Since 1989, 18 second-generation antiseizure medications have reached the market, resulting in a greatly increased range of treatment options for patients and prescribers. 30 years have passed and now is the time for an appraisal of the effect of these medications on clinical outcomes. Every antiseizure medication needs to be assessed individually, but overall second-generation drugs are less likely to cause pharmacokinetic interactions than their older counterparts. Some second-generation antiseizure medications have shown advantages in tolerability and safety, particularly in the treatment of older patients and women of childbearing potential. Disappointingly, however, none of these medications appear to be more efficacious than first-generation antiseizure medications, highlighting the need for novel strategies in epilepsy drug development. Although second-generation antiseizure medications have not substantially reduced the proportion of patients with pharmacoresistant epilepsy, their availability has enabled more opportunities to tailor treatment choice to the characteristics of the individual.

Introduction

Antiseizure medications introduced after 1989 are generally referred to as second-generation drugs. The development of these medications was primarily aimed at addressing the shortcomings of older, first-generation drugs (barbiturates, benzodiazepines, carbamazepine, ethosuximide, phenytoin, and valproic acid), such as their unfavourable pharmacokinetics and drug interaction profiles, ineffectiveness in controlling the seizures of a third of patients, and propensity to induce many adverse effects.

Three decades after their introduction, we evaluate in this Review the overall effect of second-generation antiseizure medications on epilepsy management and the extent by which these drugs have overcome the shortcomings of older, first-generation medications. We first discuss how second-generation antiseizure medications have improved clinical management by focusing on three key aspects: (1) pharmacokinetic properties and drug interaction profiles, (2) efficacy, and (3) adverse effects. Second, we discuss how access to more pharmacological treatments can be used to improve treatment choices in everyday practice. Finally, we provide an overview of future directions in the effort to develop more innovative treatments, and the potential implications of this progress on epilepsy management.

Pharmacokinetics and drug interactions

Pharmacokinetic features

Pharmacokinetics affect the concentration profiles of drugs at the site of action and govern the intensity and duration of pharmacological effects. First-generation antiseizure medications have suboptimal pharmacokinetics in several respects. These drugs are subject to extensive pharmacokinetic variability, and thus dosage must be individualised on the basis of assessments of clinical response and measurements, whenever indicated, of serum drug concentrations. For phenytoin and carbamazepine, dose adjustments are complicated by non-linear pharmacokinetics, because of Michaelis–Menten kinetics (phenytoin) and dose-dependent autoinduction (carbamazepine). Furthermore, all first-generation antiseizure medications are extensively metabolised by enzymes sensitive to induction and inhibition, and their serum concentrations and resulting clinical responses can be affected by many interacting comedications. Carbamazepine, phenytoin, and phenobarbital are potent enzyme inducers, and valproic acid inhibits several metabolic pathways, particularly glucuronidation; therefore, these medications are often a cause of clinically important drug–drug interactions.

Although the literature often states that second-generation antiseizure medications have more favourable pharmacokinetics and lower interaction potentials than older agents, available evidence suggests that this statement cannot be generalised and that each second-generation drug needs to be considered on its own merits (table 1). Like older agents, most second-generation antiseizure medications are eliminated metabolically and are susceptible to extensive pharmacokinetic variability. For some second-generation medications, such as gabapentin, rufinamide, and cannabidiol, variability in serum drug concentrations is amplified by inconsistent oral bioavailability. Stiripentol also has complex dose-dependent pharmacokinetics, similar to phenytoin. Most second-generation antiseizure medications have short half-lives and require twice daily dosing to maintain therapeutic cover during a dosing interval. However, for drugs with particularly short half-lives, such as gabapentin and tiagabine, three times daily dosing is preferred in some patients, whereas lamotrigine (when not used in combination with enzyme inducers), eslicarbazepine acetate, perampanel, and zonisamide can be given once daily. Extended-release formulations designed for once daily dosing have been developed for lamotrigine, levetiracetam, oxcarbazepine, and topiramate. The main purpose of these formulations is to improve convenience and facilitate adherence, but there is little-to-no evidence of their use being associated with improved efficacy or tolerability.
## Drugs used to treat common epilepsy syndromes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of approval</th>
<th>Main epilepsy-related indications</th>
<th>Linear kinetics</th>
<th>Oral bioavailability</th>
<th>Half-life (h)</th>
<th>Primary routes of elimination</th>
<th>Main pharmacokinetic drug interactions</th>
<th>Effects by other drugs</th>
<th>Effects on other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivaracetam</td>
<td>2016</td>
<td>Focal seizures</td>
<td>Yes</td>
<td>Almost complete</td>
<td>6–11</td>
<td>Metabolic</td>
<td>Serum brivaracetam concentrations are lowered by enzyme-inducing ASMs and possibly by cannabidiol</td>
<td>Brivaracetam increases serum concentrations of carbamazepine-10,11-epoxide</td>
<td></td>
</tr>
<tr>
<td>Eslicarbazepine acetate</td>
<td>2009</td>
<td>Focal seizures</td>
<td>Yes</td>
<td>Almost complete*</td>
<td>13–20*</td>
<td>Metabolic and renal*</td>
<td>Serum licarbazepine concentrations are lowered by enzyme-inducing ASMs</td>
<td>Eslicarbazepine acetate reduces the serum concentrations of contraceptive steroids, simvastatin, and rosuvastatin</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1993</td>
<td>Focal seizures</td>
<td>No†</td>
<td>&lt;65%†</td>
<td>5–9</td>
<td>Renal</td>
<td>Serum lacosamide concentrations are lowered by enzyme-inducing ASMs</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>2008</td>
<td>Focal seizures</td>
<td>Yes</td>
<td>Almost complete</td>
<td>12–16</td>
<td>Renal and metabolic</td>
<td>Serum lacosamide concentrations are lowered by enzyme-inducing ASMs</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>1990</td>
<td>Focal, generalised tonic-clonic and absence seizures; seizures associated with Lennox Gastaut syndrome</td>
<td>Yes</td>
<td>Almost complete</td>
<td>20–40†</td>
<td>Metabolic</td>
<td>Serum lamotrigine concentrations are increased by valproic acid and lowered by enzyme-inducing drugs and oestrogen-containing medications</td>
<td>Lamotrigine reduces the serum concentration of levonorgestrel</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1999</td>
<td>Focal, generalised tonic-clonic and myoclonic seizures</td>
<td>Yes</td>
<td>Almost complete</td>
<td>6–8</td>
<td>Metabolic and renal</td>
<td>Serum levetiracetam concentrations are lowered by enzyme-inducing ASMs</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>1990</td>
<td>Focal seizures</td>
<td>Yes</td>
<td>Almost complete*</td>
<td>7–12*</td>
<td>Metabolic and renal*</td>
<td>Serum licarbazepine concentrations are lowered by enzyme-inducing ASMs</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Perampanel</td>
<td>2012</td>
<td>Focal and generalised tonic-clonic seizures</td>
<td>Yes</td>
<td>Almost complete</td>
<td>50–130§</td>
<td>Metabolic</td>
<td>Serum perampanel concentrations are lowered by enzyme-inducing ASMs and increased by ketoconazole</td>
<td>Perampanel at doses &gt;8 mg/day (but not at doses of 4 mg/day and 8 mg/day) decreases the serum concentration of levonorgestrol</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>2004</td>
<td>Focal seizures</td>
<td>Yes</td>
<td>Almost complete</td>
<td>5–7</td>
<td>Renal</td>
<td>Serum tiagabine concentrations are lowered by enzyme-inducing ASMs</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>1996</td>
<td>Focal seizures</td>
<td>Yes</td>
<td>Almost complete</td>
<td>5–9§</td>
<td>Metabolic</td>
<td>Serum tiagabine concentrations are lowered by enzyme-inducing ASMs</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Topiramate</td>
<td>1995</td>
<td>Focal and generalised tonic-clonic seizures; seizures associated with Lennox Gastaut syndrome</td>
<td>Yes</td>
<td>Almost complete</td>
<td>20–30§</td>
<td>Metabolic and renal</td>
<td>Serum topiramate concentrations are lowered by enzyme-inducing ASMs</td>
<td>Topiramate can increase the serum concentrations of phenytoin; at doses ≥200 mg/day, topiramate can reduce the serum concentrations of ethinylestradiol</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>1989</td>
<td>Focal seizures</td>
<td>Yes</td>
<td>Almost complete</td>
<td>50–70§</td>
<td>Metabolic and renal</td>
<td>Serum zonisamide concentrations are lowered by enzyme-inducing ASMs</td>
<td>None reported</td>
<td>None reported</td>
</tr>
</tbody>
</table>

## Drugs used mainly to treat orphan epilepsy indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of approval</th>
<th>Main epilepsy-related indications</th>
<th>Linear kinetics</th>
<th>Oral bioavailability</th>
<th>Half-life (h)</th>
<th>Primary routes of elimination</th>
<th>Main pharmacokinetic drug interactions</th>
<th>Effects by other drugs</th>
<th>Effects on other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabidiol</td>
<td>2018</td>
<td>Seizures associated with Dravet syndrome and Lennox Gastaut syndrome</td>
<td>No†</td>
<td>&lt;10%†</td>
<td>10–17</td>
<td>Metabolic</td>
<td>Serum cannabidiol concentrations are increased by ketoconazole and clobazam, and lowered by enzyme-inducing drugs, the serum concentrations of the active metabolite 7-hydroxycannabidiol are increased by clobazam and decreased by stiripentol</td>
<td>Cannabidiol increases the serum concentrations of clobazam and, to a much greater extent, the serum concentrations of the active metabolite N-desmethylclobazam; preliminary data suggest that cannabidiol might also increase the serum concentrations of stiripentol, brivaracetam, warfarin, and tacrolimus</td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>2017</td>
<td>Focal seizures associated with tuberous sclerosis complex</td>
<td>Yes</td>
<td>Not reported</td>
<td>25–35</td>
<td>Metabolic</td>
<td>Serum everolimus concentrations are increased by CYP3A4 and p-glycoprotein inhibitors (eg, ketoconazole, verapamil, and erythromycin) and lowered by enzyme-inducing drugs</td>
<td>None reported</td>
<td>None reported</td>
</tr>
</tbody>
</table>

(Table 1 continues on next page)
Drug interaction potential

Drug interactions can adversely affect clinical outcomes. Second-generation medications are differentiated from first-generation medications by not sharing the prominent enzyme-inducing activity associated with classic first-generation drugs like carbamazepine, phenytoin, and barbiturates. However, some second-generation antiseizure medications can stimulate the metabolism of steroid contraceptives (table 1). Specifically, oxcarbazepine, eslicarbazepine acetate, felbamate, and high-dose perampanel can reduce the serum concentrations of oestrogens or progestogens, or both, by 40% or more, whereas lamotrigine, rufinamide, and high-dose topiramate can decrease the serum concentrations of contraceptive steroids by a smaller, but still potentially clinically significant, extent.1 With regard to enzyme-inhibiting activity, this is modest or negligible for most second-generation antiseizure medications, with stiripentol, cannabidiol, and felbamate being notable exceptions (table 1). In particular, stiripentol and cannabidiol inhibit cytochrome P450 2C19; this inhibition leads to increased serum concentrations of N-desmethylclobazam, the active metabolite of clobazam, to a clinically significant extent.10,19

Although most second-generation antiseizure medications rarely effect interactions, they can be affected by interactions caused by other drugs (table 1). For example, lamotrigine metabolism is subject to potent inhibition by valproic acid and stimulation by enzyme inducers such as carbamazepine, phenytoin, barbiturates, and oestrogen-containing medications, including contraceptive steroids.3 These interactions are clinically important and require adjustments to be made in lamotrigine dose.

Therapeutic implications

Unlike older agents, most second-generation antiseizure medications have linear pharmacokinetics (table 1), which is advantageous because a predictable relationship between daily dose and serum drug concentration facilitates dose adjustments. These medications, however, are also subject to considerable pharmacokinetic variability. Although monitoring of serum concentration was originally claimed to be unnecessary for second-generation antiseizure medications, there is now evidence that therapeutic drug monitoring can be valuable in patients receiving some of these drugs.7

Therapeutic drug monitoring of second-generation antiseizure medications is especially valuable in situations associated with major pharmacokinetic changes—eg, in the management of lamotrigine-treated women who become pregnant or start taking a combined steroid contraceptive. These conditions cause a variable and often prominent decrease in serum lamotrigine concentrations,
and a deterioration in seizure control is likely to occur when the fall exceeds a predefined threshold. In a meta-analysis of six observational studies, therapeutic drug monitoring in women treated with lamotrigine during pregnancy was found to be associated with a reduced risk of seizures recurring or worsening. Although one randomised controlled trial (RCT) did not show a favourable effect of therapeutic drug monitoring on seizure outcomes during pregnancy, the findings should be interpreted cautiously because of the trial’s methodological limitations, which included a sample size below target and the enrolment of women treated with different antiseizure drugs (not solely lamotrigine) and late in pregnancy, as recruitment was extended until 24 weeks of gestation.

Another clinically relevant feature of most second-generation antiseizure medications is a low propensity to cause metabolic drug interactions, which is especially advantageous for patients receiving other medications, as is often the case in the presence of comorbidities. Avoidance of enzyme-inducing antiseizure medications might also offer safety benefits because the induction of the metabolism of physiological substrates (eg, hormones, lipids, and vitamins) is probably responsible for some of the chronic adverse effects of first-generation drugs, including endocrine dysfunction and bone loss. However, there is no high-quality evidence that suggests that the use of second-generation over first-generation antiseizure medications is associated with lower risks of hard endpoints such as fractures and cardiovascular events.

**Seizure outcomes**

In people with newly diagnosed epilepsy, the goal of treatment is seizure freedom, which is also the main efficacy endpoint in RCTs done in these populations. However, in adjunctive therapy trials for patients with drug-resistant epilepsy, efficacy is quantified in terms of percentage seizure reduction, because few patients attain seizure freedom in these trials. As there have been no adequately powered RCTs comparing first-generation and second-generation antiseizure medications in the adjunctive therapy setting, the comparative efficacy of these drugs can only be inferred from monotherapy trials of newly diagnosed epilepsy.

**Randomised controlled trials**

In 2013, a subcommittee of the International League against Epilepsy (ILAE) published a systematic review of 64 comparative RCTs and 11 meta-analyses undertaken between 1940 and 2012, which assessed the efficacy of antiseizure medications as initial monotherapy for different seizure types and epilepsy syndromes. This review reported that the second-generation drugs levetiracetam and zonisamide join carbamazepine and phenytoin as antiseizure medications with class 1 evidence of efficacy for initial monotherapy for focal seizures in adults, whereas only ethosuximide and valproic acid had class 1 evidence of efficacy as initial monotherapy for absence seizures. No class 1 studies reviewed suggested that second-generation antiseizure medications had greater efficacy than first-generation antiseizure medications (table 2).

Since this systematic review, two class 1 RCTs compared lacosamide with controlled-release carbamazepine as initial treatment for adults with newly diagnosed focal epilepsy and found no differences in efficacy between these second-generation drugs and the comparator, similar to findings of earlier trials involving levetiracetam and zonisamide. In all these RCTs, the majority of patients achieved seizure freedom for at least 6 months on the lowest dose tested (levetiracetam 1000 mg/day, lacosamide 200 mg/day, eslicarbazepine acetate 800 mg/day, zonisamide 300 mg/day, and controlled-release carbamazepine 400–600 mg/day). A subsequent network meta-analysis reported no difference in 6-month and 12-month seizure freedom between each of these second-generation drugs and controlled-release carbamazepine in adults with focal epilepsy.

A double-blind RCT in older people (≥60 years) with new-onset focal seizures found no difference in seizure freedom rates between lamotrigine, levetiracetam, and controlled-release carbamazepine. Similarly, a post-hoc analysis of older patients (≥60 years) included in an unblinded RCT of newly diagnosed, predominantly focal epilepsy reported similar efficacy between levetiracetam and controlled-release carbamazepine or extended-release valproic acid. A subsequent meta-analysis also showed that lamotrigine, levetiracetam, and gabapentin did not have higher efficacy than carbamazepine when used as initial monotherapy for epilepsy with onset in old age.

Regarding paediatric epilepsies, a network meta-analysis of RCTs in children and adolescents (0–18 years) with newly diagnosed focal seizures found no differences in efficacy between carbamazepine, phenobarbital, phenytoin, valproic acid, lamotrigine, and oxcarbazepine, although confidence limits were wide and there was a trend favouring lamotrigine and carbamazepine. A well designed, double-blind class 1 RCT found lamotrigine to be less efficacious than ethosuximide and valproic acid as initial treatment in patients with childhood absence epilepsy. For patients with newly diagnosed infantile spasms, a Cochrane meta-analysis concluded that hormonal treatment (prednisolone or tetracosactide depot) resolved spasms faster and in more infants than the second-generation drug vigabatrin; however, this conclusion might not translate into better long-term outcomes, and, for infantile spasms associated with tuberous sclerosis, vigabatrin might have higher efficacy than hormonal treatment.

Preliminary results in abstract form from the Standard versus New Antiepileptic Drugs (SANAD) II RCT suggest that levetiracetam is inferior to valproic acid in time to 12-month and 24-month remission in patients with generalised and unclassified epilepsies; however, this RCT is not included in our summary of ILAE class 1 RCTs.
Review comparing second-generation and first-generation anti-seizure medications as initial monotherapy because of its unblinded design (table 2). In the earlier SANAD I study, lamotrigine was less efficacious, and topiramate was equally efficacious and less well tolerated, than valproic acid in patients with generalised or unclassified epilepsy.

<table>
<thead>
<tr>
<th>Adolescents and adults with focal epilepsy</th>
<th>Second-generation ASM, participants</th>
<th>First-generation ASM, participants</th>
<th>Age eligibility (mean age), years</th>
<th>Maximum duration of follow-up (weeks)</th>
<th>Efficacy or effectiveness outcomes</th>
<th>Patients with AEs (%)</th>
<th>Patients with AEs leading to withdrawal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chadwick et al (1999)24</td>
<td>Vigabatrin 1-4 g/day (n=228)</td>
<td>Carbamazepine 200-1200 mg/day</td>
<td>12-65 (36)</td>
<td>52</td>
<td>More patients on vigabatrin withdrew for lack of efficacy (23 vs 9, p&lt;0.03); no difference between treatments in time to withdrawal (PE)</td>
<td>84% (vigabatrin); 85% (carbamazepine)</td>
<td>20% (vigabatrin); 27% (carbamazepine)</td>
</tr>
<tr>
<td>Brodie et al (2007)25</td>
<td>Levetiracetam 1000-3000 mg/day (n=285)</td>
<td>Carbamazepine-CR 400-1200 mg/day</td>
<td>16 (39)</td>
<td>113</td>
<td>6-month seizure freedom rate at the last evaluated dose (PE) did not differ between treatments (72% for levetiracetam; 73% for carbamazepine-CR)‡</td>
<td>80% (levetiracetam); 81% (carbamazepine-CR)</td>
<td>14% (levetiracetam); 19% (carbamazepine-CR)</td>
</tr>
<tr>
<td>Baulac et al (2012)26</td>
<td>Zonisamide 300-500 mg/day§ (n=281)</td>
<td>Carbamazepine-CR 600-1200 mg/day§</td>
<td>18-75 (36)</td>
<td>108</td>
<td>6-month seizure freedom rate at the last evaluated dose (PE) did not differ between treatments (79% for zonisamide; 84% for carbamazepine-CR)‡</td>
<td>60% (zonisamide); 62% (carbamazepine-CR)</td>
<td>11% (zonisamide); 12% (carbamazepine-CR)</td>
</tr>
<tr>
<td>Baulac et al (2017)27</td>
<td>Lacosamide 200-600 mg/day (n=444)</td>
<td>Carbamazepine-CR 400-1200 mg/day</td>
<td>16 (42)</td>
<td>121</td>
<td>6-month seizure freedom rate at the last evaluated dose (PE) did not differ between treatments (75% for lacosamide; 72% for carbamazepine-CR)‡</td>
<td>74% (lacosamide); 75% (carbamazepine-CR)</td>
<td>11% (lacosamide); 16% (carbamazepine-CR)</td>
</tr>
<tr>
<td>Trinka et al (2018)28</td>
<td>Eslicarbazepine acetate 800-1600 mg/day (n=401)</td>
<td>Carbamazepine-CR 400-1200 mg/day</td>
<td>16 (38)</td>
<td>121</td>
<td>6-month seizure freedom rate at the last evaluated dose (PE) did not differ between treatments (71% for eslicarbazepine acetate; 76% for carbamazepine-CR)‡</td>
<td>76% (eslicarbazepine acetate); 80% (carbamazepine-CR)</td>
<td>14% (eslicarbazepine acetate); 18% (carbamazepine-CR)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Older people (≥60 years) with focal epilepsy</th>
<th>First-generation ASM, participants</th>
<th>Second-generation ASM, participants†</th>
<th>Age eligibility (mean age), years</th>
<th>Maximum duration of follow-up (weeks)</th>
<th>Efficacy or effectiveness outcomes</th>
<th>Patients with AEs (%)</th>
<th>Patients with AEs leading to withdrawal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowan et al (2005)29¶</td>
<td>Gabapentin 1500 mg/day (n=195); lamotrigine 150 mg/day (n=200)</td>
<td>Carbamazepine 600 mg/day (n=199)</td>
<td>≥60 (72)</td>
<td>48</td>
<td>Seizure freedom rate at 12 months was not significantly different across treatments (47% for gabapentin, 51% for lamotrigine, and 64% for carbamazepine); retention at 12 months (PE) was lower for carbamazepine (36%) compared with lamotrigine (56%, p=0.0001) and gabapentin (49%, p=0.01)</td>
<td>Not reported; incidence of specific AEs differed across groups</td>
<td>22% (gabapentin); 12% (lamotrigine); 31% (carbamazepine)</td>
</tr>
<tr>
<td>Werhahn et al (2015)30§</td>
<td>Levetiracetam 1000-3000 mg/day (n=122); lamotrigine 100-300 mg/day (n=117)</td>
<td>Carbamazepine-CR 400-1200 mg/day (n=121)</td>
<td>≥60 (72)</td>
<td>58</td>
<td>Seizure freedom rate at 58 weeks was not significantly different across treatments (43% for levetiracetam, 39% for lamotrigine, 33% for carbamazepine-CR); retention at week 58 (PE) was higher for levetiracetam (62%) than for carbamazepine-CR (46%, p=0.02); no difference in retention between lamotrigine (55%) and levetiracetam or carbamazepine-CR</td>
<td>89% (levetiracetam); 94% (lamotrigine); 83% (carbamazepine-CR)</td>
<td>17% (levetiracetam); 25% (lamotrigine); 32% (carbamazepine-CR)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children and adolescents with focal or generalised tonic-clonic seizures</th>
<th>First-generation ASM, participants</th>
<th>Second-generation ASM, participants†</th>
<th>Age eligibility (mean age), years</th>
<th>Maximum duration of follow-up (weeks)</th>
<th>Efficacy or effectiveness outcomes</th>
<th>Patients with AEs (%)</th>
<th>Patients with AEs leading to withdrawal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guerreo et al (1997)31</td>
<td>Oxcarbazepine 450-2400 mg/day (n=97)</td>
<td>Phenytoin 150-800 mg/day (n=96)</td>
<td>5-18 (11)</td>
<td>56</td>
<td>Seizure freedom rate for patients with at least one seizure assessment during 48 weeks maintenance (PE) did not differ between treatments (50% for oxcarbazepine; 61% for phenytoin)</td>
<td>82% (oxcarbazepine); 89% (phenytoin)</td>
<td>2% (oxcarbazepine); 15% (phenytoin)**</td>
</tr>
</tbody>
</table>

(Table 2 continues on next page)
whereas oxcarbazepine, lamotrigine, and topiramate were equally efficacious, and gabapentin was less efficacious, than the first-generation comparator carbamazepine in patients with focal epilepsies. These findings add to the evidence that second-generation antiseizure medications are not more efficacious than first-generation drugs when used for initial treatment in patients with focal and generalised epilepsies.

**Long-term outcome studies**

Several studies have investigated the long-term prognosis of drug-treated epilepsy and the value of second-generation antiseizure medications in improving outcomes in different populations. A longitudinal cohort study based in Scotland (UK) has provided an informative dataset of newly diagnosed adolescents and adults with common epilepsies. During 30 years of patient follow-up, there have been four sets of consecutive analyses; the first set of 470 patients were reported in 2002 and 2001, and the 969 patients who initiated treatment between 2002 and 2012 (figure 1). Overall, these studies do not support an improved outcome with the increased approval of antiseizure medications over the past three decades.

**Tolerability and safety**

**Comparative tolerability**

Most RCTs comparing first-generation and second-generation antiseizure medications were done in patients with new-onset focal epilepsy, used carbamazepine as a comparator, and had a primary endpoint of retention on the epilepsy treatment that patients were randomly assigned to (a combined measure of efficacy and tolerability). None of the second-generation drugs were shown to be more efficacious than carbamazepine; however, in some studies, lamotrigine resulted in a higher proportion of patients retained on treatment because of better tolerability and, in a network meta-analysis of

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**Table 2:** Summary of class 1 randomised controlled trials comparing the efficacy, effectiveness, and safety of first-generation and second-generation ASMs

<table>
<thead>
<tr>
<th>Second-generation ASM, participants</th>
<th>First-generation ASM, participants</th>
<th>Age eligibility (mean age, years)</th>
<th>Maximum duration of follow-up (weeks)</th>
<th>Efficacy or effectiveness outcomes</th>
<th>Patients with AEs (%)</th>
<th>Patients with AEs leading to withdrawal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glauser et al (2013)¹³</td>
<td>Lamotrigine up to 12 mg/kg per day or 600 mg/day, whichever was lower†† (n=149)</td>
<td>Ethosuximide up to 60 mg/kg per day or 2000 mg/day, whichever was lower†† (n=155); valproic acid up to 60 mg/kg per day or 3000 mg/day, whichever was lower†† (n=147)</td>
<td>Indefinite (at least 24 months of seizure freedom for patients not meeting treatment failure criteria)</td>
<td>Treatment failure due to lack of seizure control occurred in 55% of patients for lamotrigine compared with 36% for ethosuximide and 34% for valproic acid; freedom from treatment failure (lack of seizure control, meeting safety exit criteria, or withdrawal from any other reason) at 12 months (PE) was higher for ethosuximide (45%) and valproic acid (44%) compared with lamotrigine (21%, p=0·001 for both comparisons)</td>
<td>Not reported; incidence of specific AEs differed across groups</td>
<td>20% (lamotrigine); 25% (ethosuximide); 33% (valproic acid)</td>
</tr>
</tbody>
</table>

ASMs were given as monotherapy in adults, adolescents, and children with newly diagnosed epilepsy. AE=adverse event. ASM=antiseizure medication. CR=controlled-release. ILAE=International League Against Epilepsy. PE=primary endpoint. †Class 1 trials (as per International League Against Epilepsy) are prospective randomised controlled trials in a representative population that meet all six criteria: (1) efficacy or effectiveness (retention) as primary outcome variable; (2) treatment duration ≥ 18 weeks; (3) double blind design; (4) for superiority trials, superiority should be shown, and for non-inferiority trials or superiority trials that did not show superiority, the test drug’s efficacy or effectiveness lower limit (95% CI) should be higher than a 20% lower boundary relative to an adequate comparator’s point estimate of efficacy or effectiveness using a per-protocol study population (for age and seizure type subgroups); (5) study exit not forced by a predetermined number of treatment-emergent seizures; and (6) appropriate statistical analysis. ‡Dose range (or target doses) and number of randomised patients (safety set). §Per-protocol analysis. ¶Dose could be reduced to 200 mg/day for zonisamide and 400 mg/day for carbamazepine for patients that did not tolerate the initial target dose. ‖This trial included older patients with any seizure type (although mostly focal) who could have previously received other ASMs at subtherapeutic serum concentrations. ‌Dose could be adjusted on the basis of clinical response. **Odds of discontinuing treatment for any reason were higher for phenytoin than for oxcarbazepine (odds ratio 1·99, 95% CI 1·004–3·934). ‡‡Dose was uptitrated until seizure control was achieved or until the maximum allowed or tolerated dose was reached.

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(Continued from previous page)

**Children with absence seizures (childhood absence epilepsy)**

- **Glauser et al (2013)¹³**
  - Lamotrigine up to 12 mg/kg per day or 600 mg/day, whichever was lower†† (n=149)
  - Ethosuximide up to 60 mg/kg per day or 2000 mg/day, whichever was lower†† (n=155)
  - Valproic acid up to 60 mg/kg per day or 3000 mg/day, whichever was lower†† (n=147)

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monotherapy studies, treatment failure due to adverse events occurred significantly earlier with carbamazepine than lamotrigine. In terms of the proportion of patients who had adverse events, treatment-emergent adverse events, or discontinued treatment because of adverse events, individual class 1 RCTs did not show a significantly improved overall tolerability of levetiracetam, zonisamide, or eslicarbazepine acetate over carbamazepine (table 2). A network meta-analysis of these four RCTs also found no difference in the proportions of patients with treatment-emergent adverse events, but there were significantly fewer withdrawals due to treatment-emergent adverse events with lacosamide than carbamazepine. Another meta-analysis based on data from two studies found treatment failure due to adverse events to occur later with oxcarbazepine than with phenytoin, indicating a better tolerability of oxcarbazepine; however, neither oxcarbazepine, nor eslicarbazepine acetate, had better overall tolerability than carbamazepine, which is a more appropriate comparator than phenytoin.

According to a network meta-analysis of six RCTs involving paediatric patients with newly diagnosed focal and generalised epilepsy, the proportion of patients who withdrew because of adverse events was lower with oxcarbazepine than with phenytoin, and with lamotrigine than with carbamazepine. A class 1 RCT in children with predominantly focal epilepsy reported superior tolerability with oxcarbazepine than with phenytoin, but phenytoin might not be the most appropriate comparator for this population (table 2). A meta-analysis of ten RCTs in older people (aged ≥60 years) concluded that lamotrigine was better tolerated than carbamazepine, whereas, in a three-arm double-blind RCT also done in older people (60–95 years), levetiracetam had a better retention on treatment than carbamazepine because of superior tolerability and retention on lamotrigine was intermediate and did not differ from the two other comparators (table 2). A class 1 RCT done in an older population (aged ≥65 years) also found that withdrawals for adverse events were significantly less frequent with lamotrigine than with immediate-release carbamazepine (table 2). Similarly, a post-hoc analysis of older patients (≥60 years) included in an open-label RCT reported that discontinuations due to adverse events were higher with carbamazepine than levetiracetam or valproic acid, however there was a higher incidence of serious adverse events with levetiracetam than with carbamazepine or valproic acid.

Consistently, there is a lack of evidence that second-generation antiseizure medications have a superior overall tolerability than carbamazepine, with the exception of lamotrigine, which is generally better tolerated (especially in older people, in whom levetiracetam might also have an advantage over carbamazepine). However, these findings should be interpreted cautiously because of both the questionable comparability of the doses selected and the use in some studies of immediate-release formulations of carbamazepine, which are suboptimal for tolerability. Despite similar overall adverse events for many first-generation and second-generation antiseizure medications, the type and profile of adverse effects differ, with advantages for the use of some second-generation drugs in selected patient groups.

**Safety issues**

Three second-generation antiseizure medications had major safety issues identified after their introduction to the market. Within 1 year of its approval in 1993, felbamate use became restricted because of a high incidence of fatal aplastic anaemia and hepatic failure. Retigabine was approved in 2011, however the US Food and Drug Administration issued a warning 2 years later for blue discoloration of the skin, eyes, and retina, pigment deposition and the drug was withdrawn from the market in 2017. In 1989, vigabatrin was approved, but it was not until 1997 that the drug’s association with irreversible visual field defects was observed.

Most women with active epilepsy need to continue their treatment during pregnancy and thus an important safety aspect is the possibility of maternal use during pregnancy harming the fetus. Of the first-generation antiseizure medications, primidone, phenobarbital, valproic acid, and carbamazepine have been associated with intrauterine growth restrictions expressed as small for gestational age or small head circumference. For infants exposed to antiseizure medications, studies have shown that the greatest risk of being small for gestational age is associated with the second-generation drugs topiramate and zonisamide, and that topiramate exposure is also associated with considerable risk of microcephaly.

A 2016 Cochrane meta-analysis confirmed a high risk of major congenital malformations after prenatal exposure...
to valproic acid, with a prevalence of 10·9% (95% CI 8·9–13·1). Increased relative risks were also noted for phenobarbital (2·8, 95% CI 1·6–5·1), phenytoin (2·4, 1·1–5·0), carbamazepine (2·0, 1·2–3·4), and the second-generation antiseizure drug topiramate (3·7, 1·4–10·1), and confirmed by another meta-analysis of the same drugs. Neither meta-analysis identified increased risks for lamotrigine. Although no increased risk was identified after exposure to gabapentin, levetiracetam, oxcarbazepine, primidone, or zonisamide, the data for these drugs need to be interpreted cautiously because of the small sample sizes.

A report from the prospective International Registry of Antiepileptic Drugs and Pregnancy (EURAP) provided a direct comparison for the antiseizure medications most frequently used in monotherapy. The highest risk for major congenital malformations was with valproic acid and the lowest risk was with lamotrigine, levetiracetam, and oxcarbazepine; this risk was dose-dependent for valproic acid, phenobarbital, carbamazepine, and lamotrigine (figure 2). Although the EURAP study reported that the risk associated with topiramate was modest, the confidence limits associated with this drug were wide because of the small number of exposures, and a different study has suggested an association between topiramate and facial clefts.

Two systematic reviews and a prospective study have indicated that prenatal exposure to valproic acid is also associated with a dose-dependent reduction of intelligence quotient (IQ) in the offspring. Children exposed to valproic acid do worse in language and mathematics tests (indicative of the long-lasting nature of the effects of in utero valproic acid), as well as have a higher risk of developing autism spectrum disorder. However, the two other frequently used first-generation antiseizure medications phenytoin and carbamazepine appear to be safe in terms of IQ development up to age 6–8 years.

Lamotrigine is the only second-generation antiseizure medication for which sizeable exposure data have accumulated and has reassuring findings regarding cognitive and behavioural development, whereas data on neurodevelopment for other second-generation drugs are insufficient or missing. The most informative prospective study included 42 pregnant patients treated with levetiracetam, 27 with topiramate, and 14 with gabapentin, and found no evidence indicating adverse effects on offspring cognitive development at age 5–9 years. Another prospective study in 181 children aged 6–7 years reported behavioural problems, as assessed by parents, in 32% of children exposed to valproic acid, 14% exposed to carbamazepine, 16% exposed to lamotrigine, and 14% exposed to levetiracetam.

In response to these findings and the regulatory restrictions on the use of valproic acid, prescription patterns for women with epilepsy have changed substantially during the past two decades. For pregnant women, the use of valproic acid and carbamazepine has substantially declined, and the use of lamotrigine and levetiracetam has substantially increased. This shift has been associated with a small, non-significant, annual reduction in the prevalence of major congenital malformations in the UK and Ireland pregnancy registry. In the larger EURAP registry, a significant 27% decrease from the time period 2000–05 to the period 2010–13 in the prevalence of major congenital malformations was observed in parallel with changes in antiseizure medication use (figure 3). Hence, although individual second-generation drugs such as topiramate seem to carry clinically significant teratogenic risks, and most others have not been adequately assessed, the availability of lamotrigine and levetiracetam as alternatives to valproic acid appears to have reduced the risk of major congenital malformations in the offspring of women treated with antiseizure medications. The availability of these safer medications is especially valuable for the management of idiopathic generalised epilepsies, for which fewer alternatives to valproic acid were available before the introduction of second-generation antiseizure drugs.

### Implications for drug selection

As discussed, the antiseizure medications introduced in the past 30 years have had little effect on the proportion of patients who achieve seizure freedom. However, some of these medications brought tolerability and safety advances, which might be especially relevant for specific patient groups. In fact, a key principle in epilepsy management is that treatment should be tailored to individual characteristics. In this respect, each of the available antiseizure medications has a distinct profile, and the advent of second-generation...
Changes over time in the proportion of antiseizure monotherapies and the prevalence of major congenital malformations in the offspring of monotherapy-exposed women

Changes over time in the proportion of different antiseizure monotherapies are expressed as a percentage of all monotherapy exposures. Prevalence estimates for major congenital malformations in the offspring of women exposed to monotherapy include 95% CIs and the number of offspring at each timepoint and are taken from the EURAP pregnancy registry during the period 2000–13. Data are from Tomson et al.77 ASM=antiseizure medication.

Conclusions and future directions

Extensive evidence on drug interaction potential, efficacy, and safety of the second-generation antiseizure drugs has expanded opportunities for tailored treatment choices.1 Examples of second-generation medications that are increasingly preferred as first-line treatment include lamotrigine and levetiracetam for older patients or for women of childbearing potential, levetiracetam for patients with hepatic failure, and lamotrigine for patients with comorbid depression.58 The availability of second-generation antiseizure medications has also expanded treatment options for orphan indications such as Dravet syndrome and Lennox-Gastaut syndrome. As data on comparative effectiveness accrue, specific second-generation drugs might become first-line options for some conditions, as this is the case for vigabatrin for patients with infantile spasms associated with tuberous sclerosis.70,71 For many second-generation medications, the introduction of generic (non-brand) formulations has also improved their accessibility, but overall these drugs remain more costly than first-generation agents.84

Although many second-generation drugs have mechanisms of action similar to older agents (in particular, sodium channel blockade), some exert antiseizure effects through novel mechanisms, and this difference affects their use.56 Mechanisms of action can be taken into consideration when making treatment decisions. In particular, many clinicians prefer to switch to a medication with a different mechanism of action when a first monotherapy has not worked because of insufficient effectiveness, even though there is no high-level evidence to support or refute this approach.92 For example, in a patient with focal seizures unresponsive to a sodium channel blocker (carbamazepine, phenytoin, lamotrigine, oxcarbazepine, or lacosamide), subsequent preferred choices might include levetiracetam (SV2A modulator), perampanel (AMPA antagonist), clobazam (GABAergic enhancer), or topiramate (a drug with multiple actions), rather than another sodium channel blocker.

Mechanisms of action need also be considered when combining antiseizure medications because of evidence of potential pharmacodynamic interactions. Two medications showing a potentially favourable pharmacodynamic interaction are valproic acid and lamotrigine, the combination of which can be effective in controlling seizures unresponsive to either drug alone.87 The value of combining these drugs as initial therapy was tested in a RCT involving 207 patients with newly diagnosed focal or generalised tonic–clonic seizures (excluding women planning pregnancy or not using appropriate contraception),83 and in which the proportion of patients achieving seizure freedom during the 52-week maintenance period was significantly higher in patients treated with lamotrigine in combination with valproic acid (64%) than in those treated with carbamazepine monotherapy (48%).

Starting treatment with a combination of antiseizure drugs conflicts with current practice of using polytherapy only when monotherapy is not effective. However, there is an increasing interest in testing the merits of early combination therapy, particularly in syndromes with high failure rates on initial monotherapy. A multicentre trial, in which 377 infants with new-onset epileptic spasms were randomly assigned to receive hormonal therapy (prednisolone or tetracosactide depot) alone or in combination with vigabatrin, reported that combination therapy was significantly more effective at stopping infantile spasms,85 but the superiority of combined treatment was not sustained after long-term follow-up of 18 months.85

Unfavourable pharmacodynamic interactions can also occur, particularly for combinations of drugs sharing common adverse effects or common mechanisms of action, and most notably with combinations of sodium channel blockers.1 In a US study that analysed data from a large health claims database, patients with focal seizures treated with combinations of sodium channel blockers or with combinations of GABAergic drugs had shorter retention on treatment (mean 344 days) than those treated with combinations of antiseizure medications that had different modes of action (313 days).86 Patients receiving combinations of drugs with different modes of action were also at lower risk for emergency department visits (odds ratio, 0.853; 95% CI 0.742–0.980).

Figure 3: Changes with time in the proportion of antiseizure monotherapies and the prevalence of major congenital malformations in the offspring of monotherapy-exposed women

Changes with time in the proportion of antiseizure monotherapies and the prevalence of major congenital malformations in the offspring of monotherapy-exposed women.

Prevalence estimates for major congenital malformations in the offspring of monotherapy-exposed women are shown as a percentage of all monotherapy exposures. Prevalence estimates are shown with 95% CIs and the number of offspring at each timepoint. Data are from Tomson et al.77
medications has accumulated over the past 30 years. The introduction of these drugs has improved epilepsy management by widening treatment options in a broad range of epilepsy syndromes. Patient groups for which these medications can be particularly advantageous include women of childbearing potential, older people, patients receiving other medications at risk for drug interactions, and patients with comorbid conditions, such as migraine, anxiety, bipolar depression, and neurogenic pain. A definite shortcoming of second-generation medications, such as levetiracetam, also offer safety advantages in patients with a history of hypersensitivity reactions to antiseizure drugs possessing an aromatic structure. Despite up to three decades of clinical experience, the full therapeutic potential of second-generation antiseizure medications remains incompletely characterised, mainly because of the paucity of unbiased comparative effectiveness trials, and the poor quality of efficacy data for most syndromes, particularly generalised epilepsies and epilepsies with onset in infancy and early childhood.

A definite shortcoming of second-generation antiseizure medications is their failure to provide a superior efficacy to first-generation agents and reduce the proportion of individuals with pharmacoresistant epilepsy by a major extent. Therefore, the search for more efficacious medications should continue. The fact that the medications introduced in the past 30 years have been largely discovered by use of traditional preclinical models, and by targeting seizures rather than the underlying disease, is one of the reasons for the little progress made in reducing the burden of drug resistance. A change in the approaches used for drug discovery is needed and is being made possible by advances in our understanding of the molecular mechanisms underlying different causes of epilepsy, the processes involved in epileptogenesis, and the mechanisms of pharmacoresistance.

Future treatments are likely to become increasingly personalised and target the molecular mechanisms responsible for the manifestations, or the development, of epilepsy. Areas in which important progress is being made include the targeting of molecular defects due to epilepsy gene mutations, autoimmune mechanisms, neuroinflammation, and dysfunction in the brain–gut–microbiome axis. This research is facilitated by increasing the use of models that reproduce the causes of epilepsy that have been identified in humans. Ongoing projects focus not only on discovery of new chemical entities, but also on the repurposing of medications used for other indications and non-pharmacological interventions such as gene therapies and stem cell therapies. Ultimately, these research efforts could provide truly novel therapies that no longer solely treat symptoms (antiseizure medications), but could also target comorbidities, prevent the development of epilepsy, or improve the course of the disease.

Contributors
All authors contributed equally to the conception of this Review and to the interpretation of the evidence. EP drafted the introduction, the sections on pharmacokinetics and drug interactions, and conclusions and future perspectives, and coordinated the preparation of the manuscript. PK searched the literature, drafted the search strategy and selection criteria section, and collaborated with MJB in drafting the section on seizure outcomes. TT drafted the summary and the section on tolerability and safety. All authors reviewed the overall manuscript draft and contributed to its finalisation.

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