy

A recently published, phase II, double-blind, placebo-controlled study showed that retigabine (600, 900 and 1200 mg/day) was dose-dependently effective as adjunctive therapy in partial-onset seizures, with 50% responder rates of 23%, 29% and 35%, respectively, for the three doses, compared with 13% in the placebo group.[72] No sex differences were observed in another study, which included 47 female and 48 male patients (aged 16–70 years).[73] A phase III study is ongoing.[8] Results from two phase II studies determined the maximal tolerated dose of retigabine, 1200 mg/day, and a titration schedule of an increase by 150 mg/day every week should be the aim.[8] A third, phase II, randomized, double-blind, placebo-controlled trial of 399 patients with partial seizures, investigated the efficacy and tolerability of retigabine and demonstrated a 50% responder rate of about 30% with doses ranging from 600 to 1200 mg/day, and it was elevated to almost 50% in 222 patients who continued with retigabine 900 mg/day for a median time of 1 year as adjunctive AED therapy.[8]

2.5.3 Toxicity and Tolerability

Preclinical toxicity studies lasting up to 1 year in rodents and non-rodents have shown that retigabine was well tolerated. Dependence liability was not observed, and the main CNS-related effects were sedation accompanied by hyperexcitability and decreased body temperature.[8,72] Results from phase II and III studies demonstrated that dose-related adverse effects, such as sedation, dizziness, cognitive impairment, vertigo, unsteady gait and diplopia, were reported, and no changes in clinical laboratory data were observed.[8,72]

2.6 Rufinamide

The triazol derivative rufinamide (1-[(2,6-difluorophenyl)methyl]-1-hydro-1,2,3-triazole-4 carboxamide) is a novel compound unrelated to other AEDs.

2.6.1 Pharmacology

The mechanisms of action of rufinamide are still under investigation, but it has been suggested from *in vitro* studies that it prolongs the inactivation state of voltage-gated sodium channels like many other AEDs, and it has not shown any significant bind-

ing to GABA, glutamate or monoaminergic receptors.[8,74] A recent study demonstrated the anticonvulsant efficacy of rufinamide in several rodent models for partial and generalized seizures (MES and chemically-induced seizures).[75]

Rufinamide is well absorbed (>85%), has low protein binding (34%) and a Vd of 50–80 L. It is metabolized by enzymatic hydrolysis, independent of CYP isoenzymes, to an inactive metabolite and is primarily renally excreted (<2% of a dose is excreted unchanged), and the $t_{1/2}$ is 6–10 hours.[8,74,76] It was recently demonstrated, in a population kinetic study with rufinamide given as an add-on therapy to valproate, that an increase in the rufinamide serum concentration was more prominent in children than adolescents and adults (70% vs 26 and 16%, respectively), possibly because of the higher serum concentrations in the children.[76] The drug may increase the serum concentration of coadministered phenytoin (<21%), but has no clinically relevant interactions with other AEDs because the clearance of rufinamide is not dependent on CYP isoenzymes.[8,76] Rufinamide may increase the clearance of oral hormonal contraceptives as a result of a weak induction of CYP3A4.[74,76] It is unlikely that rufinamide is an inducer of CYP1A2 because the clearance of olanazapine, a substrate for this enzyme, is unaffected.[74,76]

2.6.2 Efficacy

Rufinamide is licensed as adjunctive therapy in children and adults with Lennox-Gastaut syndrome (LGS). It was approved in Europe in 2007. Four clinical studies have been described and reviewed; two studies with rufinamide as add-on treatment in partial seizures (patients aged >15 years); one monotherapy study versus placebo (patients aged >12 years); and one add-on treatment study in children (aged >4 years) with LGS.[8,74,77] Doses of 200–3600 mg/day have been tested in clinical trials, with a mean dose of 1700 mg/day and exposure up to 4 years, predominately in adults.[74] A clinical study of 138 patients with LGS included children aged from 4 years old with a titration period of 1–2 weeks and maintenance of 10 weeks, with a mean dose of 45 mg/kg/day and showed a 33% reduction in seizures, and approximately a 50% reduction in seizure severity and atonic seizures.[77]

2.6.3 Toxicity and Tolerability

Rufinamide has been well tolerated in animals and behavioural toxicity has been similar to or better than established AEDs, with a greater protective index in rodents.[8,78] Safety of rufinamide was investigated in patients (n = 138, median age 14 years) with LGS for 84 days and showed a similar safety profile in an extension phase of the study with a mean exposure duration of 432 days (n = 124).[74] This study showed that rufinamide was well tolerated, and most adverse events were mild to moderate in severity (somnolence, vomiting, pyrexia and diarrhoea) and infrequently led to discontinuation, unlike in the 10-week study in LGS patients, where somnolence and vomiting occurred more often than in the placebo group (12% and 18%, respectively).[74,77] In a study in paediatric patients with LGS, 6.8% (n = 5) of the patients receiving rufinamide therapy developed rash, compared with 1.6% in the placebo group. This may lead to serious AED hypersensitivity syndrome, which has been reported, and close follow-up in these patients is recommended.[74]

2.7 Stiripentol

Stiripentol is structurally unrelated to other AEDs, belonging to the aromatic allylic alcohols. It has been studied and used for more than 10 years in France and Canada, but has experienced a delay in its development because of its pharmacokinetic interaction potential.[79]

2.7.1 Pharmacology

The anticonvulsant properties of stiripentol *in vitro* have suggested that the compound possesses its effects through enhancement of GABAergic neurotransmission by increasing GABA release, inhibiting GABA reuptake and activation of $GABA_A$ receptors in a barbiturate-like manner.[79,80] These findings suggest that stiripentol has an independent anticonvulsant effect, and that the clinical effect of the drug is not just a consequence of increasing serum concentrations of concomitantly used AEDs.

Pharmacokinetic studies of stiripentol have shown that it is rapidly absorbed with a C_{max} 1.5 hours after oral intake and it is 99% bound to plasma proteins.[81] The clearance of stiripentol decreases with increasing dosage as a result of non-linear (Michaelis-Menten) pharmacokinetics.[81] This makes individual dose administration and drug monitoring especially important because a small increase in the drug dose may lead to an unexpectedly high increase in the plasma concentration of the drug. Patients treated with enzyme-inducing AEDs (phenytoin, phenobarbital, carbamazepine) exhibit higher clearance of stiripentol.[8] Stiripentol is a potent inhibitor of CYP3A4, CYP1A2 and CYP2C19, and thereby affects numerous other drugs, including other AEDs, such as phenytoin, carbamazepine, phenobarbital, valproate and clobazam. The concentrations of the metabolites of these AEDs are consequently decreased, and it is thought that this is the mechanism responsible for an increase in tolerability of the original drugs, in particular for carbamazepine and its epoxide metabolite.[79]

2.7.2 Efficacy

Several clinical studies, open and randomized, have been conducted and are reviewed in detail by Chiron and colleagues.[79] The clinical studies with stiripentol carried out in adult patients with epilepsy have been disappointing, while studies in children demonstrated a specific efficacy in severe myoclonic epilepsy in infancy (Dravet's syndrome, a rare but severe disorder often resistant to conventional AEDs). In a placebo-controlled study of 64 children with Dravet's syndrome (aged 3–18 years) conducted in France and Italy, the children received concomitant medication with valproate or clobazam. Stiripentol was superior to placebo and about two-thirds of stiripentol recipients were responders (≥50% seizure reduction).[82] In a large open-label study of 200 patients (aged from 1 month to 20.5 years old) combining stiripentol with carbamazepine or clobazam, the seizure frequency decreased by >50% in partial epilepsy and Dravet's syndrome, and two-thirds and one-half of the patients, respectively, were responders (defined as those with a ≥50% seizure reduction).[83] In addition, clinical experience from France has suggested a beneficial effect of stiripentol used in combination with carbamazepine in 67 children with pharmaco-resistant partial epilepsy, even though statistical significance was not shown in the double-blind phase.[84] A recent meta-analysis review compared the available studies of stiripentol in Dravet's syndrome.[84] Two randomized controlled studies showed efficacy of stiripentol and 23 uncontrolled studies did not provide valid information.[84]

2.7.3 Toxicity and Tolerability

Chronic toxicity, reproduction, mutagenicity and carcinogenic studies have been conducted and did not show any marked toxicity in the high doses tested. However, there was a tendency for liver hypertrophy, possibly because of the intense drug metabolizing capacity of stiripentol.[8] A total of 400 patient-years of tolerability data are provided by the conducted clinical trials where adverse events were reported by half of the patients but could be minimized by a reduction in the dosage of co-medication.[79] The most commonly reported adverse events included loss of appetite, drowsiness, cognitive impairment, ataxia, diplopia, nausea, abdominal pain and occasionally asymptomatic neutropenia.[79,82-84]

3. Future Prospects and Challenges

In summary, the new drugs described in this review may have possible advantages compared with existing drugs, which will be important for their future clinical applications. An advantage for the future use of lacosamide is the recent development of an intravenous formulation for patients temporarily unable to take oral medication, containing identical drug substance as the oral formulation, and it is isotonic, does not require dilution prior to use and is stable at room temperature.[8] Retigabine is a drug of special interest in the field of pharmacogenetics as it may affect mutant potassium channels involved in certain forms of epilepsy and peripheral nerve hyperexcitability.[85] It is expected that retigabine will be marketed in the near future. Future studies will demonstrate the place of the orphan

drugs brivaracetam, rufinamide and stiripentol in the treatment of epilepsy.

During development and clinical use of new AEDs, some future challenges need to be addressed. Therapeutic drug monitoring (TDM) should be an integral part of drug development because the establishment of individual therapeutic serum concentrations for the patient makes TDM a valuable tool for optimizing drug therapy for new as well as older AEDs.[86,87] Every new AED in development is also studied in other indications in addition to epilepsy to expand their possible clinical use. To find and develop suitable preclinical models to study relevant mechanisms of action in pathophysiological processes other than epilepsy are important challenges.[88] Several recent studies suggest broader therapeutic use in the future, even though many of the studies are still at a preclinical stage. Eslicarbazepine is undergoing phase II trials for bipolar disorder.[8] Retigabine may also have antimanic properties, as demonstrated in an experimental rat model.[89] Carisbamate possesses disease-modifying properties in amygdala-kindled rats that developed allodynia and hyperexcitability, suggesting that the drug may also be effective in preventing the development of neuropathic pain.[90] Lacosamide and brivaracetam are undergoing evaluation as monotherapy in neuropathic pain.[8,91]

In addition to the AEDs reviewed in this article, several others are currently undergoing clinical trials at earlier stages. These include the valproate derivative propylisopropyl acetamide, the α-amino-3-hydroyx-5-methyl-4-isoxazolepropionic acid (AMPA)-receptor antagonists talampanel and NS1209, and ganaxolone, a derivative of neurosteroids. Several of these agents also have potential as broad-spectrum CNS active drugs with neuroprotective properties.[1,8] Further investigation and development of new potential broad-spectrum drugs are important for improved treatment of patients with epilepsy and other related disorders in the future.

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