In the last decade, 10 new antiepileptic drugs (AEDs) have been introduced that offer appreciable advantages in terms of their favourable pharmacokinetics, improved tolerability and lower potential for drug interactions. However, despite the large therapeutic range of old and new AEDs, ~30% of the patients with epilepsy are still not seizure free and, consequently, there is a substantial need to develop new AEDs. The new AEDs currently in development can be divided into two categories: drugs with completely new chemical structures such as lacosamide (formally harkoseride), retigabine, rufinamide and talampanel; and drugs that are derivatives or analogues of existing AEDs that can be regarded as second-generation or follow-up compounds of established AEDs. This article focuses on the second category and thus critically reviews the following second-generation compounds: eslicarbazepine acetate or BIA-2-093 and 10-hydroxy carbazepine (carbamazepine derivatives); valrocemide and NPS 1776 (isovaleramide; valproic acid derivatives); pregabalin and XP13512 (Gabapentin derivatives); brivaracetam (ucb 34714) and seletracetam (ucb 44212; levetiracetam derivatives); and fluorofelbamate (a felbamate derivative). In addition, a series of valproic acid derivatives that are currently in preclinical stage has also been evaluated because some lead compounds of this series have a promising potential to become new antiepileptics and CNS drugs. For any of these follow-up compounds to become a successful second generation to an existing AED, it has to be more potent, safer and possess favourable pharmacokinetics, including low potential for pharmacokinetic and pharmacodynamic drug interactions.

Keywords: antiepileptic drugs, carbamazepine, felbamate, gabapentin, levetiracetam, oxcarbazepine, second generation to antiepileptic drugs, valproic acid


1. Introduction

In the last decade, 10 new antiepileptic drugs (AEDs) have been introduced that offer appreciable advantages in terms of their favourable pharmacokinetics, improved tolerability and lower potential for drug interactions [1-5]. In addition, the availability of old and new AEDs with various activity spectra and different tolerability profiles enables clinicians to better tailor drug choice to the characteristics of the individual patient [3]. Yet the new AEDs developed so far are not completely effective because (altogether) they result in a seizure-free status in ≤15 – 20% of previously refractory patients [3]. Thus, in spite of the large therapeutic range of old and new AEDs, ~30% of the epileptic patients are still not seizure free and thus there is a substantial need to develop new AEDs [4].

Most of the new AEDs that are in development are currently in clinical trials (Table 1) [1,4,5]. The new AEDs presented in Table 1 can be divided into two
New antiepileptic drugs that are second generation to existing antiepileptic drugs

Table 1. New antiepileptic drugs in development.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase of development</th>
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<tbody>
<tr>
<td>Brivaracetam</td>
<td>I</td>
</tr>
<tr>
<td>Eslicarbazepine acetate</td>
<td>III</td>
</tr>
<tr>
<td>Fluorofelbamate</td>
<td>Preclinical</td>
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<tr>
<td>Ganaxolone</td>
<td>II</td>
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<tr>
<td>Lacosamide</td>
<td>II</td>
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<tr>
<td>NPS 1776</td>
<td>II</td>
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<tr>
<td>Pregabalin</td>
<td>Approved</td>
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<tr>
<td>Retigabine</td>
<td>II</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>III</td>
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<td>RWJ-333369</td>
<td>II</td>
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<tr>
<td>Seletracetam</td>
<td>I</td>
</tr>
<tr>
<td>Striipentol</td>
<td>III</td>
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<tr>
<td>Talampanel</td>
<td>II</td>
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<tr>
<td>Valrocemide</td>
<td>II</td>
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<tr>
<td>XP13512</td>
<td>II</td>
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categories: completely new chemical structures, such as lacosamide (formally harkoseride), retigabine, rufinamide and talampanel; and derivatives of existing AEDs that can be regarded as second generation to existing AEDs, such as carbamazepine (CBZ), valproic acid (VPA), pregabalin, felbamate and levetiracetam. Although the completely new AEDs were developed empirically and (in many cases) serendipitously, the design of second-generation AEDs was aimed to widen the CNS activity, as well as to improve efficacy, safety, tolerability and the pharmacokinetic profile of the existing AEDs.

This review focuses on the second category and thus critically reviews the following second-generation compounds: eslicarbazepine acetate or BIA-2-093 and 10-hydroxy-carbazepine (monohydroxy derivative [MHD]; CBZ derivatives); valrocemide and NPS 1776 (VPA derivatives); pregabalin and XP13512 (gabapentin derivatives); brivaracetam (ucc 34714) or seletracetam (ucc 44212; levetiracetam derivatives) and fluorofelbamate (felbamate derivative). In addition, a series of VPA derivatives currently in preclinical stage has been evaluated, as some lead compounds of this series have shown promising potential to become new AEDs and CNS drugs [6].

The second-generation AEDs also include two marketed AEDs that are beyond the scope of this paper: oxcarbazepine (OXC), a second generation to CBZ; and levetiracetam, a compound related to piracetam and similar acetam nootropic agents [1].

With the exception of levetiracetam follow-up compounds, the design of most second-generation AEDs was motivated by pharmacokinetic principles aimed to enhance absorption and plasma exposure (area under the curve [AUC]) of the active entity (e.g., gabapentin) and/or to avoid or circumvent the formation of toxic metabolites (e.g., VPA). The development of brivaracetam and seletracetam (as second generation to levetiracetam) stemmed from the recognition of the unique pharmacological profile of levetiracetam, which correlates with a new mechanism of action involving an interaction with a novel binding site recently discovered to be the synaptic vesicle protein 2A (SV2A) [7].

Most of the second-generation AEDs currently under development are analogues of the old and established AEDs, VPA and CBZ. These two CNS drugs generate worldwide annual sales of > US$1 billion and $600 million, respectively, making them particularly attractive targets for further development [4,6]. Similar economic driving forces are behind the development of second generations to gabapentin and levetiracetam. US sales of gabapentin alone in 2004 were US$2.7 billion, and levetiracetam’s annual sales worldwide have grown steadily and are expected to be close to US$1 billion in 2006. Fluorofelbamate, a felbamate analogue currently in preclinical development, was designed to have clinical efficacy similar to felbamate but without the serious adverse effects. Unlike felbamate, the hydrogen in the 2-position of the propanediol moiety of fluorofelbamate is substituted by a fluorine. This substitution is thought to prevent the formation of the reactive toxic metabolite of felbamate (atropaldehyde [ATPAL]) [1,8].

2. Second generation to carbamazepine

A second-generation CBZ that does not cause skin rash or diplopia and will not be susceptible to enzyme induction may capture a majority of the CBZ market. A total of four attempts have been made so far to develop compounds that are second generation to CBZ: the pharmacodynamic-based design of ADCI [9]; the pharmacokinetic-based design of OXC; the monohydroxy derivative of OXC (MHD or licarbazepine); and eslicarbazepine acetate (BIA-2-093) or 10-acetoxy-(S)-licarbazepine [1,10,11]. ADCI combined CBZ and the NMDA antagonist dizocilpine (MK-801) in its chemical structure; thus ADCI has a wider CNS spectrum of activity than CBZ because it acts as a selective, low-affinity NMDA antagonist as well as voltage-dependent Na+ channel blocker [9]. However, the clinical development of the (+)-enantiomer of ADCI (SGB-017) was terminated in 1999 at the end of Phase I studies due to liver toxicity.

Unlike CBZ, its follow-up compound OXC does not undergo inducible cytochrome CYP3A4-mediated oxidative metabolism. Instead, OXC undergoes rapid presystemic metabolic 10-keto reduction to its active MHD, 10-hydroxy-carbazepine or licarbazepine. The bio-transformation of OXC to MHD is stereoselective with (S)-MHD having an exposure (AUC) fivefold that of (R)-MHD [10,12]. Thus MHD, and more so (S)-MHD, can be regarded as the major active entity following OXC treatment. Consequently, MHD and eslicarbazepine acetate are currently...
being developed as follow-up compounds to OXC. MHD is being developed as a racemate mainly for bipolar disorder. Previously, MHD was also developed as an intravenous infusion and reached Phase III clinical trials (TRI 477) for patients who are unable to ingest an oral preparation of CBZ or OXC [13]. The water solubility of MHD is better than OXC and CBZ, but it is not adequate for intravenous bolus or for use in status epilepticus [11-13].

Elasticarbazepine acetate ([S]-licarbazepine acetate or BIA-2-093) was found to be the most active of a series of MHD (or OXC) derivatives in the anticonvulsant maximal electroshock (MES) rat model [14]. It is rapidly converted predominantly (95%) to (S)-MHD (Figure 1) following oral administration to humans. The bioavailability of BIA-2-093 was measured in terms of the exposure (AUC) of the two MHD enantiomers and found to be > 16% that observed after intake of an equivalent molar dose of OXC [1,15-18]. The drug is currently in Phase III clinical trials for epilepsy [19] and Phase II trials for bipolar disorder.

Studies in humans have shown that elasticarbazepine acetate is rapidly and extensively metabolised to licarbazepine or MHD, with (S)-MHD being the most prevalent enantiomer following oral administration (95%) in plasma; thus elasticarbazepine acetate is a prodrug to (S)-MHD, which is the primary active entity following its treatment. A minor part of (S)-MHD can be subsequently oxidised to OXC (Figure 1), which is reduced back to (S)-MHD or to its enantiomer (R)-MHD [17,18]. The (R)-enantiomer of elasticarbazepine acetate (BIA-2-059) also possesses anticonvulsant activity, but to a lesser extent; in animals, it is metabolised to (R)-MHD and subsequently to the inactive metabolite 10,11-trans-diol-carbamazepine [18]. The propensity of BIA-2-059 to undergo metabolic inactivation to 10,11-trans-diol-carbamazepine makes its (S)-enantiomer, BIA-2-093, a better candidate for development as an antiepileptic and CNS drug [16-18].

Following single doses of BIA-2-093 20 – 1200 mg p.o., the concentrations of the parent compounds were generally not measurable and the plasma exposure (AUC) of both enantiomers of MHD tended to increase in a greater than dose-proportional manner over the studied dose range [15]. Following repetitive dosing (MHD 400 – 1200 mg/day for 8 days), the AUC of MHD increased in an approximately dose-proportional manner and MHD half-life was in the range of 9 – 13 h. MHD pharmacokinetics were similar following repetitive administration of elasticarbazepine acetate 600 mg/day to young and elderly subjects [15].

In a recent double-blind, add-on, placebo-controlled exploratory trial [19] in 143 adult patients with partial-onset seizures, patients were randomly assigned to one of three groups: treatment with elasticarbazepine acetate once daily (n = 50), elasticarbazepine acetate twice daily (n = 46); or placebo (n = 47) for 12 weeks. The administered dose was 400 mg/day for the first 4 weeks; the dose was subsequently increased to 800 and 1200 mg/day at 4-week intervals. The percentage of responders in the once-daily group was significantly higher (p < 0.05) when patients were treated with daily doses of 800 and 1200 mg compared with placebo, and no significant difference was found between the once- and twice-daily groups. Statistically significant reduction in the number of seizures was achieved both with 800 and 1200 mg/day versus placebo, but the results obtained with the once-daily regimen also tended to be superior to those in the twice-daily group. The most frequently reported adverse events were nausea, headache, dizziness and somnolence; thus elasticarbazepine acetate was found to be effective and well tolerated as an adjunctive therapy for patients with partial-onset seizures. However, it was more effective when administered once rather than twice daily [19].

Thus OXC is an improved second generation to CBZ because it is not susceptible to induction or autoinduction and, consequently, has a low potential for drug interactions. However, as a consequence that OXC does not act as a drug on its own but rather as a prodrug to MHD (primarily [S]-MHD) in humans, elasticarbazepine acetate and MHD (racemate) are now being developed as a second generation to OXC or third generation to CBZ.

3. Second generation to valproic acid

VPA, one of the established AEDs, is the least potent of the major AEDs in animal models. Yet, due to its wide spectrum of antiepileptic activity, VPA is the most prescribed AED [20,21]. It is also an effective (and FDA-approved) drug in migraine prophylaxis and in the treatment of bipolar disorders [21,22].

There are scientific and industrial incentives to develop second-generation drugs to VPA [4,6]. First, it is a simple molecule as it is an iso-octanoic acid, and thus a useful parent compound for synthesising analogues and derivatives that can be CNS-active follow-up compounds to VPA. Second, VPA is not as potent as CBZ, phenytoin and phenobarbital as an anticonvulsant and, therefore, there is ‘flexibility’ to develop analogues that will be more potent than the parent compound. Third, VPA has two rare – but severe – side effects (teratogenicity and hepatotoxicity) that restrict its use in women of child-bearing age and children. VPA also has the less rare adverse effect of cognitive impairment in offspring of a mother taking this drug.

Structure–activity relationship (SAR) studies mapped the structural elements of the VPA molecule that are required for teratogenicity, hepatotoxicity and anticonvulsant activity [6]. In addition, VPA amide analogues were more potent anticonvulsants than their corresponding acids and, unlike valproyl ester derivatives, act as drugs on their own and not as prodrugs to their corresponding acids [6]. Consequently, it is possible to design non-teratogenic and non-hepatotoxic CNS-active VPA analogues and derivatives [6,23-25].

SAR studies indicate that VPA analogues and derivatives (Figure 2) should fulfill three structural requirements to be teratogenic: possess a carboxylic acid in their structure; have

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**Figure 1**

**Figure 2**
New antiepileptic drugs that are second generation to existing antiepileptic drugs

branching in C-2 with two side chains containing at least three carbon atoms in each side chain; and possess a hydrogen atom at C-2 [26-28]. A CNS-active VPA derivative lacking any one of these structural requirements has the potential to become a non-teratogenic entity [6,26-28].

Unlike teratogenicity, the current thinking suggests that VPA-induced hepatotoxicity (microvesicular steatosis) is not caused by the parent compound but by VPA metabolite(s) with a terminal double bond, such as 4-ene-VPA and 2,4-diene-VPA. These metabolites, especially 4-ene-VPA, are believed to form an intermediary acylcoenzyme A (acyl-CoA) thioester leading to CoA depletion in the liver and, consequently, to hepatotoxicity [29-31,32]. Blocking the formation of these two metabolites should prevent or at least minimise the VPA-induced hepatotoxicity [29-31]. Thus a pharmacokinetic-based design is an attractive and feasible approach to design compounds that are second generation to VPA and are non-teratogenic and non-hepatotoxic CNS-active VPA derivatives.

In a review published in 2003, the author and colleagues discussed a comprehensive list of compounds that are second generation to VPA [6]; therefore, only the lead compounds with the potential to become new antiepileptics and CNS drugs are discussed in the present review. Currently, the leading compounds that are second generation to VPA can be divided into three groups (Figure 2): aliphatic amide analogues and derivatives of VPA, which are chiral and achiral constitutional isomers of valpromide (VPD) the primary amide of VPA; Figure 2 [33]; amide derivatives of a cyclopropyl analogue of VPA (2,2,3,3-tetramethylcyclopropane carboxylic acid [TMCA]; Figure 2); and conjugation products between VPA and the neuroinhibitory amino acids, GABA, glycine, taurine and their corresponding primary amides (Figure 2).

3.1 Aliphatic amide analogues and derivatives of VPA

VPD (Figure 1) is approved as an antipsychotic and AED in several European countries [33]. Although VPD is 3 – 5 times more potent than VPA and is not teratogenic in animal models, it serves as a prodrug to VPA in humans (unlike mice, rats or dogs); therefore, its better anticonvulsant activity and lack of teratogenicity in animal models does not apply to humans [6,33].

Consequently, following a series of structure–pharmacokinetic–pharmacodynamic relationship studies, three CNS-active constitutional isomers of VPD have emerged as lead compounds: valnoctamide (VCD), propylisopropyl acetamide (PID) and diisopropyl acetamide (DID; Figure 2) [23,34-36]. VCD, PID and DID are more potent anticonvulsants compared with VPA and their corresponding acids; in mice, rats or dogs, VCD, PID and DID acted as drugs on their own and not as prodrugs to their corresponding acids. PID and VCD are CNS-active
non-teratogenic chiral compounds that are more potent than VPA, and showed stereoselective pharmacokinetics and pharmacodynamics (anticonvulsant activity) [23,34,35]. (R)-PID was more potent as an anticonvulsant than (S)-PID and (2S,3S)-VCD was more potent than (2R,3S)-VCD [23,34,35]. (R)-PID and (2S,3S)-VCD were also very active in two animal models of difficult to treat seizures (namely the hippocampal-kindled rat model and the 6-Hz psychomotor seizure model in mice), thus suggesting that these amides will be useful in therapy-resistant epileptic patients [23,34].

3.2 Cyclopropyl analogue and derivatives of VPA

TMCA (Figure 2) is a cyclopropyl analogue of VPA with two quaternary carbons in the β-position to the carboxylic acid with a terminal double bond (Δ3), analogous to 4-ene-VPA that cannot be biotransformed to hepatotoxic metabolites. However, TMCA showed low anticonvulsant activity and did not demonstrate separation between its anticonvulsant activity and neurotoxicity in rodents [25]. Unlike TMCA, its amide derivatives – 2,2,3,3-tetramethylcyclopropanecarbamide (TMCD), N-methyl-TMCD (MTMCD) and 2,2,3,3-tetramethylcyclopropanecarbonylurea (TMC urea; Figure 2) – all possess anticonvulsant activity in rodent models, such as the MES and subcutaneous metrazole tests with an improved protective index compared with VPA [24,37].

SAR studies with amide derivatives of TMCA led to some conclusions regarding the structural requirements for anticonvulsant activity in this series of compounds. TMC urea was the most potent compound in the rat MES test (median effective dose [ED50]: 29 mg/kg) with a protective index (median therapeutic dose [TD50]:ED50) of 18.5 in the MES test compared with 1.6 for VPA [24]. Furthermore, both MTMCD and TMC urea are non-teratogenic and non-hepatotoxic [24,39,40].

The author recently found that MTMCD and TMC urea possess an antiallodynic activity in the rat spinal nerve ligation model for neuropathic pain and are ∼ 7 and 1.5 times more potent than VPA [25]. In the spinal nerve ligation model, MTMCD was equipotent to gabapentin (currently, the leading AED in neuropathic pain treatment). In another study [41], MTMCD was found to be equipotent to VPA and lithium in various models for bipolar disorders. Thus the tetramethylcyclopropyl analogues of VPA amides (i.e., MTMCD and TMC urea) have the potential to become new AEDs and CNS drugs that will be second generation to VPA.

3.3 VPA derivatives currently in clinical trials

Valrocemide (valproyl glycinamide; the conjugation product between VPA and glycinamide) and NPS 1776 (isovaleramide, an amide of a five-carbon VPA analogue) are currently in Phase II clinical trials for epilepsy [1,6,42]. In addition, a recent study demonstrated that VCD (racemate; Figure 2), previously utilised in Europe as an anxiolytic agent (valnocatmide) [6], has activity as an add-on drug to risperidone in patients with bipolar disorder [43].

The design of valrocemide was motivated by pharmacokinetic considerations whose goals were: to enhance
New antiepileptic drugs that are second generation to existing antiepileptic drugs

Figure 3. Chemical structures of gabapentin, pregabalin and XP13512.
*Indicates the chiral centre.

brain penetration of a glycine derivative; and to utilise the glycaminide to glycine biotransformation to a known VPA metabolite (valproyl glycine) as a major hydrolytic non-oxidative metabolic pathway [1]. Unlike valrocemide, the conjugation products between VPA and other neuroinhibitory transmitters, GABA, glycine and taurine were inactive as anti-convulsants [1,6]. In addition to epilepsy, valrocemide demonstrated activity in animal models for neuropathic pain and bipolar disorder.

NPS 1776 is currently under development by NPS Pharmaceuticals [1], NPS 1776 is effective in electrically- and chemically induced seizure models in mice as well as in the kindled rat. It is also significantly less teratogenic than VPA in animal models. Unlike VPA, NPS 1776 has only 5 carbons in its molecule and consequently has a short half-life of 2.4 h that may require a sustained-release (SR) formulation for twice-daily dosing [1].

Another VPA derivative that has reached clinical trials is SPD-421 (formally DP-VPA), which is a phosphatidylcholine ester prodrug of VPA that is based on targeted delivery of VPA to the epileptic seizure focus [44,45]. A phospholipid carrier serves as a chemical drug delivery system (prodrug) for VPA and cleavage from the inactive SPD-421 to VPA is regulated by phospholipase A2, an enzyme characteristically elevated in seizures. SPD-421 entered Phase II clinical trials for epilepsy in October 2000 but its development was stopped in 2002.

3.4 Other therapeutic utilisations of VPA and its derivatives

Outside the domain of epilepsy, a three-carbon homologue of VPA arundic acid (ONO-2506 or \([\beta]-2\)-propyloctanoic acid) has been under clinical development for the potential treatment of stroke (Phase II trial, injectable formulation), as well as Alzheimer’s and Parkinson’s diseases (Phase I trial, oral formulation) [46]. The success of the clinical trials of ONO-2506 would triple the market size of VPA and its derivatives. Unfortunately, the independent Data Safety Monitoring Board (after an interim analysis) recommended that ONO Pharmaceuticals discontinues its Phase II clinical study in acute stroke in the US and Canada of ONO-2506 in May 2005. The analysis demonstrated that it is highly unlikely that an ONO-2506 injection would show statistically significant efficacy compared with placebo in the current study design. ONO Pharmaceuticals is still pursuing the clinical trials of ONO-2506 in neurodegenerative diseases.

The recent new utilisation of VPA as a plausible anticancer agent is unrelated to its antiepileptic and CNS activity. Both the anticancer activity of VPA and its teratogenicity were found to be connected to its ability to inhibit the enzyme histone deacetylase [47]. SAR studies might provide the required insight into the molecular structures or pharmacophore that are responsible for a VPA analogue or derivative to possess histone deacetylase inhibition and, consequently, a potential antitumour activity [48,49].

4. Second generation to gabapentin

4.1 Pregabalin

Pregabalin (Figure 3) was approved in 2004 in Europe and the US, and is a second generation to gabapentin for the treatment of peripheral neuropathic pain and as adjunctive therapy for partial seizures in patients with epilepsy. Although pregabalin is closely related to GABA (as is gabapentin), there is little evidence that it exerts its pharmacological activity through direct interaction with GABA receptors [50]. It has been shown that pregabalin (as with gabapentin) binds with high affinity to \(\alpha2-\delta\) subunits of voltage-gated Ca\(^{2+}\) channels. The potent binding of pregabalin and gabapentin might explain their antiepileptic and antiallodynic activity as Ca\(^{2+}\) influx is reduced at nerve terminals, and thereby the release of several excitatory neurotransmitters (such as glutamate, noradrenaline and substance P) is also reduced [50]. Both pregabalin and gabapentin are substrates of the system L-neutral amino acid (or L-isoleucine) transporter that is involved in their oral absorption. A recent SAR study [51] showed that the system L-amino acid transporter is also required for these two CNS drugs and their active derivatives to gain access to the CNS. Consequently, pregabalin derivatives that were not substrates of this transporter did not possess anticonvulsant, analgesic or anxiolytic activity.

Pregabalin is more potent than gabapentin in preclinical models of epilepsy, neuropathic pain and anxiety [51]. The oral availability of pregabalin (90%) is higher than that of gabapentin (60%) and its pharmacokinetics is linear at a dose range of 150 – 600 mg/day [1].
4.2 XP13512

XP13512 ([α]-1-((α-isobutanoyloxyethoxy)carbonyl]amino-nomethyl)-1-cyclohexane acetic acid or N-[isobutyloxyethoxy]carbonyl gabapentin; Figure 3) is a novel prodrug of gabapentin that was designed to be actively absorbed throughout the intestine to overcome the capacity-limited oral absorption of gabapentin [52,53]. The oral bioavailability of gabapentin is dose dependent, decreasing from ~ 60% (with gabapentin 300 mg) to ~ 35% with doses used to treat epilepsy or neuropathic pain. The mechanism responsible for this dose-dependent and incomplete oral absorption is a narrow absorption window due to a saturable, solute transporter localised in the upper small intestine [54,55]. XP13512 is stable at physiological pH; following oral administration, it is almost completely absorbed and converted (by nonspecific esterases in tissues) to gabapentin. The oral availability of gabapentin from XP13512 was > 95% and 84% in rats and monkeys, respectively. In monkeys, the oral bioavailability was threefold that of gabapentin [53]. In contrast to gabapentin, XP13512 is absorbed by pH-dependent (pKa: 5) passive diffusion and by active transport that is mediated by at least two high-capacity nutrient transporters broadly distributed throughout the intestine monocarboxylate transporter and Na+-dependent multivitamin transporter. Consequently, oral administration of XP13512 to rats and monkeys resulted in improved bioavailability and dose proportionality compared with gabapentin [52,53]. The wide absorption window of XP13512 may enable its formulation in a SR dosage form.

Following single- and multiple-dose studies in healthy subjects, XP13512 showed dose-proportional exposure (AUC) with a high bioavailability (> 70%) compared with gabapentin. In a 3-way randomised, cross-over design study [56], a group of 12 healthy subjects received a SR formulation of XP13512 with and without food. The same subjects also received gabapentin for comparison purposes. The SR formulation of XP13512 demonstrated greater and sustained gabapentin exposure compared with gabapentin and was well tolerated. XP13512 is currently in Phase IIa clinical trials for post-herpetic neuralgia and restless legs syndrome.

5. Second generation to levetiracetam

5.1 Brivaracetam

Brivaracetam and seletracetam (Figure 4) are second generation to levetiracetam, which (in turn) is second generation to piracetam. From a screening of ~ 12,000 compounds for their affinity to the SV2A, brivaracetam was one of the most successful outcomes and displayed a significantly higher affinity (pKᵢ: 7.1) than levetiracetam (pKᵢ: 6.1) for SV2A [1,57,58]. The development of brivaracetam was motivated by the discovery of the new mechanism of action of levetiracetam involving an interaction with a novel binding site, the SV2A [7].

In anticonvulsant animal models, brivaracetam was more potent than levetiracetam in the corneally kindled mice (ED₅₀ values: 1.2 versus 7.3 mg/kg) and audiogenic seizure-susceptible mice (ED₅₀ values: 2.4 versus 30 mg/kg). Brivaracetam was also more potent than levetiracetam in preventing the development of seizures in the amygdala-kindled and in the genetic absence epilepsy rats from Strasbourg rats [59]. In all of these anticonvulsant models, it exhibited a good safety margin as reflected by high therapeutic index values. The drug was also active in animal models for neuropathic pain and essential tremor.

Brivaracetam showed potent anticonvulsant activity in an animal model of acute, partially drug-resistant self-sustaining status epilepticus; however, this was with higher doses than those that were effective in animal models of partial and generalised epilepsy [59].

5.2 Seletracetam

Like brivaracetam, seletracetam also has a higher affinity than levetiracetam to the SV2A protein and it displays a higher potency than levetiracetam in anticonvulsant animal (rodent) models. Seletracetam showed no inhibition of neuronal Na⁺ channels and was devoid of any direct action on both inhibitory and excitatory neurotransmission, except for a minor inhibition of the plateau phase of the NMDA current [60,61]. Seletracetam inhibits high voltage-activated Ca²⁺ current, a mechanism that might contribute to its antiepileptic activity [62].

Seletracetam was inactive in the classical MES and metrazole tests, but was active in the corneally kindled mice, hippocampal-kindled rats, audiogenic seizure-susceptible mice and genetic absence epilepsy rats from Strasbourg rats [63].

Both brivaracetam and seletracetam are currently in exploratory clinical trials, including studies in patients with partial seizures.

6. Fluorofelbamate: second generation to felbamate

Fluorofelbamate was designed as a second-generation drug to felbamate without the serious side effects of the latter and is currently in preclinical testing [1]. The substitution of a fluorine in place of a hydrogen at the β-position to the carbamate is thought to prevent the formation of the reactive toxic metabolite of felbamate ATPAL (2-phenylpropanal) [8].

Fluorofelbamate has a broad spectrum of activity in various anticonvulsant animal models including a self-sustaining status epilepticus animal model [64]. The ED₅₀ of fluorofelbamate is equivalent to and/or 3–8-fold higher than that of felbamate, and its protective index in the rat MES model is ~ 167 [1]. Fluorofelbamate also has a neuroprotective activity and it protects against chemically induced ischaemia in cultural hippocampal neurons and CA1 injury in hippocampal slices [65]. Fluorofelbamate caused a slight but statistically significant decrease in responses to kainite and NMDA receptor activation, and a decrease in voltage-dependent Na⁺ channels; however, the mechanism
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A number of experiments using pooled human liver S9 fractions has suggested that the potential metabolite of fluoro-felbamate, 2-fluoro-2-phenyl-1,3-propadiol monocarbamate, undergoes a metabolic pathway that can generate ATPAL-like reactive metabolites [1].

The hypothesis that the formation of the reactive ATPAL metabolite is the sole cause for the aplastic anaemia and hepatotoxicity that occurred following felbamate treatment is essential to the understanding of the mechanism of these fatal side effects and to the clinical development of fluoro-felbamate as a successful second generation to felbamate.

7. Expert opinion

A new AED can be successful if at least one of the following criteria are met: greater efficacy in refractory epilepsy; the ability to prevent or delay the onset of epilepsy (epileptogenesis) and/or potential for disease modification; broad use in other non-epileptic CNS disorders; fewer side effects and/or better tolerability; and improved ease of use (rapid titration, linear pharmacokinetics, lack of drug interaction, and once- or twice-daily dosing). Most of the new AEDs listed in Table 1 have the potential to meet some of these criteria. If they meet the broad-use (third) criteria, there is both a scientific and economic incentive for their development.

VPA is the most popular AED for second-generation drugs and indeed two of its amide derivatives (VPD and VCD) have been marketed in some European countries for > 35 years [6]. However, the CNS-active primary amide of VPA (VPD) failed to become a second generation to VPA due to its presystemic biotransformation to VPA [33]. The marketing of VCD, a constitutional isomer of VPD that acts as a drug on its own and not as a prodrug to its corresponding acid, was stopped a few years ago presumably due to commercial reasons. Nevertheless, the prominent CNS activity of VCD in animal models for epilepsy and neuropathic pain [34,36] and its activity in patients with bipolar disorder [43] coupled with its long clinical experience in Europe makes VCD an attractive candidate to become a successful second generation to VPA. VCD can be developed first as a racemate and, subsequently following a chiral switch, as an individual stereoisomer.

A broad-spectrum drug, such as VPA, is used widely in the treatment of patients with multiple seizure types; however, as the drug needs to be taken chronically, the adverse events associated with VPA treatment are of major concern. If a non-teratogenic and non-hepatotoxic CNS drug is developed, it could also be available to children and women of childbearing age, as there are (currently) major potential disadvantages in using VPA for these patient groups. This implies that there is a need for the design and development of a more potent second generation to VPA compound without its major side effects of teratogenicity and hepatotoxicity. Several reports in the literature suggest that it is possible to develop a second-generation VPA with such attributes.

A pharmacokinetic-based design of non-teratogenic amide derivatives of VPA was undertaken and it led to the development of valrocemide, VCD, (2S,3S)-VCD, (R)-PID, MTMCD and TMC urea (Figure 5). These compounds have displayed promising activity in various animal models for epilepsy, neuropathic pain and bipolar disorder. The selection of the best candidate for clinical trials can be carried out only after a complete toxicological package (which is mandatory for Phase I clinical trials) and an investigational new drug submission. Even with their promising performances in various animal models of epilepsy and neuropathic pain and lack of teratogenicity, only clinical trials in refractory epileptic patients or other target patient populations will provide a definitive answer regarding the actual potential in becoming second generation to VPA.

At present, there are three second-generation to VPA compounds undergoing clinical trials (valrocemide, NPS 1776 and VCD), each of which emerged from different design strategies. At present, valrocemide is in Phase II clinical trials. It was found to be non-teratogenic and more potent than VPA in animal studies. In humans, it is mainly biotransformed to valproyl glycine and only 5% of the dose is
New antiepileptic drugs that are second generation to existing antiepileptic drugs

Figure 5. Chemical structures of felbamate and fluorofelbamate.

![Chemical structures of felbamate and fluorofelbamate](image)

biotransformed to VPA. NPS 1776 is being developed as a new AED, but its pharmacokinetic profile (including short half-life) is a drawback. VCD has recently demonstrated activity in patients with bipolar disorder [43].

Although the development of second generations to existing AEDs based on pharmacokinetic- and/or pharmacodynamic-based design can complement existing strategies in drug development, other needs must be addressed. Thus the new AEDs that are currently being developed should also have a potential in non-epileptic CNS disorders, such as neuropathic pain, migraine prophylaxis and bipolar disorder, which will triple the market potential of any new AED and will make its costly development worthwhile despite the 10 new AEDs that have entered the market in the last decade.

The present strategies for the development of new AEDs are: screening of new compounds in various anticonvulsant animal (rodent) models, designing second-generation AEDs by modifying the structure of existing AEDs and targeting specific physiological substrates [66,67].

Second-generation AEDs are likely to work with a mechanism of action similar to that of their parent compounds and thus may not provide the incentive of a new mechanism of action. However, this disadvantage might be outweighed by the advantage of having extensive information about pharmacokinetic, toxicological and pharmacodynamic problems associated with the parent drug and by relying on the vast array of anticonvulsant animal models that have a proven reputation and prediction capabilities since the discovery of phenytoin in 1938 [68]. In addition, the design of second-generation AEDs is less risky economically for the industry than the development of a completely new chemical entity that possesses a new mechanism of action; thus it is not too speculative to predict that eslicarbazepine acetate is more likely to become a second generation to CBZ than a CBZ derivative with a new mechanism of action (such as ADCI).

In the Holy Scripture it is written ‘If there is not flour there is no Torah’. This also has applies to academia and industry. To achieve commercialisation, academic initiatives must present an incentive to the pharmaceutical industry. If the current clinical trial of ONO-2506 [46] in neurodegenerative diseases and of VPA in cancer patients is successful [47-49], it may serve as a model and incentive for future research that opens the way for the possible utilisation of AEDs or other VPA derivatives in the treatment of Parkinson’s and Alzheimer’s diseases. Thus the design and development of broad-spectrum AEDs will be more attractive to industry as their utilisation in epilepsy may open doors for subsequent therapeutic use (following regulatory approval) in other non-epileptic CNS disorders.

Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


• A comprehensive review of new AEDs that are in development.


• An extensive review on second generation to VPA.


• A paper on the unique mechanism of action of levetiracetam and its second-generation drugs.


10. VOLOSOV A, XIANDONG S, PERUCCA E et al.: Enantioselective pharmacokinetics of 10-hydroxy...
New antiepileptic drugs that are second generation to existing antiepileptic drugs


A SAR paper that describes the rationale in the development of eslicarbazepine acetate (BIA 2-093).


This paper describes ONO-2506 (arundic acid), a second generation to valproic acid, and its potential in neurodegenerative diseases.

40. SOBOLO, YAGEN B., WHITE HS et al.: Preclinical evaluation of 2,2,3,3-tetramethylcyclopropanecarbonyl-urea, a novel second generation to valproic acid, antiepileptic drug. Neuropharmacology (Submitted).


47. This paper describes ONO-2506 (arundic acid), a second generation to VPA, and its potential in neurodegenerative diseases.


