New generation antiepileptic drugs: what do they offer in terms of improved tolerability and safety?

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***Abstract*:** Over the last two decades a total of 11 antiepileptic drugs (AEDs) have been introduced to the US market. Randomized, placebo-controlled trials have yielded information about each drug's efficacy, tolerability, and safety profile; however, few studies have compared the newer generation AEDs directly with the older generation. Comparative studies are not always straightforward in their interpretation, as many characteristics of drugs, both favorable and unfavorable, may not be highlighted by such studies. In general, findings from the literature suggest that the newer generation AEDs (including vigabatrin, felbamate, gabapentin, lamotrigine, tiagabine, topiramate, levetiracetam, oxcarbazepine, zonisamide, pregabalin, rufinamide, and lacosamide) enjoy both improved tolerability and safety compared with older agents such as phenobarbital, phenytoin, carbamazepine, and valproate. This is partially supported by some of the findings of the QSS and the TTA Committee of the American Academy of Neurology (AAN), whose review of four AEDs (gabapentin, lamotrigine, topiramate, and tiagabine) is discussed. Briefly, when compared with carbamazepine, lamotrigine was better tolerated; topiramate adverse events (AEs) were fairly comparable to carbamazepine and valproate; and tiagabine compared with placebo was associated with a higher discontinuation rate due to AEs. The findings of the SANAD trial are also presented; when administered to patients with partial epilepsy, carbamazepine was most likely to fail due to AEs, and lamotrigine and gabapentin were least likely to fail due to AEs. When administered to patients with idiopathic generalized epilepsy, topiramate was most frequently associated with AE-related discontinuation, followed by valproate; and while valproate was the most efficacious drug in this arm of the study, lamotrigine was more tolerable. What makes the SANAD study valuable and somewhat unique is its head-to-head comparison of one drug with another. Such comparative trials are overall lacking for new AEDs, although some conclusions can be drawn from the available data. In the end, however, AED selection must be based on individual patient and drug characteristics.

***Keywords*:** adverse event, antiepileptic drug, safety, SANAD, tolerability, toxicity

Introduction

Determining the most appropriate antiepileptic drug (AED) for a patient can be a daunting task. A physician's selection is often driven by three main drug properties: efficacy, tolerability, and safety. Although drug efficacy may be one of the most important features to consider, a drug's tolerability and safety profile can be the main reasons a patient becomes disenchanted with and discontinues a drug. For years when only a limited number of AEDs were available, many patients were forced to choose between a life of seizures or a life of intolerable drug side effects. With the newer generation of AEDs came the hope of not simply superior efficacy, but also reduced adverse events (AEs) and improved safety.

The perfect drug would be one that is rapidly absorbed, reaches a steady state within one or two doses, can be dosed once daily, and does not interact with or alter the metabolism of other medications. Such a drug would act discriminately at a specific neuronal receptor thus avoiding unwanted, extraneous actions. The drug would have no untoward side effects,

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would be excellently tolerated by patients, and would not cause central nervous system (CNS) or systemic toxicities. Unfortunately, such a drug does not exist in the current antiepileptic armamentarium, and epileptologists must select among existing drugs to find the optimal choice for a given patient.

Antiepileptic drugs can be compared in two ways. The first is to identify AEs that occurred in randomized placebo-controlled add-on trials of one drug *versus* another drug. It is not easy to compare new and old drugs in this fashion, because randomized trials were performed with different methodology at the time that the older drugs underwent clinical trials. Another way is to perform a randomized head-to-head trial directly comparing the new drug with an old drug. This has been done for a number of the newer drugs, including gabapentin, topiramate, levetiracetam, lamotrigine, tiagabine, and vigabatrin. Where such data are available, they have been included. For the drugs that have only surfaced in the last several years, such comparative studies are not available. In these cases, common AEs seen in placebo-controlled add-on trials have been identified. However, it is important to keep in mind that add-on trials may amplify the occurrence of AEs due to pharmacodynamic factors. For many of the brand-new drugs, such as rufinamide and lacosamide, side-effect profiles are not available for use as monotherapy.

It is important to keep in mind that AEs may be experienced very differently by individual patients. Also, specific patient characteristics, such as age, gender, concomitant therapies, and concurrent medical and neurologic conditions may increase the likelihood that any given patient will experience AEs. It is for this reason that AED selection must be individualized.

In light of the above, it is not difficult to understand why randomized controlled comparison trials may not be as useful for selection of ideal drugs for a given patient. Controlled trials, by their nature, provide an assessment of AE frequency within populations. Populations consist of a number of subpopulations that may react differently, thereby limiting the AE data specificity when applied to individual patients. However, randomized trials do provide information on overall incidence of AEs experienced, and this in and of itself can be useful.

Another issue in the comparison of two drugs in a head-to-head trial is that of dose. In some trials, patients are titrated to the effective dose needed to control seizures. In other head-to-head trials, however, a single dose is selected for all participants. In these cases, the likelihood of AEs will be very highly associated with the dose that was chosen for the trial. If a high dose was selected, this may make the treatment appear less well tolerated. For this reason, we have included doses in all of our discussions below.

A number of different categories of AEs may occur as a result of administration of medication. Head-to-head trials are most useful for assessing dose-related AEs. These are AEs that occur in few patients at lower doses, whereas at higher doses the majority of patients may experience them. Head-to-head trials are less useful for assessing other types of AEs such as idiosyncratic AEs. These include serious drug reactions such as Stevens Johnson syndrome, hepatic failure, pancreatitis, and aplastic anemia. These events tend to occur very infrequently, and often not a single event will occur among the several hundred patients enrolled in a typical head-to-head comparison trial. Other types of AEs that are poorly evaluated in head-to-head trials are those that occur only after the patient has been exposed to the drug for some period of time. Examples would be cerebellar ataxia from phenytoin use, and bone density reduction from enzyme-inducing AEDs. Most head-to-head trials involve monotherapy. Therefore, the pharmacodynamic AEs (those caused by combining one drug with another) are not addressed. Another category of AEs that is not addressed by head-to-head trials is that of teratogenicity. For all of these types of AEs, other sources of data will be necessary.

Lastly, a drug's mechanism of action (MOA) may help to explain why certain AEs are experienced by patients. An extensive review of each AED's MOA is beyond the scope of this review; however, a summary is provided in Table 1 for the reader's reference.

Historical perspective

In 1857, Sir Charles Locock first used potassium bromide to treat patients with catamenial epilepsy [Krall *et al.* 1978; Copelman and Andreev, 1962], although who should receive the credit for its introduction as a true 'antiepileptic' agent is debatable [Friedlander, 2000]. Although clinical controlled trials were nonexistent, bromides were

Table 1. Antiepileptic drugs (AEDs): mechanisms of action.

AED name	Primary mechanism(s) of action
The *older* generation	
Bromides	Unknown; potentially stabilize neuronal membranes via hyperpolarization [Ryan and Baumann, 1999]
Phenobarbital (PB)	Enhance γ-aminobutyric acid (GABA) inhibition [Bourgeois, 2011]
Primidone (PRM)	May act synergistically with potassium bromide to reduce high-frequency repetitive neuronal firing [Bourgeois, 2011]
Phenytoin (PHT)	Use-dependent inhibition of sodium channels, thus blocking repetitive firing of action potentials [Morita and Glauser, 2011]
Ethosuximide (ESM)	Reduction of low-threshold T-type calcium currents in thalamic neurons [Kanner *et al.* 2011]
Carbamazepine (CBZ)	Use-dependent inhibition of sodium channels, thus blocking repetitive firing of action potentials [Guerreiro, 2011]
Valproate (VPA)	Precise mechanism unknown; multiple GABA-related actions, N-methyl *D*-aspartate (NMDA) receptor antagonist, and histone deacetylase inhibitor [Birnbaum *et al.* 2011]
The *newer* generation	
Vigabatrin (VGB)	Specifically and irreversibly inhibits GABA-T; may also stimulate GABA release [Thiele, 2011]
Felbamate (FBM)	Binds to open channels of the NMDA subtype glutamate receptor (thus, blocking sodium and calcium conduction); also possesses other properties, such as inhibition of voltage-gated sodium channels [Faught, 2011]
Gabapentin (GBP) and pregabalin (PGB)	Precise mechanism unknown; bind to the $\alpha_2\delta$ modulatory subunit of voltage-sensitive calcium channels [Mclean and Gidal, 2011]
Lamotrigine (LTG)	Blocks sodium channels; inhibits high-voltage-activated calcium currents [Gilliam and Gidal, 2011]
Tiagabine (TGB)	Enhances GABA-mediated inhibition by blocking GABA reuptake [Ekstein and Schachter, 2011]
Topiramate (TPM)	Multiple mechanisms: blocks the kainate/α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA) glutamate receptor subtype; blocks voltage-activated sodium channels; enhances GABA-mediated chloride flux at $GABA_A$ receptors; reduces amplitude of high-voltage-activated calcium currents; and activates potassium conduction [Rosenfeld, 2011].
Levetiracetam (LEV)	Precise mechanism unknown; binds SV2A, a presynaptic protein, on synaptic vesicles [Sirven and Drazkowski, 2011]
Oxcarbazepine (OXC)	Blocks voltage-dependent ionic membrane conduction (particularly sodium, potassium, and calcium) thereby stabilizing membranes and reducing synaptic impulse propagation; acts on N-type calcium channels [Guerreiro and Guerreiro, 2011]
Zonisamide (ZNS)	Blocks T-type calcium channels, inhibits slow sodium channels, and inhibits glutamate release [Welty, 2011]
Rufinamide (RFN)	Exact mechanism of action unknown; prolongs inactivation of voltage-dependent sodium channels [Krauss and Darnley, 2011]
Lacosamide (LCM)	Selectively enhances the slow inactivation of voltage-gated sodium channels; inhibits the collapsing response mediator protein 2 (CRMP-2) thereby possibly inhibiting neuronal growth that may occur in chronic epilepsy [Sheth and Abram, 2011]

found to reduce seizure frequency and became more widely used. Physicians who were dubious of their antiepileptic potential combined bromides with other agents such as borax and belladonna to increase efficacy [Shorvon, 2009; Livingston and Pearson, 1953]. Patients treated with bromides often remained on the drug for long periods of time, and many developed side effects including but not limited to dose-related drowsiness, restlessness, headache, delirium, acneiform rashes, granulomatous skin lesions, loss of appetite, and psychosis [Ryan and Baumann, 1999; Krall *et al.* 1978; Livingston and Pearson, 1953]. Many patients suffered through the AEs of bromides likely due to a lack of alternative treatment options. Their present day use is quite uncommon.

Phenobarbital became widely used as a sedative and hypnotic agent in 1912 and was subsequently recommended for epilepsy treatment by Hauptmann in 1919 [Shorvon, 2009].

It gradually gained in popularity during the 1920s, eventually supplanting bromide therapy as the mainstay of epilepsy treatment by the 1940s [Shorvon, 2009]. Like bromide therapy, the use of phenobarbital was not preceded by formal clinical trials, its use largely determined by clinical experience in the community [Krall *et al.* 1978]. Although phenobarbital continues to be an effective AED and has less toxicity than bromides [Krall *et al.* 1978] it is not without side effects, the more common being sedation, depression, and paradoxical hyperactivity in children [Westward, 2009]. Neurologic toxicity (such as ataxia, nystagmus, dysarthria) can occur with increased doses [Bourgeois, 2011]. More extreme respiratory and circulatory collapse can also occur, particularly when toxic amounts of the drug have been ingested [Wolf and Forsythe, 1978].

It was not until the introduction of Merritt and Putnam's electroshock model of epilepsy that a platform existed to test compounds preclinically for their antiepileptic potential [Putnam and Merritt, 1937]. Prior to its introduction to the market in 1938, phenytoin underwent preclinical testing using the Merritt–Putnam animal (cat) electroshock model, demonstrating its efficacy in seizure prevention [Putnam and Merritt, 1937]. This was a pivotal event in the future shaping of preclinical drug trials. Soon thereafter safety requirements were added via the Federal Food, Drug, and Cosmetic Act of 1938 in order for a drug to receive approval [Krall *et al.* 1978]. The introduction of toxicity testing by Goodman followed in 1949 [Krall *et al.* 1978]. Over the ensuing years more regulations and requirements were added, increasing the cost of drug development but also leading to improved understanding of potential toxicities of agents. It is likely in large part due to the latter evolution in drug development that present-day AEDs in general are safer and better tolerated by patients. Tolerability and safety of the new generation AEDs was addressed in 2004 by the Therapeutics and Technology Assessment (TTA) Subcommittee and the Quality Standards Subcommittee (QSS); comparisons were made between the newer generation and older generation of drugs. The findings and conclusions are discussed below.

Adverse effects and safety profiles of specific AEDs: new *versus* old

The tolerability and toxicities of two older generation AEDs (bromides and phenobarbital) were discussed in the previous section. Phenytoin, which was introduced in 1938 and later officially approved by the US Food and Drug Administration (FDA) in 1953, is known for its various side effects affecting the CNS and other organ systems, including but not limited to nystagmus, ataxia, diplopia, drowsiness, impaired concentration, gingival hyperplasia, hirsutism, acne, hepatotoxicity, and idiosyncratic reactions including lupus-like reactions and aplastic anemia [Morita and Glauser, 2011; Ziegler, 1978]. Ethosuximide was marketed in 1960, and possesses a fairly narrow therapeutic indication for absence epilepsy. Its AE profile includes but is not limited to nausea, abdominal discomfort, anorexia, drowsiness, dizziness, and numerous idiosyncratic reactions [Goren and Onat, 2007]. Carbamazepine was introduced in 1974. Common AEs include drowsiness, loss of coordination, vertigo, and weight gain [Hogan *et al.* 2000; Pellock, 1987]. Rash, hyponatremia, leucopenia, rare cases of hepatotoxicity, and other idiosyncratic reactions have also been reported [Bjornsson, 2008; Dong *et al.* 2005; Tohen *et al.* 1995; Mattson *et al.* 1985]. Valproate came to the market in 1978 and has since been associated with various side effects, some of the more common and/or formidable being dose-related tremor (less with controlled-release formulations), hair loss, weight gain, nausea, vomiting, hepatotoxicity, acute hemorrhagic pancreatitis, thrombocytopenia, and hyperammonemia; lethargy is also reported, but less commonly [Gerstner *et al.* 2008; Rinnerthaler *et al.* 2005; Davis *et al.* 1994]. Valproate is also associated with the greatest risk for major congenital malformations (MCMs) among the existing AEDs [Morrow *et al.* 2006]. Dates of introduction to the US market of both the older generation and newer generation AEDs are provided in Table 2.

A 10-center Veterans Administration (VA) Center study conducted in the 1980s compared the efficacy, toxicity, and tolerability of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures [Mattson *et al.* 1985]. They found that primidone caused a higher incidence of intolerable side effects such as nausea, vomiting, dizziness, and sedation compared with the other agents [Mattson *et al.* 1985]. Phenobarbital was associated with the lowest incidence of motor disturbance and gastrointestinal (GI) side effects compared to the other AEDs, but with more sedation and hyperactivity, while phenytoin caused more dysmorphic side

Table 2. Introduction of old and new generation antiepileptic drugs (AEDs).

AED name	Time of approval for use in the United States
The *older* generation	
Bromides	1857*
Phenobarbital (PB) and other barbiturates	1920s–1940s*
Phenytoin (PHT)	1938*; approved in 1953 by the FDA
Ethosuximide (ESM)	1960
Carbamazepine (CBZ)	1974
Valproate (VPA)	1978
The *newer* generation	
Vigabatrin (VGB)	Received initial approval in Europe in 1989, approved for use in the US in 2009
Felbamate (FBM)	1993
Gabapentin (GBP)	1993
Lamotrigine (LTG)	1994
Tiagabine (TGB)	1997
Topiramate (TPM)	1997
Levetiracetam (LEV)	1999
Oxcarbazepine (OXC)	2000
Zonisamide (ZNS)	2000
Pregabalin (PGB)	2005
Rufinamide (RFN)	2008
Lacosamide (LCM)	2009

*Indicates time of development.
FDA, US Food and Drug Administration.

effects and rash. Toxicity alone was least likely to cause patient dropouts in those patients on carbamazepine therapy, which appeared to be better tolerated by patients. Overall, potentially life-threatening side effects were rare, with one case each of lymphoma and a lupus-like syndrome in patients treated with phenytoin, and two cases of transient psychosis with primidone [Mattson *et al.* 1985]. Laboratory abnormalities (decreases in white blood cell counts and elevations in liver enzymes) were documented commonly, but no clinically important changes were noted [Mattson *et al.* 1985].

Numerous randomized controlled trials have compared the efficacy and tolerability of newer generation AEDs to the older drugs [Beghi, 2004; Perucca, 2002]. In 2004, the QSS and the TTA Committee of the American Academy of Neurology (AAN) developed a practice parameter which considered the efficacy and tolerability of newer generation AEDs, including gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide [French *et al.* 2004]. An extensive review of the literature dating from 1987–2003 was conducted. One major question the meta-analysis sought to answer was 'How do the efficacy and tolerability of the new AEDs compare with those of older AEDs in patients with newly diagnosed epilepsy?' [French *et al.* 2004].

Breaking the QSS/TTA study down by drug

Gabapentin

One class I study [Chadwick *et al.* 1998] was found comparing three different doses of gabapentin (300, 900, and 1800 mg/day) with carbamazepine dosed at 600 mg/day; discontinuation rate due to AEs was higher in the carbamazepine-treated patients than among the higher-dosed gabapentin-treated patients, with dizziness, fatigue, and somnolence more frequent in the carbamazepine-treated group. Pooled information from four class I add-on placebo-controlled trials [Anhut *et al.* 1999; The US Gabapentin Study Group No. 5, 1993; Sivenius *et al.* 1991; UK Gabapentin Study Group, 1990] revealed a discontinuation rate due to AEs of 3–11.5% in gabapentin-treated patients [French *et al.* 2004]. Again, the most frequent AEs were somnolence, dizziness, and fatigue [French *et al.* 2004]. Reports of serious idiosyncratic reactions to gabapentin have been few. Gabapentin is not known to cause blood dyscrasias, hepatic toxicity, Stevens Johnson syndrome or serious hypersensitivity syndromes.

Lamotrigine

Three studies were analyzed: one comparing the efficacy and safety of lamotrigine (titrated to 150 mg/day) *versus* immediate-release carbamazepine (titrated to 600 mg/day) [Brodie *et al.* 1995];

one comparing efficacy and safety of lamotrigine (maximum dose of 500 mg/day) in elderly patients with immediate-release carbamazepine (maximum dose of 2000 mg/day) [Brodie *et al.* 1999]; and one comparing lamotrigine (dosed between 150–400 mg/day) with phenytoin (dosed at 300–600 mg/day) [Steiner *et al.* 1999]. The two lamotrigine *versus* carbamazepine studies found that a higher number of patients experienced side effects resulting in discontinuation when taking carbamazepine, and one study found a significantly higher rate of rash in the carbamazepine-treated group [French *et al.* 2004]. Interestingly, the lamotrigine *versus* phenytoin study found a fairly similar discontinuation rate due to AEs in each treatment group; however, a higher incidence of asthenia, somnolence and ataxia was noted in the phenytoin-treated group. Rash occurred more frequently in the lamotrigine group. Lamotrigine is not known to cause hepatotoxicity. However, it is associated with serious hypersensitivity reactions that increase in frequency with rapidity of titration, with decreasing age, and with concomitant valproate use. This has led to the current recommendation of very slow initiation. Nonetheless, Stevens Johnson syndrome, toxic epidermal necrolysis and other hypersensitivity reactions occur at a frequency of between 1 and 10 per 10,000 new users [Mockenhaupt *et al.* 2005]. Other neurologic AEs include dizziness, nausea, and headache most commonly, particularly when administered in combination with valproate [Steiner *et al.* 1999].

Topiramate

One study compared the efficacy and safety of different doses of topiramate (100 and 200 mg/day) with valproate (1250 mg/day) and carbamazepine (600 mg/day) [Privitera *et al.* 2003]. Discontinuation rates due to AEs were fairly comparable between the three drugs, ranging between 19% and 28% in the topiramate-treated patients (varied based on dose used), 23% in the valproate-treated patients, and 25% in the carbamazepine-treated patients [Privitera *et al.* 2003]. Topiramate is not associated with blood dyscrasias. Rare hepatic failure has been reported, particularly with concomitant valproate use [Bumb *et al.* 2003]. The most common idiosyncratic adverse event associated with topiramate use is renal calculi, which may occur in 1.5% of patients with chronic use [Shorvon, 1996]. Other side effects include paresthesias, hypohydrosis (especially in children), and metabolic acidosis. Cognitive impairment, including difficulty with naming and memory can occur in a dose-dependent fashion [Loring *et al.* 2011].

Tiagabine

Tiagabine has found limited use as an add-on agent in partial epilepsy largely due to its rare association with nonconvulsive status epilepticus [Eckardt and Steinhoff, 1998]. Overall, it is a well-tolerated medication, the most common AEs being dizziness, asthenia, amnesia, nervousness, and abdominal pain [Kalviainen *et al.* 1998; Schacter *et al.* 1998; Sachdeo *et al.* 1997]. Three studies [Uthman *et al.* 1998; Sachdeo *et al.* 1997; Richens *et al.* 1993] were included in the QSS and TTA meta-analysis; tiagabine doses ranging from 15 to 56 mg/day were used as add-on therapy in patients with partial epilepsy. The discontinuation rate due to AEs from tiagabine ranged from 8% to 20% in patients on drug, compared to 8 to 9% for patients on placebo [French *et al.* 2004]. The five most frequent AEs were dizziness, tremor, abnormal thinking, nervousness, and abdominal pain [French *et al.* 2004].

Other studies not included in the original QSS and TTA meta-analysis have compared tiagabine more directly with other AEDs. A head-to-head trial assessing the effects of tiagabine (8–80 mg/day) *versus* carbamazepine (200–2000 mg/day) and phenytoin (60–1000 mg/day) on mood and cognition was performed by Dodrill and colleagues; there were no significant differences among the three agents [Dodrill *et al.* 2000]. A separate multicenter, open-label, randomized, parallel group study compared the efficacy, tolerability, and safety of two dosing regimens (target dose of 40 mg/day divided into either two or three doses) of tiagabine as adjunctive therapy in patients with partial seizures. A total of 77 patients (44%) on twice-daily tiagabine and 58 (33.7%) on thrice-daily tiagabine withdrew from the study [Biraben *et al.* 2001]. Of these, 46 (26.3%) and 37 (21.5%) withdrew due to AEs; somnolence, dizziness, asthenia, and tremor were the most frequent [Biraben *et al.* 2001]. Five patients in the twice-daily group and two patients in the thrice-daily group had a serious AE (confusion in two patients, psychosis, depression and dysarthria, and amblyopia and paranoia) [Biraben *et al.* 2001]. There were no notable changes in mean clinical chemistry values from baseline for both treatment groups, and no clinically significant changes in

hematology values or vital signs were observed during the study [Biraben *et al.* 2001].

While other idiosyncratic AEs are uncommon with tiagabine, as noted above the serious idiosyncratic adverse event associated with its use has been nonconvulsive status epilepticus [Koepp *et al.* 2005].

Oxcarbazepine

Three class I studies and one class II study were found which compared oxcarbazepine with older AEDs; the first study [Bill *et al.* 1997] compared oxcarbazepine (600–2100 mg/day) with phenytoin (100–560 mg/day); the second study [Christe *et al.* 1997] compared oxcarbazepine (600–2400 mg/day) with valproate (600–2700 mg/day); the third study [Dam *et al.* 1989] compared oxcarbazepine (300–1800 mg/day) with immediate-release carbamazepine (300–1400 mg/day); and the fourth study [Guerreiro *et al.* 1997] compared oxcarbazepine (100–1350 mg/day) with phenytoin (100–400 mg/day) in children and adolescents. In both studies comparing oxcarbazepine with phenytoin, and in the oxcarbazepine *versus* immediate-release carbamazepine study, oxcarbazepine was better tolerated with lower discontinuation rates among the oxcarbazepine-treated groups. There were no differences in discontinuation due to AEs, however, in the oxcarbazepine *versus* valproate study.

Some of the more common AEs associated with oxcarbazepine include fatigue, headache, dizziness, ataxia, diplopia, nausea, vomiting, rash, and others [Guerreiro and Guerreiro, 2011; Bill *et al.* 1997; Christe *et al.* 1997; Guerreiro *et al.* 1997; Dam *et al.* 1989]. Oxcarbazepine use has also been associated with several safety issues, including hyponatremia (with 2.7% of patients having a serum sodium of <125 mmol/L) [Harden, 2000], allergic rash, and Stevens Johnson syndrome.

Zonisamide

Two class I placebo-controlled studies [Faught *et al.* 2001; Schmidt *et al.* 1993] which compared zonisamide (at doses of 20 mg/kg in the Schmidt and colleagues study, and doses of 100, 200, and 400 mg/day in the study by Faught and colleagues) with placebo were reviewed. The discontinuation rates were 10% for both placebo and zonisamide-treated patients. Fatigue, dizziness, somnolence, anorexia, and abnormal thinking were the five most common AEs reported; others included renal calculi, rash, and depression [French *et al.* 2004].

A more recent study by Zaccara and Specchio, not included in the initial TTA and QQS report, reviewed nine open-label studies in which patients received zonisamide (doses ranging between 50 and 1100 mg/day) for at least 6 months as either add-on or monotherapy [Zaccara and Specchio, 2009]. Between 4% and 24% of patients discontinued the experimental drug due to AEs (most commonly somnolence and dizziness); anorexia, headache, nausea, and irritability were also commonly noted [Zaccara and Specchio, 2009]. Oligohydrosis, rash, and weight loss have been documented, with renal stones a rare occurrence [Kothare and Kaleyias, 2008]. Pooled safety data from all US/European clinical trials identified 15/1296 (1.2%) patients with symptomatic renal calculi [Kothare and Kaleyias, 2008]. Across all placebo-controlled studies with zonisamide, treatment-related AEs were reported for 61% and 49% of zonisamide *versus* placebo, respectively [Brodie and Mansbach, 2008]. However, these AEs were generally of mild-to-moderate severity. Zonisamide tolerability is improved with slower drug titration [Baulac and Leppick, 2007]. Postmarketing data from the United States and Japan, which includes information from over 1 million patients and 2 million patient-years of exposure, supports a relatively benign safety profile of zonisamide [Brodie *et al.* 2005].

Levetiracetam

Three class I studies (two add-on studies and one monotherapy study) were included in the meta-analysis [Ben-Menachem and Flater, 2000; Cereghino *et al.* 2000; Shorvon *et al.* 2000]. Discontinuation of levetiracetam (doses ranging from 1000 to 3000 mg/day) due to AEs ranged between 7% and 13% (compared with placebo discontinuation of 5–8%), but the rate of discontinuation was unrelated to levetiracetam dose [French *et al.* 2004]. However, in a separate study which initiated levetiracetam at high doses (2000 or 4000 mg/day) without titration, higher rates of somnolence and asthenia were noted on the higher dose of drug [Betts *et al.* 2000]. Overall, dizziness, somnolence, asthenia, headache, and infection were the most frequently reported AEs [French *et al.* 2004], with behavioral problems, depression, and psychosis also noted.

A second 1-year follow-up study of levetiracetam used as add-on therapy at doses of 250–3000 mg/day, not included in the initial TTA and QQS report, also found levetiracetam to be well tolerated, with AEs leading to 17 discontinuations ($N = 98$) [Ben-Menachem and Gilland, 2003]. Tiredness was the primary AE, with low numbers of patients also reporting irritation, pruritis, increased seizures, and psychosis [Ben-Menachem and Gilland, 2003]. When compared with phenytoin (dosed at 200–800 mg/day) in a separate study assessing efficacy and tolerability in patients who had undergone supratentorial neurosurgery, levetiracetam (dosed at 500–3000 mg/day) was associated with significantly fewer early AEs than phenytoin, and had a higher 1-year retention rate [Milligan *et al.* 2008]. A recent meta-analysis was conducted which indirectly compared levetiracetam with other second-generation AEDs, gathering data from trials identified in the Cochrane Library 2002 [Otoul *et al.* 2005]. Levetiracetam (dosed from 1000 to 4000 mg/day) was as equally well tolerated as lamotrigine (75–400 mg/day) and gabapentin (600–1800 mg/day); had a lower withdrawal rate than topiramate (200–1000 mg/day) and oxcarbazepine (600–2400 mg/day); and overall did not differ significantly from tiagabine (16–56 mg/day) and zonisamide (100–400 mg/day), with favorable withdrawal rate trends [Otoul *et al.* 2005]. A more recent randomized double-blind trial compared levetiracetam at doses from 500 mg twice daily up to 1500 mg twice daily to controlled release carbamazepine 400 mg per day up to 1200 mg per day, with dose depending on patient response. Dropout rates were essentially identical for the two drugs. Depression and insomnia were more often experienced by patients randomized to levetiracetam, whereas back pain was experienced more frequently in patients randomized to controlled release carbamazepine. Weight gain was slightly higher on carbamazepine (Brodie *et al.* 2007).

Levetiracetam has not been associated with idiosyncratic AEs such as hepatic failure, Stevens Johnson syndrome, organ failure, or blood dyscrasias.

Conclusion

The TTA Subcommittee and QQS report concluded that the new AEDs may be better tolerated than the standard older generation AEDs; however, it emphasized that other parameters such as better safety and pharmacokinetics could not be commented on [French *et al.* 2004]. As side effects appeared to increase in all drugs as doses were titrated, and slower titrations were associated with better tolerability, the mantra 'start low and go slow' was recommended [French *et al.* 2004].

Other new generation AEDs

Several new generation AEDs were not included in the TTA Subcommittee and QQS report either because they had been reviewed in other arenas, or because the drug had not yet come to market, and are discussed below.

Vigabatrin

Vigabatrin has seen relatively restricted use in patients with infantile spasms and cortical dysplasia who remain refractory to other medications, namely due to the now well-established risk of visual field deficits incurred through retinal nerve fiber layer toxicity. The drug is otherwise fairly well tolerated by patients. One study conducted across 10 epilepsy centers in Canada assessed the efficacy and tolerability of vigabatrin as add-on therapy (dosed from 1000 to 4000 mg/day) in patients with refractory partial epilepsy, and found that vigabatrin was extremely well tolerated or well tolerated by 72.4% of patients receiving the drug [Bruni *et al.* 2000]. The most common AEs were headache, fatigue, dizziness, and drowsiness [Bruni *et al.* 2000]. Safety assessments which analyzed changes in vitals and clinical laboratory evaluations did not reveal any clinically significant findings [Bruni *et al.* 2000]. A separate open long-term comparative study of vigabatrin (50–60 mg/kg/day) *versus* carbamazepine (15–20 mg/kg/day) in newly diagnosed partial seizures in children also found vigabatrin to be well tolerated, with a better side-effect profile in comparison with carbamazepine [Zamponi and Cardinali, 1999]. In the latter study, the most frequent AEs were irritability/excitability and weight gain [Zamponi and Cardinali, 1999].

Felbamate

Felbamate was approved for use in the US in 1993 but was withdrawn from the market following its implication in the development of fulminant hepatic failure and aplastic anemia. The drug was later re-introduced to the market with strict blood monitoring parameters and is currently used as an add-on agent in cases of refractory epilepsy. Based on the available data, the estimated incidence of aplastic anemia in patients exposed to felbamate is 127 per million users

[Kaufman, 1997] and that of hepatic failure is estimated at 64 per million patients treated [Pellock, 1999]. A recent review of the Cochrane Epilepsy Group Specialized Register included findings from three randomized-controlled clinical trials [Bourgeois *et al.* 1993; Leppik *et al.* 1991; Theodore *et al.* 1991]. Owing to the methodological variances of the studies a formal meta-analysis was not performed; however, the main AEs noted across the three trials (with felbamate doses of 1600–3600 mg/day) were headache, nausea, and dizziness [Shi *et al.* 2011]. A total of six patients withdrew from the studies due to AEs [Shi *et al.* 2011]. The potentially fatal major toxicities associated with felbamate (hepatic failure and aplastic anemia) were not encountered; however, this could be due to a number of factors including trial duration and number of enrolled patients [Shi *et al.* 2011].

Pregabalin

Overall pregabalin, which was introduced to the US market in 2005, was well tolerated in clinical trials, with primarily mild or moderate AEs noted. Across pivotal clinical trials (which administered pregabalin at doses of 50–600 mg/day), the most common AEs experienced were dizziness, somnolence, asthenia, ataxia, blurred vision, and weight gain. Dropout rates were dose related [Beydoun *et al.* 2008]. A 76-center, double-blind, randomized, placebo-controlled, parallel-group study reported that CNS-related AEs tended to be dose related, were mild-to-moderate in intensity, occurred soon after pregabalin initiation, and infrequently resulted in discontinuation [French *et al.* 2003]. Among pregabalin-treated patients (50–600 mg/day), dizziness resulted in discontinuation in 15 patients (4.2%), and somnolence resulted in the discontinuation of 11 patients (3.1%), and there was a dose-related incidence of weight gain (ranging from 1.1% at the lowest dose to 12.4% at the highest dose) [French *et al.* 2003]. A separate analysis of pooled data from four clinical trials revealed good tolerability of pregabalin at doses of 150–600 mg/day, with an odds ratio (OR) of withdrawing from the study due to any reason of 1.71 (95% confidence interval [CI] 1.24–2.35) [Gil-Nagel *et al.* 2008]. Again, dizziness and somnolence were the most commonly reported AEs. Weight gain appeared to be dose related, leading to study withdrawal in only 0.74% of pregabalin-treated subjects [Gil-Nagel *et al.* 2008].

To date, pregabalin use, like its predecessor gabapentin, has been relatively devoid of serious idiosyncratic adverse events such as hepatotoxicity, Stevens Johnson syndrome and blood dyscrasias.

Rufinamide

Rufinaminde came to the US market in 2008 and is primarily indicated for use as adjunctive treatment of seizures in Lennox–Gastaut syndrome. Safety and tolerability data from the entire pediatric population in the rufinamide epilepsy clinical development program was reviewed by Wheless and colleagues [Wheless *et al.* 2009]. The most common AEs in rufinamide-treated patients (10–45 mg/kg/day, with a median dose of 41.96 mg/kg/day) in the double-blind studies were somnolence (17.0%), vomiting (16.5%), and headache (16.0%), the majority of which were mild to moderate in severity [Wheless *et al.* 2009]. In the double-blind plus open-label extension population, the most common serious AEs were aggravated seizures, status epilepticus, and pneumonia [Wheless *et al.* 2009]. Changes in laboratory values, vital signs, and weight were generally clinically insignificant, although ECG change and QT prolongation were each experienced in one patient (0.3%) in the double-blind plus open-label extension population [Wheless *et al.* 2009]. Five possible cases of AED hypersensitivity syndrome were identified retrospectively [Wheless *et al.* 2009]. In the double-blind plus open-label extension population, 12.5% of patients discontinued treatment due to an AE. Clinically notable decreases in weight occurred only in rufinamide-treated patients (11 [5.9%] of 188) [Wheless *et al.* 2009]. Similar findings were noted in the European long-term experience which observed patients over an 18-month period (mean final dose of 38.2 ± 17.3 mg/kg/day) [Kluger *et al.* 2010]; the most frequently occurring AEs were fatigue (18.3%), vomiting (15.0%), and loss of appetite (10.0%). No serious AEs were observed.

Lacosamide

Lacosamide is the newest AED to come to market at the time of the writing of this paper. An analysis of pooled data from three randomized, double-blind, multicenter, placebo-controlled phase II/III trials was performed by Chung and colleagues [Chung *et al.* 2010]. Doses of 200, 400, and 600 mg/day of lacosamide were administered to patients and the most common AEs were: dizziness (31%), headache (13%), nausea (11%), and diplopia (11%).

All appeared to be dose related with the exception of headache [Chung *et al.* 2010]. Three serious AEs were noted: dizziness (1.5% in the lacosamide 600 mg/day group); nystagmus (1.0% in the lacosamide 600 mg/day group); and convulsion (1.1% in the lacosamide 200 and 400 mg/day groups). Treatment was discontinued due to AEs in 17% of patients [Chung *et al.* 2010]. In clinical trials, lacosamide did not appear to be associated with any changes in clinical laboratory tests and vital sign measurements; a small increase in the mean PR interval was noted; however, there were no reports of associated AEs and similar increases in PR intervals have been found with other AEDs [Chung, 2010]. Whether lacosamide will be better tolerated than its AED predecessors has yet to be determined, as head-to-head comparison trials have yet to be performed.

Conclusion

To summarize, there are numerous potential AEs a patient can experience from each individual AED. While it is not possible to discuss every potential AE of every drug, the most commonly observed AEs in clinical trials have been mentioned and are provided for the reader's convenience in Table 3.

New *versus* old: what have we learned from the SANAD and other trials?

After reviewing the above, it is clear that the newer generation AEDs are not without their share of AEs, some better tolerated than others. As noted above, comparing the newer generation with the older generation of AEDs is challenging for many reasons. One recent large randomized study was performed specifically to compare new and old drugs in terms of both efficacy and tolerability. It was entitled SANAD, which stands for 'Standard And New Antiepileptic Drugs', and was conducted by Marson and colleagues [Marson *et al.* 2007].

The SANAD trial randomized over 1000 patients with epilepsy to six AEDs and was composed of two arms: arm A randomized patients with partial epilepsy to carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate, while arm B randomized patients with idiopathic generalized epilepsy to valproate, lamotrigine, or topiramate. Guidelines for doses and titration of AEDs in adults were as follows: carbamazepine, titrated to maintenance dose of 600 mg/day over 4 weeks; valproate titrated to 1000 mg/day over 2–3 weeks; lamotrigine titrated to 150 mg/day over 6 weeks; gabapentin titrated to 1200 mg/day over 1–2 weeks; topiramate titrated to 150 mg/day over 6 weeks; and oxcarbazepine titrated to 900 mg/day over 3 weeks. The primary outcome was 'effectiveness', as measured by remaining on randomized drug. In arm A, lamotrigine (a new drug) was found to be more effective than carbamazepine (the old drug) largely attributed to lamotrigine's superior tolerability [Marson *et al.* 2007]. There were no significant differences in quality of life across the treatment groups. Carbamazepine therapy was most likely to fail due to AEs, and lamotrigine and gabapentin were least likely to fail due to the presence of AEs [Marson *et al.* 2007]. Oxcarbazepine was relatively similar in tolerability and failure rates to lamotrigine, and topiramate fell in between the two extremes. Rash was the AE most associated with treatment failure, and was most commonly reported by those patients receiving carbamazepine and oxcarbazepine [Marson *et al.* 2007]. In arm B, topiramate was most frequently associated with AE-related discontinuation, followed by valproate. Lamotrigine was less likely to cause treatment failure due to unacceptable side effects; however, lamotrigine was more likely to lead to discontinuation due to inadequate seizure control [Marson *et al.* 2007]. Of note, although an older AED, valproate, was found to be the 'winner' in arm B, it was on the basis of efficacy, not tolerability, and a newer AED, lamotrigine, was more tolerable. The SANAD study is also exemplary of the point that some of the most important AEs associated with valproate use such as hepatic failure and pancreatitis and teratogenicity (see above) are rare causes of treatment 'failure', as defined in the study, and therefore would not have been considered in the analysis. However, these are important issues for drug selection.

Two studies comparing carbamazepine with lamotrigine have been performed in the elderly. One study found lamotrigine to be better tolerated than immediate-release carbamazepine, but this was not as clearly seen in a second study where sustained release carbamazepine was used [Saetre *et al.* 2007; Brodie *et al.* 1999]. One highly cited randomized controlled trial compared the new AEDs lamotrigine and gabapentin with the older drug carbamazepine in elderly patients with newly diagnosed epilepsy. Tolerability was better with the new AEDs, but again immediate release carbamazepine was used [Rowan *et al.* 2005].

Table 3. Side effects of the antiepileptic drugs (AEDs) compared.

AED name	Potential adverse effects (not fully inclusive)
The *older* generation	
Bromides	Drowsiness, restlessness, headache, delirium, acneiform rashes, granulomatous skin lesions, loss of appetite, and psychosis
Phenobarbital (PB) and other barbiturates	Sedation, depression, and paradoxical hyperactivity in children; neurologic toxicity (such as dysarthria, ataxia, nystagmus) with increasing doses; rare hematologic toxicity
Phenytoin (PHT)	Nystagmus, ataxia, diplopia, drowsiness, impaired concentration, gingival hyperplasia, hirsutism, acne, hepatotoxicity and idiosyncratic reactions including lupus-like reactions and aplastic anemia
Ethosuximide (ESM)	Nausea, abdominal discomfort, anorexia, drowsiness, dizziness, and numerous idiosyncratic reactions; rare hematologic toxicity
Carbamazepine (CBZ)	Nausea, dizziness, drowsiness, diplopia, weight gain, rash, Stevens Johnson syndrome, toxic epidermal necrolysis, hyponatremia, leucopenia, rare cases of hepatotoxicity, and other idiosyncratic reactions
Valproate (VPA)	Dose-related tremor (less with controlled-release formulations), hair loss, weight gain, nausea, vomiting, hepatotoxicity, acute hemorrhagic pancreatitis, thrombocytopenia, and hyperammonemia; less commonly, lethargy
The *newer* generation	
Vigabatrin (VGB)	Headache, fatigue, dizziness and drowsiness; depression, permanent visual field deficits
Felbamate (FBM)	Headache, nausea, dizziness; weight loss, fulminant hepatic failure and aplastic anemia
Gabapentin (GBP)	Somnolence, dizziness fatigue, weight gain
Lamotrigine (LTG)	Hypersensitivity reactions, Stevens Johnson syndrome (increased occurrence with rapid titration); dizziness, nausea, insomnia, and headache
Tiagabine (TGB)	Dizziness, tremor, abnormal thinking, nervousness and abdominal pain, rare psychosis, rare non-convulsive status epilepticus
Topiramate (TPM)	Drowsiness, paresthesias, metabolic acidosis, oligohydrosis, Renal calculi (most commonly reported idiosyncratic reaction), rare hepatic failure; impaired language fluency and cognition, weight loss, acute glaucoma (rare)
Levetiracetam (LEV)	Dizziness, somnolence, asthenia, headache; irritability, behavioral problems, depression and psychosis
Oxcarbazepine (OXC)	Fatigue, headache, dizziness, ataxia, diplopia, nausea, vomiting, rash and others; hyponatremia, Stevens Johnson syndrome
Zonisamide (ZNS)	Fatigue, dizziness, somnolence, anorexia, and abnormal thinking, rash, Stevens Johnson syndrome, renal calculi, aplastic anemia, oligohydrosis
Pregabalin (PGB)	Dizziness, somnolence, weight gain
Rufinamide (RFN)	Fatigue, vomiting, loss of appetite, somnolence, headache; aggravated seizures, status epilepticus
Lacosamide (LCM)	Dizziness, headache, nausea, diplopia

Other studies comparing new *versus* old AEDs have been performed, including one by Lathers and colleagues, which utilized relative ORs to evaluate the AEs of two newer generation AEDs (topiramate and lamotrigine) compared with phenobarbital. Applying this method, they found that the sedation rates for topiramate compared equally with phenobarbital, but were 2.1–4 times worse than the rate of lamotrigine [Lathers *et al.* 2003]. Frequently, the newer generation AEDs have been compared with carbamazepine, the standard agent used to treat partial epilepsy. Many of these smaller population studies have been discussed above.

A recently published study [Glauser *et al.* 2010] compared two old and one new AED for absence seizures, a common pediatric epilepsy seizure type. The primary outcome was freedom from treatment failure. Again, the old AEDs (ethosuximide and valproate) were the 'winners', compared with the new AED (lamotrigine) but again this was due to superior ability to control seizures. There were no differences among the three drugs in terms of discontinuation due to AEs, but valproate was more likely to cause attention deficit problems, so ethosuximide was declared the winner based on both efficacy and tolerability.

One retrospective study of 461 patients treated with new and old generation AEDs was performed in Spain. The newer generation AEDs (including gabapentin, lamotrigine, vigabatrin,

topiramate, tiagabine, oxcarbazepine, and levetiracetam) were withdrawn in 19.1% of patients due to AEs, while the older generation AEDs (including valproate, carbamazepine, phenytoin, phenobarbital, ethosuximide, clonazepam, primidone, and clobazam) were withdrawn in 9.3% of patients due to AEs [Guevara *et al.* 2005]. The authors concluded that older AEDs are better tolerated than newer AEDs, with tiagabine being the worst tolerated of all of the drugs. Whether the way the AEDs were initiated, titrated, and co-administered had any effects on the development of AEs is unknown as information on dosages and titration schemes were not included in this publication.

General concepts: old *versus* new AEDs

Another aspect of newer AEDs compared with older AEDs relates to hepatic enzyme induction. Four of the major older AEDs (phenytoin, carbamazepine, phenobarbital, and primidone) are hepatic enzyme inducers, and one (valproate) is a hepatic enzyme inhibitor. Recent evidence has supported the concept that these effects have safety implications, as body homeostasis is altered. In the case of the inducing AEDs, this may result in an increase in cardiovascular risk (increase in serum lipids and C-reactive protein), and alteration of sex steroids. Valproate inhibition of hepatic enzymes may contribute to polycystic ovarian syndrome [Mintzer, 2010].

The effect on bone mineral density (BMD) and overall bone health is another issue that may distinguish new AEDs from old. The potential effects of the older-generation AEDs (particularly phenytoin) on BMD is documented [Carbone *et al.* 2010; Pack and Walczak, 2008]; however, this is an area still actively being researched particularly regarding the newer generation agents. Teratogenic effects and risk of congenital malformations (CMs) related to AED therapy during pregnancy is another major concern, and multiple pregnancy registries are actively collecting data. Results of one systematic literature review indicate the risk of CMs in children born of women with epilepsy was significantly higher for children exposed to valproate monotherapy, and to polytherapy of two or more drugs when the polytherapy combination included phenobarbital, phenytoin, or valproate [Meador *et al.* 2008]. Yet carbamazepine, once thought to be problematic during pregnancy, has shown surprisingly low teratogenicity in pregnancy registries, and compares favorably with the newer drugs such as lamotrigine, which had been assumed to be safer. A recent editorial even deemed it the drug of choice for pregnancy [Nulman, 2010]. These findings were also supported by an evidence-based review performed by the QSS and TTA Committee [Harden *et al.* 2009]. Effects of the newer generation AEDs on pregnancy and the development of major CMs largely have yet to be determined. Lastly, in 2008 the US FDA warned of a statistically significant 1.80-fold increased risk for suicidality associated with 11 AEDs (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide). Many in the epilepsy community have questioned these findings [Hesdorffer and Kanner, 2009; Shneker *et al.* 2009] suggesting more research and clinical trials should be conducted. As data continue to be gathered on the newer generation AEDs, we will hopefully be able to reflect more intelligently on the issues of BMD, teratogenicity, suicidality, and other potential pitfalls that have yet to be discovered.

A glimpse of the future

There are several new AEDs that are either in the licensing phase or still undergoing clinical trials. These include eslicarbazepine acetate, brivaracetam, and retigabine.

Eslicarbazepine acetate, recently licensed as an adjunctive agent in partial epilepsy, is structurally linked to carbamazepine and oxcarbazepine. It is converted into the major active metabolite S-licarbazepine [Gazzola *et al.* 2011; Almeida and Soares-da-Silva, 2007]. The exact MOA is unknown, although S-licarbazepine stabilizes the inactive state of voltage-gated sodium channels [Gazzola *et al.* 2011; Almeida and Soares-da-Silva, 2007]. In phase III clinical trials (which used eslicarbazepine doses of 400, 800, and 1200 mg/day), eslicarbazepine was well tolerated, with the most common AEs reported to include dizziness, headache, and somnolence. [Elger *et al.* 2008a; Hufnagel *et al.* 2008; Lopes-Lima *et al.* 2008]. Hyponatremia and rash were rare.

Brivaracetam is a pyrrolidone derivative in the same class as levetiracetam that continues to undergo clinical trials. Like levetiracetam, brivaracetam binds to the synaptic vesicle protein 2A, but with higher affinity; brivaracetam also inhibits sodium channels [Gazzola *et al.* 2011; Zona *et al.* 2010]. An exploratory, phase IIb, double-blind, randomized, parallel-group,

placebo-controlled study using brivaracetam doses of 5, 20, or 50 mg/day was performed; tolerability was good, with only 2.6% of patients discontinuing drug due to AEs, compared with 3.7% of patients in the placebo arm [French *et al.* 2010]. The most common AEs were mild to moderate in intensity, and included headache, somnolence, influenza, dizziness, neutropenia, and fatigue [French *et al.* 2010]. No clinically significant changes were noted in laboratory values, vital signs, body weight, physical and neurologic examinations, and EKG measurements [French *et al.* 2010]. Phase III clinical trials are currently ongoing.

Retigabine is a structurally novel compound that acts by opening the KCNQ potassium channel, leading to neuronal hyperpolarization [Gazzola *et al.* 2011; Main *et al.* 2000]. Two large-scale, phase III clinical trials have been conducted; RESTORE-1 compared a retigabine dose of 1200 mg with placebo, and RESTORE-2 compared retigabine doses of 600 mg and 900 mg with placebo. In both studies, AEs leading to discontinuation (which occurred in 27%, 26%, 17% *versus* 6% of patients on retigabine 1200, 900, 600 mg, *versus* placebo, respectively) included dizziness, somnolence, headache, and fatigue [Brodie *et al.* 2010; Brodie and Mansbach, 2008; French and Mansbach, 2008]. Confusion and dysarthria were noted at the higher 1200 mg dose. Some bladder findings from retigabine were discovered during preclinical toxicology testing, and rare cases of bladder dysfunction felt to be due to retigabine have been noted in clinical trials [Stephen and Brodie, 2011; Brodie *et al.* 2010]. License application for use as an add-on agent in partial epilepsy has been submitted.

How the latter three AEDs, if and when they all reach the market, will fare in terms of tolerability and efficacy compared with the current armamentarium of agents has yet to be determined. Future head-to-head clinical trials will be of value.

Conclusions

Clearly, it is impossible to conclude that 'all old AEDs are bad' or 'all new AEDs are good'. As can be seen above, the character of AED side effects is highly specific, and as already mentioned, highly individual. Some of the newer AEDs such as gabapentin, levetiracetam, tiagabine, and pregabalin are unlikely to cause systemic safety issues, whereas these were associated with all of the older AEDs. The absence of hepatic enzyme induction/inhibition with most of the newer AEDs provides one major advantage. As noted, add-on comparative trials are lacking for new AEDs (there has never been a comparative trial in which patients have been randomized to the addition of an old AED *versus* a new AED) but several of the new AEDs seem to cause less pharmacodynamic burden when added on to other AEDs. In the end, drug selection must be based on individual patient and drug characteristics.

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Conflict of interest statement

JA French has served on the scientific advisory board of UCB, Johnson & Johnson, Eisai, Novartis, Valeant, Icagen, Intranasal, Sepracor, Vertex and Marinus. Dr. French has received funding for travel from UCB, Kyowa, Eisai, Johnson & Johnson, Valeant, and GlaxoSmithKline. Dr. French is the president of the Epilepsy Study Consortium that receives money from multiple pharmaceutical companies; 25% of her salary is paid by the consortium. She has received research support from SK, Valeant, Pfizer, UCB, Eisai, Johnson & Johnson, Vertex the NIH, the Milken Foundation and the Epilepsy Research Foundation. Dr. Gazzola declares no conflicts of interest in preparing this article.

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