Epilepsy has been recognized as a unique disorder for thousands of years, and references to its symptoms occur throughout history, from Babylonian tablets to the Bible. Today approximately three million Americans, or 0.5 to one percent of the population, suffer from epilepsy, which is diagnosed following two or more unprovoked seizures. Despite the introduction of many new antiepileptic drugs (AEDs) since the 1990s, offering favourable pharmacokinetics, improved tolerability, and lower potential for drug-drug interactions, as many as 30 percent of patients with epilepsy have recurrent seizures. Thus, there is a continuing need for new medication in this patient population, and the recent approval of four new drugs (lacosamide, vigabatrin, rufinamide and ezogabine) may provide the clinician with more options and the potential to provide individualized care. This is of importance as it has been reported that seizure remission can occur in up to five percent of patients per year with refractory epilepsy following adjustment of treatment.¹ In addition to these approved drugs, there are also numerous pipeline drugs at different stages of development, from pre-clinical to clinical phases, and others still have already filed a New Drug Application (NDA) with the FDA. Thus, there is great hope that many more patients will reach the goal of seizure reduction or elimination in the not-too-distant future.

Refractory Partial Seizures
Lacosamide (Vimpat; UCB) was approved in October 2008 and ezogabine (Potiga; Valeant/GSK) in June 2011 as adjunctive therapy for adult patients with refractory partial-onset seizures, while vigabatrin (Sabril; Lundbeck) gained approval for sale in the US in August 2009 as adjunctive therapy for adult patients with refractory complex partial seizures (CPS) for whom the potential benefit outweighs the risk of vision defects. A Phase III open label trial is also currently underway to assess the long-term use and safety of lacosamide as a monotherapy for partial-onset seizures. All three drugs have demonstrated effectiveness against a variety of seizure types in animal models and exhibit novel modes of action when compared to available AEDs and to each other. While there is little or no clinical evidence to support “rational polytherapy” at present,² the availability of drugs with novel mechanisms may prove beneficial in the long-term for treatment of this seizure type.

Modes of Action
Ezogabine primarily activates neuronal KCNQ2 (KV7.2) potassium channels, which help regulate neu-
ronal responsivity to excitatory input by opposing the depolarizing sodium current, and also potentiates GABAA receptor-mediated inhibition. Lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, prolonging the resting state of this channel, and modulates collapsin response mediator protein-2 (CRMP-2), a protein involved in neuronal growth and differentiation. Vigabatrin is a close structural analogue of GABA and targets the GABAergic system by selectively inhibiting GABA-transaminase (GABA-T), the enzyme responsible for GABA metabolism. Thus, vigabatrin increases the concentration of GABA, resulting in decreased neuronal excitability.

**Pharmacology**

Ezogabine, lacosamide and vigabatrin all display favorable pharmacological characteristics for an AED and fare well when compared with currently prescribed drugs. They are rapidly absorbed after oral administration with high bioavailability and linear pharmacokinetics in typical dose ranges. Of note, ezogabine is extensively metabolized in the liver, with an elimination half-life of seven to 11 hours, requiring three daily doses, which may cause non-intentional lack of adherence. Vigabatrin is eliminated primarily by the kidney, with little metabolic transformation occurring. Its half-life is approximately eight hours, but plasma levels are not correlated with clinical effect, instead being dependent on the rate of GABA-T re-synthesis. Lacosamide and vigabatrin exhibit low or no binding to plasma proteins, and thus are unlikely to be associated with pharmacokinetic interactions involving displacement of plasma proteins. Ezogabine is approximately 80 percent plasma protein bound. These drugs typically do not induce or inhibit hepatic CYP450 enzymes, except for vigabatrin which has been shown to induce activity of CYP2C9/CYP2C9 in vivo at concentrations above those of therapeutic doses. They also do not interact with oral contraceptives. Lacosamide shows no interaction with concomitant AEDs, while carbamazepine and phenytoin moderately increased the clearance of ezogabine, requiring adjustment of ezogabine dose if co-administered with these drugs. Vigabatrin has been reported to reduce the average plasma concentration of phenytoin by 16-20 percent.

**Efficacy**

The effectiveness of ezogabine and lacosamide in the treatment of refractory partial-onset seizures in patients with epilepsy has been established in three large, randomized, double-blind, placebo controlled studies each. In the case of ezogabine, there were significant changes in seizure frequency from baseline at all doses of drug (600, 900 and 1200mg/day) in one or more studies versus placebo. This full dose range may give physicians flexibility in prescribing ezogabine. Similarly, lacosamide was found to significantly reduce seizure frequency at all doses (200, 400 and 600mg/day) when compared to placebo in one or more studies. In these studies, the efficacy of lacosamide 600mg/day was similar to that of lacosamide 400mg/day, suggesting that it may show a narrow effective dose range.

The effectiveness of vigabatrin as adjunctive therapy for CPS was established in two pivotal placebo-controlled, double-blind, parallel-group studies in patients with refractory CPS. It was found to be statistically superior to placebo in both studies in reducing mean monthly seizure frequency at doses of 3g/day and 6g/day. The 6g/day dose was not superior to the 3g/day dose, nor was a dose of 1g/day superior to placebo.

**Safety**

In all pivotal controlled trials of these drugs, a similar proportion of patients reported at least one AE while taking study drug and placebo (ezogabine: 81 percent vs 75 percent; lacosamide: 76 percent vs 56 percent; vigabatrin: 97 percent vs 94 percent). In the case of ezogabine, AEs were largely CNS and dose-related, with dizziness, somnolence and fatigue occurring in more than 10 percent of patients and at a higher rate than the placebo group. Headache was reported at a similar level with both ezogabine (15 percent) and placebo (16 percent). The most common AE in patients treated with vigabatrin included fatigue, somnolence, dizziness, nystagmus, tremor, nasopharyngitis, blurred vision, diarrhea, and irritability. Weight gain was reported in almost eight percent of patients in the vigabatrin-treated group.
compared to three percent in the placebo group. For lacosamide, the most common AEs were related to the CNS and gastrointestinal system (dizziness, headache, nausea and diplopia), were dose-related and most frequent during the titration phase. Serious adverse events (SAEs) were reported by nine percent of all ezogabine-treated patients and six percent of placebo treated patients, with convulsion being the only SAE being reported by more than one percent of patients in each group. SAEs were reported by seven percent and almost two percent of patients in the vigabatrin and placebo group, respectively. Those occurring in more than one percent of patients included status epilepticus, convulsions and pneumonia. Ezogabine may also cause dose-related bladder dysfunction in some patients, with dysuria, urinary hesitance and urinary retention being reported by 2.3 percent, 2.2 percent and 0.9 percent of the patients. Furthermore, numerous studies indicate that peripheral visual field defects (pVFDs) occurred in approximately 30-50 percent of patients on long-term vigabatrin therapy.

Withdrawal rate was higher with all drug treatments when compared to placebo, with 25 percent of patients in the ezogabine group versus 11 percent in the placebo group discontinuing. 18 percent of patients in the lacosamide group versus five percent in the placebo group discontinuing, and 11 percent of patients in the vigabatrin group versus two percent in the placebo group discontinuing. In the ezogabine group, dizziness, confusion, somnolence and fatigue were the primary reasons for discontinuation, while dizziness was the most common AEs resulting in withdrawal in patients randomized to lacosamide. Headache was the only AE reported in more than one percent of patients in the vigabatrin group.

**Pipeline Drugs for Refractory Partial Seizures**

Brivaracetam (UCB), perampanel (E2007; Eisai Inc.) and eslicarbazepine acetate (Stedesa; Sepracor) are three drugs in late stage development for the treatment of refractory partial onset seizures in patients with epilepsy. In fact, Eisai submitted a New Drug Application (NDA) for perampanel to the FDA in May 2011, with the FDA issuing a Refusal to File letter in July 2011, requesting reformatting and reanalysis of some datasets. However, according to the company website, Eisai believes that no new non-clinical or clinical studies are required to support this filing. Furthermore, in May 2010, the FDA issued a Complete Response Letter to Sepracor following submission of an NDA for eslicarbazepine acetate by the company in March 2009, indicating that they would not approve the application at the time. The company is currently recruiting investigators for clinical trials to further evaluate the safety and efficacy of eslicarbazepine acetate.
Mode of Action

While perampanel is a first-in-class highly selective, non-competitive antagonist of the AMPA-type glutamate receptor, brivaracetam and eslicarbazepine acetate are structural analogues of existing compounds with improved properties. For example, brivaracetam is a novel structural derivative of levetiracetam (Keppra; UCB) and like levetiracetam also displays high affinity for synaptic vesicle protein 2A (SV2A). In fact, it was identified as having a 10-fold higher affinity for SV2A than levetiracetam, and was more potent and efficacious than levetiracetam in several animal models of seizure. It additionally shows inhibitory activity at neuronal voltage-gated sodium channels. Eslicarbazepine acetate is a prodrug of eslicarbazepine, and a third-generation AED in the carbamazepine family. While it is structurally similar to oxcarbazepine and carbamazepine, a substitution at the 10,11-position of the dibenzazepine nucleus results in a different metabolism, and it does not undergo epoxidation. It is not subject to auto-induction. Eslicarbazepine functions in a similar manner as oxcarbazepine and carbamazepine, blocking the neuronal voltage-gated sodium channel.

Pharmacology

Like the three recently approved drugs discussed above, brivaracetam, perampanel and eslicarbazepine acetate also display favorable pharmacokinetics, typically displaying high absorption after oral administrations and dose-proportional pharmacokinetics. Of note, eslicarbazepine acetate is rapidly and extensively reduced by liver esterases to the main active metabolite eslicarbazepine. Brivaracetam and eslicarbazepine display relatively low plasma protein binding, while perampanel is largely plasma protein bound (95 percent). These drugs typically do not alter the plasma concentration of concomitant AEDs. However, brivaracetam significantly increased baseline levels of carbamazepine epoxide, a strong CYP-inducing AED reduced perampanel plasma concentration, and carbamazepine, phenytoin and phenobarbital led to potentially clinically meaningful reductions in eslicarbazepine acetate exposure.

Efficacy and Safety

The efficacy and safety of all three drugs have been evaluated in large, randomized, double-blind, placebo-controlled trials in adults with partial epilepsy inadequately controlled with AEDs. It was reported that brivaracetam significantly reduced partial-onset seizure frequency when compared to placebo at 50mg/day in one study and at 100mg/day at the nominal 0.05 level in the other study, with 50mg/day not being significant. The drug was typically well tolerated at all doses examined, with a similar proportion of patients reporting at least one TEAE in the brivaracetam and placebo groups and few patients discontinuing due to TEAEs. An additional Phase III flexible-dose trial confirmed the safety and tolerability of brivaracetam in patients with uncontrolled focal or primary generalized epilepsy. Both perampanel and eslicarbazepine acetate significantly reduced median seizure frequency and significantly increased 50 percent responder rate in comparison to placebo at 4, 8 and 12mg/day and 800mg and 1200mg/day, respectively. No statistically significant differences were found between eslicarbazepine acetate 400mg/day and placebo. Furthermore, both drugs were typically well tolerated, with the most common adverse events being somnolence, dizziness, fatigue and headache in the perampanel study and dizziness, somnolence, nausea, diplopia and headache in the eslicarbazepine acetate study. A one-year open label extension study with eslicarbazepine acetate also showed significant improvements in quality of life and depressive symptoms compared with baseline measurements.

Infantile Spasms

Vigabatrin (Sabril; Lundbeck) is also designated as an orphan drug for the treatment of infantile spasms (IS) in infants one month to two years, which is a rare and catastrophic form of childhood epilepsy that is often refractory to therapy. As is the case for CPS, vigabatrin is indicated for patients in whom the potential benefit outweighs the risk of vision defects. Vigabatrin was the first FDA approved ther-
apy for the treatment of IS and, thus, the current availability of this drug in the US is likely to be a great benefit to patients. Furthermore, evidence suggests that it should be considered the first choice treatment for IS due to tuberous sclerosis, with hormone therapies, such as ACTH, being preferred for the treatment of IS related to other etiologies in the short term. However, both treatments have similar efficacy after one year.

The effectiveness of this drug was demonstrated in three well-controlled trials, with the most pivotal and largest trial evaluating 221 patients with confirmed IS. Patients were randomized to receive high or low dose range vigabatrin. Seventeen of 107 patients in the high dose group (16 percent) achieved spasm freedom for seven consecutive days beginning within the first 14 days of treatment compared with eight of 114 patients in the low dose group (seven percent), with the difference between doses being statistically significant (p = 0.04). When the criterion used to establish spasm frequency was relaxed, cessation rates for the high- and low-dose treatment groups were 31 percent (33/107) and 13 percent (15/114), respectively (chi-square test, p = 0.001). In all controlled studies, 85 percent of patients (N = 261) treated with vigabatrin and 35 percent (N = 20) treated with placebo reported at least one AE. Those occurring in more than 15 percent of vigabatrin-treated patients included upper respiratory tract infection, otitis media, viral infection, somnolence, sedation, irritability and pyrexia. Seventeen patients (6.5 percent) treated with vigabatrin discontinued from the study due to AEs. No patients withdrew from the study in the placebo group. SAEs were reported in almost 29 percent of patients in the vigabatrin group and no patients in the placebo group, with pneumonia and status epilepticus being the most common. MRI signal changes have also been reported in some infants IS receiving vigabatrin.

Mode of Action and Pharmacology
Rufinamide is a structurally novel triazole-derivative AED that has shown broad spectrum anticonvulsant properties at nontoxic doses in animal models. It has been proposed that rufinamide prolongs the inactive state of voltage-gated sodium channels, thus limiting high-frequency neuronal firing. This is in contrast to classical AEDs, such as carbamazepine, phenytoin and lamotrigine, which act on fast inactivation of these channels. Like the other recently approved drugs, rufinamide exhibits a favorable pharmacokinetic profile. It is well absorbed after oral administration, with an oral bioavailability of > 85 percent. It is not a substrate of CYP450 enzymes, instead being extensively metabolized via hydrolysis by carboxylesterases. It has half-life of 6 to 10 hours and metabolites are primarily renally excreted. Rufinamide is a weak inducer of the CYP3A4 enzyme and may decrease

**Lennox-Gastaut Syndrome**

Rufinamide (Banzel; Eisai) also gained orphan drug status and was approved in November 2008 as adjunctive therapy for the treatment of generalized seizures associated with Lennox-Gastaut syndrome (LGS) in children four years and older and adults. LGS is a rare and devastating form of epilepsy, which usually begins in childhood, and is refractory to medication in up to 96 percent of patients. Therefore, this drug is a welcome addition to the treatment armamentarium. Broad-spectrum AEDs are typically preferred in the treatment of LGS, as they may have activity against multiple seizure types. Valproate is typically the treatment of choice for initial therapy of LGS, despite the absence of controlled clinical trials assessing efficacy, with felbamate, topiramate, and lamotrigine being effective as adjunctive therapies. However, the use of felbamate is constrained due to AEs. One advantage of rufinamide may be that it can be rapidly titrated to the required dose, with the majority of patients in the clinical trial discussed above tolerating titration to recommended dose in seven to 14 days. It has been suggested that rufinamide use is most appropriate when LGS patients have failed valproate, topiramate, and lamotrigine and before felbamate, other newer AEDs, vagus nerve stimulation, or corpus callosotomy is considered.
plasma levels of oral contraceptives and triazolam. Drug-drug interactions have also been reported with concomitant AEDs, including carbamazepine, phenobarbital, phenytoin, and primidone and valproate, which may be more marked in the pediatric population.

**Efficacy and Safety**

Approval of rufinamide was based on one multicenter, randomized, double-blind, placebo-controlled trial in 138 patients with LGS, which showed that it reduced total seizure frequency by 33 percent and the frequency of tonic-atonic (“drop-attack”) seizures by 43 percent, which were both significantly different than the changes observed with placebo (p=0.0015 and p<0.0001, respectively). Caregivers also reported a reduction in seizure severity of 53 percent in the rufinamide group, versus 31 percent for placebo (p=0.0041). Addition of rufinamide to concomitant AEs was typically well tolerated, with a similar incidence of TEAEs as placebo (81.1 percent vs 81.3 percent, respectively). The most common AEs in the rufinamide group, reported by at least 10 percent of patients, were somnolence, vomiting and pyrexia. Six patients (eight percent) in this group discontinued treatment because of AEs, which included vomiting, somnolence, and rash. SAEs were reported by two patients in each group. Furthermore, cognitive or psychiatric AEs were more common in the placebo group (23 percent) than in the rufinamide group (eight percent). Of note, rufinamide has recently been approved as an oral suspension, and a clinical trial is currently recruiting patients one to less than four years of age with inadequately controlled LGS.

**Pipeline Drugs for LGS**

Clobazam (Onfi; Lundbeck), an oral 1, 5-benzodiazepine, is approved for the treatment of anxiety and/or adjunctive treatment of epilepsy in more than 100 countries, but not in the US. It is currently being developed as adjunctive treatment for seizures associated with LGS in patients two years and older, and, in March 2011, the FDA accepted for review an NDA from Lundbeck for this indication. Like other benzodiazepines, it has agonist activity at GABAA receptors, and has shown anticonvulsant properties in animal models of epilepsy. It is rapidly absorbed after oral administration, with high bioavailability.

However, significant interindividual variation exists in peak drug plasma concentration. Clobazam is eliminated by oxidation in the liver, with elimination half-life of about 10-50 hours, again with marked variation. It is also largely plasma protein bound, with the proportion of bound to unbound drug being largely independent of clobazam concentration. Certain types of medications may interact with clobazam, and these include anesthetics, analgesics, anticonvulsants, anxiolytics, some antidepressants, antipsychotics, sedatives, and CYP450 inhibitors. It may also specifically interact with the AEDs carbamazepine, phenytoin, and valproic acid, and cimetidine, nitrous oxide, and lithium. Alcohol has been reported to increase the bioavailability of clobazam by 50 percent, thus enhancing its effects. As with other benzodiazepines, tolerance, dependence and withdrawal can develop. The efficacy and safety of clobazam in the treatment of seizures associated with LGS has been reported in a Phase II and Phase III study. In particular, the randomized, double-blind, placebo-controlled Phase III study demonstrated that clobazam significantly reduced the average weekly rate of drop seizures at 0.5 and 1.0mg/kg/day from baseline to maintenance versus placebo. Secondary endpoints, including responder rates and decrease in total seizure rate, were also significantly improved at these doses of clobazam when compared to placebo. The most common TEAEs were somnolence, lethargy, drooling, fever and constipation, which were similar to those reported in the Phase II study. SAEs occurring in more than two patients were lobar pneumonia and pneumonia, and occurred in both clobazam and placebo treatment arms.

**Future Outlook**

Despite the introduction of many AEDs since the 1990s, up to a third of patients with epilepsy continue to have uncontrolled seizures, thus representing a great unmet need. Therefore, the continued development of new AEDs, which exhibit efficacy, ease of use...
and safety, is essential. While the drugs approved since 2008 are unlikely to have a significant impact on patients with controlled epilepsy, they have the potential to improve the quality of life of those patients with refractory epilepsy. Furthermore, the introduction of new drugs for IS and LGS, two rare, catastrophic, and often refractory forms of epilepsy, may be expected to substantially improve patient care. There are also many drugs not discussed here that are currently in development, some that are structurally novel, such as the neuroactive steroid ganaxolone (Marinus Pharmaceuticals), and others that are derivatives of existing drugs, such as the highly-selective vigabatrin analogue, CPP-115 (Catalyst Pharmaceutical Partners).

To further advance the treatment options for patients with epilepsy, it has been suggested that what we now require are unique methods for developing novel chemical entities that do not mirror current AEDs, different approaches for identifying and testing new treatments that do not rely solely on preventing seizures in animal models, and a better understanding of the neurobiology underpinning pharmacoresistance. It can only be hoped that these needs are met promptly.

Dr. Williams has no relevant conflicts of interest.

Emma Williams, PhD earned her PhD in Neuroscience from Trinity College in Dublin, investigating ways to generate neurons, and in particular, dopamine neurons, from embryonic and induced pluripotent stem cells. After spending countless hours in cell culture, she recently moved to the US to undertake an alternative science career away from the bench.