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Update on Anticonvulsant Drugs

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Abstract In 2009, the US Food and Drug Administration approved three medications for the treatment of epilepsy: rufinamide, lacosamide, and vigabatrin. In addition, extended-release formulations of lamotrigine and levetiracetam were approved recently. When added to the dozen medications for treating epilepsy, the choice is a luxury in terms of additional options, but also a challenge for practitioners to use them all with expertise. Recently, there has been much interest surrounding medications for epilepsy and their possible association with osteoporosis, safety during pregnancy, biological equivalence to generic versions, and possible association with higher rates of suicidality. This review discusses these issues and provides a current overview for the medical management of epilepsy.

Keywords Epilepsy · Treatment · Medications · Anticonvulsant · Suicide · Pregnancy · Generics · Hypersensitivity syndrome · Therapeutic monitoring · Bone health · Lacosamide · Rufinamide · Vigabatrin

Introduction

Although classically referred to as *antiepilepsy drugs* (AEDs), these medications provide symptomatic treatment of seizures; no medications have been shown to modify the course of epilepsy itself. The goal of epilepsy treatment, whether by medical or surgical means, was simply stated by the Centers for Disease Control and Prevention to be "no seizures, no side effects." A drug that completely controls seizures but results in constant tiredness should not be considered an acceptable treatment. With more severe seizure disorders, the principle remains the same: to ensure the effects of chronic daily side effects of AEDs are not worse than those of the intermittent seizures.

AEDs are structurally unrelated molecules. Their pharmacokinetics and mechanisms of action are varied [1], which may be related to the variety of adverse effects and dosing schedules, which are very important in the choice of drug for a particular patient. The dramatic increase in the available agents over the past decades (Table 1), many with improved tolerability profiles (Table 2), makes seizure freedom without adverse effects a reality for increasing numbers of patients.

The chronic adverse effects of AEDs are also relevant. Studies have identified long-term problems with bone health and with neurodevelopment with in utero exposure, although data generally are not as available for the newer AEDs. An increase in suicidality was considered an AED class effect by the US Food and Drug Administration (FDA), which has raised controversy, and there remains confusion surrounding the bioequivalence and seizure protection properties of generic versions of AEDs.

General Principles: Selection and Use of Antiseizure Drugs

The first step in AED selection is matching for appropriate seizure type (Fig. 1). The various valproate (VPA) formulations are considered the gold standard for treatment of the idiopathic (primary) generalized epilepsies [2, 3],

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Table 1 Practical aspects of antiepileptic drug use

Drug	Year approved	Dosage form(s)	Usual adult starting dosage, *mg/d*	Usual adult dosage, *mg/d*	Dosing schedule	Minimum titration time, *d*	Usual effective plasma concentration, *μg/mL*	Pediatric maintenance dosage, *mg/kg/d*	Parameters to monitor
Carbamazepine	1974	Tabs	200	800–1600	TID	7–14	8–12	10–30	LFT, Na, CBC
Carbamazepine XR	1996 1997	Tabs capsules	200	800–1600	BID	7–14	8–12	10–30	LFT, Na, CBC
Clonazepam	1996	Tabs (ODT)	0.5	0.5–1.5	BID–TID	1–7	–	0.1–0.2	–
Ethosuxamide	1960	Capsules solution	250	750–1500	BID	7–14	40–100	15–40	CBC, LFT
Felbamate	1993	Tabs solution	600	2400–3600	BID–TID	14–21	20–140[a]	15–60	CBC, LFT, reticulocytes
Gabapentin	1993	Tabs capsules	1800	1800–3600	TID–QID	1–14	4–16	30–90	None
Lacosamide	2009	Tabs IV	100	400	BID	28	NE	NE	None
Lamotrigine IR	1994	Tabs (ODT) chewtabs	12.5–50[b]	100–600[b]	QD–BID	28–42	2–16	5–15[b]	None
Lamotrigine XR	2009	Tabs	12.5–50[b]	100–600[b]	QD–BID	28–42	2–16	5–15[b]	None
Levetiracetam IR	1999	Tabs solution IV	1000	1000–3000	BID–TID	1	5–45[a]	60	None
Levetiracetam XR	2008	Tabs	1000	1000–3000	QD–BID	1	5–45	60	None
Oxcarbazepine	2000	Tabs solution	300	1200–2400	BID–TID	7–14	10–35[c]	20–40	CBC, Na
Phenobarbital	1912	Tabs IV	90	90–180	QD	1	15–40	3–5	LFT
Phenytoin	1938	capsules suspension chewtabs IV	300	300–400	QD	1	10–20	4–8	LFT
Fosphenytoin	1996	IV, IM	10–20 PE/kg	4–6 PE/kg/d	QD	1	10–20	–	ECG
Pregabalin	1994	Capsules	150	150–600	BID–TID	1	NE	NE	None
Primidone	–	Tabs	100–125	750–1500	TID	10	5–12 μg	10–25	LFT
Rufinamide	2009	Tabs	800	3200	BID	–	NE	45, up to 3,200 mg/d	ECG
Tiagabine	1997	Tabs	4	32–56	BID–QID	28–42	NE	Up to 32 mg/d	None
Topiramate	1996	Tabs	25	200–600	BID	28–42	4–10	5–6	None
Valproate	1978	Capsules IV sprinkles solution	500	1000–3000	TID	7–14	50–120	15–60	LFT, NH_3, plt
Divalproate	1996	Tabs	500	1000–3000	BID	7–14	50–120	15–60	LFT, NH_3, plt
Divalproate XR	2000	Tabs	500	1000–3500	QD–BID	7–28	50–120	15–70	LFT, NH_3, plt
Vigabatrin	2009	Tabs solution	1000	3000	BID	29	NE	150	Ophth
Zonisamide	2000	Capsules	100	100–600	QD–BID	1	10–40[a]	4–8	None

In general, older patients (>65 years) may require lower doses of all drugs because of reduced renal clearance and/or hepatic function. Laboratory values should be monitored, in general, at the initiation of treatment, once on the maintenance dosage, and then every 6 months at most (usually), or as needed to assess for adverse effects. The exception is felbamate, for which values should be monitored every 2–4 weeks during the first year of treatment and at least every 3 months thereafter

BID twice daily, *CBC* complete blood count, *ECG* electrocardiogram, *IM* intramuscular, *IR* immediate release, *IV* intravenous, *LFT* liver function test, *NE* not established, NH_3 ammonia, *ODT* orally dispersible tablet, *Ophth* mandatory quarterly ophthalmologic assessments, *PE* phenytoin equivalents (75 mg fosphenytoin is equivalent to 50 mg phenytoin), *plt* platelets, *QD* once daily, *QID* four times daily, *TID* three times daily, *XR* extended release

[a] Not established; represents the usual concentration in patients receiving a therapeutic dosage

[b] Varies with concomitant antiepileptic drug (lower with enzyme inducers, higher with enzyme inhibitors)

[c] Concentration of 10-monohydroxy derivative (MHD), the active metabolite

Table 2 Advantages and disadvantages of antiepileptic drugs

Drug	Advantages	Disadvantages
Carbamazepine	Inexpensive	Drug interactions (including OC)
	Mood stabilizer	Hypersensitivity
	Treats some neuropathic pain	Possible bone density loss
	Known rate of teratogenesis	Rare sedation
		Hyponatremia, leukopenia (usually asymptomatic)
		Rare aplastic anemia
Clonazepam	Broad spectrum; appears effective for myoclonus	Tachyphylaxis
	Useful for anxiety Can be used as abortive/rescue therapy	Physical addiction and dependence
Ethosuximide	Oral solution available	Narrow spectrum; only for absence seizures
		Potential to worsen irritability
Felbamate	Oral solution available	Serious potential side effects, including liver failure and aplastic anemia
Gabapentin	No drug interactions	TID/QID dosing
	Rapid titration Useful for neuropathic pain and spasticity	Dose-dependent absorption
Lacosamide	No drug interactions	Sedation
Lamotrigine	Broad spectrum	Hypersensitivity
	Few drug interactions	Slow titration
	QD/BID dosing Useful in bipolar disease	Levels affected by OC
Levetiracetam	No drug interactions Rapid titration	Possible neurobehavioral side effects
	BID dosing; XR provides QD option	
Oxcarbazepine	Few drug interactions	Interferes with OC
	Rapid titration	Hypersensitivity
		Hyponatremia
Phenobarbital	Inexpensive	Sedation
	QD dosing	Withdrawal
	IV available	Drug interactions (including OC)
		Possible bone density loss
Phenytoin	Inexpensive	Complicated pharmacokinetics
	QD dosing	Drug interactions (including OC)
	IV available	Highly protein bound
	IM available as fosphenytoin	Hypersensitivity
		Bone density loss
		Sedation
		Cosmetic effects
Pregabalin	No drug interactions Rapid titration	Weight gain
	Useful in neuropathic pain and spasticity	
	Some anxiolytic effects	
Rufinamide	Specifically effective in LGS	GI side effects
Tiagabine	Few drug interactions	Highly protein bound
		Slow titration
		Cognitive, GI effects
Topiramate	Broad spectrum	Slow titration
	Few drug interactions	Cognitive effects
	BID dosing	Interferes with OC
	Useful in migraine	Potential for weight loss
	Potential for weight loss	Renal stones (rare)

Table 2 (continued)

Drug	Advantages	Disadvantages
Vigabatrin	Proven efficacy in infantile spasms	Risk for loss of visual field—in-depth ophthalmologic assessments required
		Potential for psychiatric side effects
		Weight gain
Valproic acid and derivatives	Broad spectrum	Drug interactions
	Useful in migraine, bipolar disease	High protein binding
	IV, sprinkles, and QD forms available	Dose-dependent hematologic toxicity (including thrombocytopenia and acquired von Willebrand disease)
	Gold standard in idiopathic generalized epilepsy	Tremor, parkinsonism
		Weight gain
		Teratogenic and in utero neurodevelopmental risks
		Rare sedation
		Hepatic toxicity, esp. in pediatrics
Zonisamide	Broad spectrum	Hypersensitivity
	Few drug interactions	Potential for weight loss
	Potential for weight loss	Possible mood worsening
	Mild antiparkinsonian agent May provide headache prophylaxis	Rare renal stones
	QD dosing	

BID twice daily, *GI* gastrointestinal, *IM* intramuscular, *IV* intravenous, *LGS* Lennox-Gastaut syndrome, *OC* oral contraceptives, *QD* once daily, *QID* four times daily, *TID* three times daily, *XR* extended release

although their first-line use is diminishing. Levetiracetam (LVT), lamotrigine (LTG), zonisamide (ZNS), topiramate (TPM), clonazepam, clobazam, and now rufinamide (RFN) are considered *broad spectrum*, meaning they can treat any seizure type. These agents may be tried before VPA to avoid its potential side effects, particularly teratogenesis in women of childbearing age [4]. Other AEDs are considered narrow spectrum, as they treat only partial seizures (simple or complex) and both secondary and primary generalized tonic–clonic seizures. These agents may worsen other

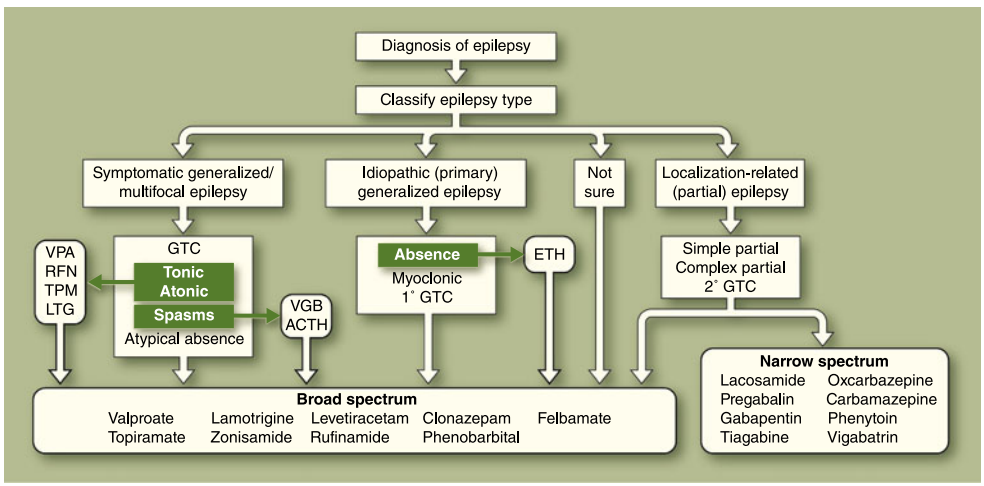

Fig. 1 An algorithm outlining steps in the choice of an antiepileptic drug for a patient diagnosed with epilepsy. The first step is to determine the epilepsy syndrome and seizure types. When these are unknown, broad-spectrum agents are safest. There are several choices for each seizure type, but the choices are narrowed based on the potential for intolerable side effects, of which psychobehavioral and weight effects are among the most concerning for patients. Enzyme inducers generally are considered second line for patients with long-term adverse effects, such as bone density loss, and to decrease the complexity of drug–drug interactions. ACTH—adrenocorticotropic hormone; ETH—ethosuximide; GTC—generalized tonic–clonic (seizure); LTG—lamotrigine; RFN—rufinamide; TPM—topiramate; VGB—vigabatrin; VPA—valproate

primary generalized seizures, such as absence or myoclonic seizures. Individual drugs may be better suited to specific seizures—for example, ethosuximide for absence seizures and clonazepam for myoclonic seizures [5].

There have not been large variations in the proven efficacy of AEDs for partial seizures. Head-to-head trials have been performed testing the effectiveness, or retention, of medications, which is affected by both efficacy and tolerability [6, 7]. There are no adequate predictors as to whether a specific AED will be efficacious in any individual patient; one may be effective when another is not. Thus, once seizure type has been taken into account, much of drug selection involves choosing medications with side effect profiles least likely to cause additional problems, or using other properties of certain AEDs to help the patient in comorbid conditions (Table 3). Examples include the use of TPM in patients who also have chronic headache, LTG in patients with depression or bipolar disease, ZNS for patients who wish to lose weight, or pregabalin (PGB) for those who wish to gain weight. Pharmacokinetic properties such as once-daily dosing may be particularly important for some college students or others in whom compliance is difficult. Finally, with most AEDs now having multiple generic versions, cost may play a role in drug selection and in the decision to stay with the brand-name version. Specific AEDs may have more published data to support monotherapy use [8•, 9•, 10], although most have been used successfully in clinical practice regardless of labeled indication.

About half of patients achieve seizure freedom with the first agent attempted, but the chance decreases precipitously with subsequent trials [11]. When the first AED fails, the decision to add another medication in combination versus changing to a single new medication is debatable. Some experts advocate using polytherapy only after three monotherapy trials have failed [12]. One rationale is that polytherapy has a higher chance of causing side effects that would reduce quality of life more than continued seizures. Other authors lean toward using add-on combination therapy earlier [13], as delays to seizure freedom risk irreversible psychosocial consequences. The decision, much like the choice of AED, comes down to what is best for that individual patient.

Most older AEDs have between seven and 18 licensed generic versions. The FDA requires generics to contain the same active compounds as the branded agent. Testing in healthy individuals must show 95% confidence intervals of both peak serum concentration and total absorption falling between 80% and 125% of those of the brand-name agent. For many conditions, this amount of variability may be clinically unimportant. In epilepsy, the margin between efficacy and side effects may be small, and a relatively small decrease in the delivered dose might result in breakthrough seizures, with potentially disastrous consequences. An increase in absorption might result in toxicity. Changing from one generic with a relatively low resulting concentration (compared with the brand) to another generic with a relatively high concentration might amplify fluctuations in serum concentration from one prescription to the next. In rare cases, patients also may develop adverse effects related to the inert matrix of the tablet or capsule, such as an allergic reaction to dye. If the development of such an effect requires stopping or changing medication, even temporarily, seizures in a previously well-controlled patient may occur and result in injury, driver's license suspension, or even death. The American Academy of Neurology published strong statements against substitution of generic for brand-name AEDs without the consent of the ordering physician [14•]. However, the random nature of seizures and the heterogeneity of epilepsy create problems in proving causality, and the debate over generic medications and therapeutic equivalence continues [15••].

Plasma drug levels are commonly monitored with older agents, and levels are available for most newer drugs as

Table 3 Psychobehavioral and weight gain/loss effects of antiepileptic drugs

	Mood/anxiety/irritability		
	Possibly helpful	Potential to worsen	Unknown/minimal
Potential weight gain	Valproate Gabapentin Pregabalin	Vigabatrin Phenobarbital	–
Weight neutral	Lamotrigine Carbamazepine Oxcarbazepine Clonazepam	Levetiracetam Primidone	Lacosamide Rufinamide Phenytoin
Potential weight loss	–	Ethosuximide Zonisamide Topiramate Felbamate	–

well. Most older AEDs (phenytoin [PHT], carbamazepine [CBZ], phenobarbital [PB]) have a narrow, well-defined therapeutic range, although specific patients vary in terms of a level that is effective and one that causes toxic symptoms. Plasma level monitoring is not required "routinely," particularly for newer drugs, but may be helpful in specific clinical situations, including establishment of a drug level baseline once the patient is seizure-free, suspected toxicity, suspected noncompliance, medico-legal verification of treatment, lack or loss of therapeutic effect, and verification of level when change is suspected due to age, secondary disease, changing physiologic state (eg, pregnancy), or drug–drug interaction [16].

Update on Adverse Events

Rashes and Drug-Induced Hypersensitivity Syndrome/ DRESS Syndrome

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome has been receiving greater attention. This rare but potentially fatal condition is characterized by relatively late onset; slow evolution, often mimicking an infectious illness with fever, rash, hepatic dysfunction, hematologic abnormalities, and lymphadenopathy; and reactivation of human herpesvirus [17]. When specific to AEDs, it also may be termed *anticonvulsant hypersensitivity syndrome*, of which PHT, CBZ, PB, LTG, oxcarbazepine (OXC), and primidone (PRM) have been implicated as a cause in the pediatric population [18]. Onset typically is within 2 months to 3 months of initiation of the implicated AED, and severity may worsen despite its discontinuation.

A retrospective database review of nearly 2,000 patients at an epilepsy center showed an overall rash rate of 2.8%, but in these patients, the risk of rash from exposure to another AED was 8.8% [19]. Cross-reactivity of rashes was generally high between AEDs, particularly between PHT and CBZ [20]. Pharmacogenomics and ethnicity also may be important: CBZ-induced Stevens-Johnson syndrome is strongly associated with HLA-B*1502 in Taiwan and Hong Kong and in those of Asian descent in Europe, but not in Japanese or other Caucasians. It appears specific to people of Han Chinese descent [21].

Suicidality

Since 2008, the FDA has mandated the product labeling of all AEDs to include a warning about increased risks of suicidality. This decision was based on a meta-analysis of 199 randomized clinical trials of 11 AEDs, not only for conditions of epilepsy, but also for mood disorders and pain. The data showed a 1.8-fold risk of suicidal thoughts or acts in patients on active study drug versus placebo. Although suicidality, and mood disorders in general, are of definite concern in patients with epilepsy, arguments against broad class labeling include known differences in the mechanisms of action and adverse effects of individual agents, and the nature of spontaneous adverse event reporting in drug trials [22••]. Nonetheless, this labeling requires patients and practitioners to be prepared for questions. The FDA warning does not mean a patient will develop suicidality; however, patients, families, and practitioners must be vigilant for warning signs. A recent survey showed that most academic neurologists counsel their patients about neurobehavioral effects, but fewer than half specifically address suicide [23]. One approach includes a discussion of the risk of future seizures outweighing the risk of developing suicidality, which was measured at 3.4 per 1,000 patients with epilepsy. With new medico-legal implications, neurologists should document a past and current history of mood disorders and suicidality. A family history of psychiatric disorders also is related to developing behavioral side effects on AEDs. The Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is a simple six-item scale on which a total score ≥15 should raise concerns for more urgent psychiatric assessment.

Bone Metabolism

Chronic use of AEDs may adversely affect bone density, although the relationship has not been fully elucidated. Bone homeostasis is a complicated and an active process requiring parathyroid hormones, adequate serum calcium through intestinal absorption and renal reabsorption, and vitamin D. Putative mechanisms of bone loss include liver induction causing increased vitamin D breakdown, calcitonin deficiency, and effects on calcium absorption. Studies show decreased bone mineral density with the use of benzodiazepines, CBZ, PHT, PB, PRM, VPA, gabapentin (GBP), OXC, and ZNS [24••]. No worsening has been reported with LTG, LVT, or TPM. Bone mineral density testing is now recommended routinely for patients at higher risk for osteoporosis (nonambulatory, elderly, Caucasian patients), but a baseline for any patient may be considered; half the pediatric population in one study had low bone density, particularly patients with cerebral palsy, severe mental retardation, or gait impairment [25].

Pregnancy and Antiepileptic Drugs

A meta-analysis of pregnancy outcomes included 59 studies of more than 65,000 pregnancies in women with epilepsy (WWE) compared with more than 1.8 million without epilepsy [26]. Congenital malformations were significantly more frequent in WWE (7.08%) than in those without

epilepsy (2.28%). The highest incidence of malformations was seen with polytherapy that included PHT, PB, or VPA (16.78%); a high rate was also seen with VPA monotherapy (10.73%). Malformations that were most significantly higher in WWE were hernia, ear/neck/face malformations, cleft lip, and spina bifida. Most of the newer AEDs were not individually assessed because of limited outcome data. The prospective Neurodevelopmental Effects of Antiepileptic Drugs study showed an additional risk of in utero VPA exposure—impaired fluency and originality—compared with children exposed to LTG or CBZ [27].

The American Academy of Neurology and the American Epilepsy Society published a series of evidence-based practice parameters regarding management issues in WWE. With respect to pregnancy-related complications, there were limited high-quality studies, yet they suggested a moderately increased (≤1.5 times) risk of cesarean delivery for WWE on AEDs, and a possible increased risk of premature contractions, labor, and delivery in WWE who smoke [28••]. There were insufficient data to comment on pregnancy-induced hypertension, bleeding complications, or spontaneous abortion. The data supported a low rate (8–16%) of seizure recurrence during pregnancy if WWE were seizure-free 9–12 months before pregnancy but could not make statements on change in seizure frequency or potential for status epilepticus. The recommendations regarding major congenital malformations (defined as having surgical, medical, or cosmetic importance) were similar: avoid VPA in monotherapy or polytherapy, specifically in the first trimester, compared with CBZ and possibly PHT and LTG [29]. The group also indicated a likely dose–risk relationship for malformations with VPA and LTG. The risks of some adverse perinatal outcomes, small size for gestational age, and a 1-minute Apgar score less than 7 were elevated. The summary of this practice parameter is that avoidance of VPA exposure and polytherapy in the first trimester of pregnancy appears to be the most important factor. Family planning is important; most women do not know they are pregnant until after 1 month of pregnancy; medication changes at this point may not prevent malformations and might introduce new risks. Despite the knowledge that VPA is clearly worse than the other first-generation medications, there are insufficient data to make comments on most of the newer medications. Encouraging WWE to enlist in the Pregnancy Registry (http://www.aedpregnancyregistry.org) is the most helpful way to continue to collect prospective data.

Although the use of folate is still recommended, there is no high-quality evidence to suggest a dosage or even to support its benefit [30], and it is unlikely a placebo-controlled study will ever be done. Some experts advocate 4 mg/d for those at high risk and planning a pregnancy; however, 1 mg/d for all women of childbearing age is common practice.

Stopping AEDs during pregnancy is considered a large theoretical risk, with the potential for anoxia and trauma from the physical effects of seizures, although no high-quality data exist. The Taiwan national data set found that WWE who had seizures during pregnancy were at significantly but moderately higher risk (odds ratio, 1.34) of delivering newborns small for gestational age [31]. About one third of WWE experience increased seizures during pregnancy, possibly as a result of falling AED drug levels, especially in the second half of pregnancy, because of the increased volume of distribution and clearance of the drug. AED drug levels should be followed closely during pregnancy. The perinatal risk of hemorrhage led to the recommendation that WWE who take drugs that interfere with vitamin K_1 metabolism take oral vitamin K_1, 20 mg/d, for a minimum of 2 weeks before expected delivery [32].

Breastfeeding

The practice parameter group found no evidence to contraindicate breastfeeding for WWE taking AEDs. There was good evidence that PHT, CBZ, PB, and VPA do not cross into breast milk in clinically significant amounts (likely because of high protein binding); LVT and PRM probably—and GPN, LTG, and TPM may possibly—penetrate in potentially clinically important amounts [30]. Despite the relatively high breast milk levels, LVT is not found in high levels in infants, possibly because of their very fast metabolism of LVT [33].

Characteristics of the Newest Antiepileptic Drugs

Rufinamide

RFN received orphan drug approval by the FDA in January 2009 as add-on therapy for seizures in patients aged 4 years and older with Lennox-Gastaut syndrome, based on a randomized double-blinded clinical trial in 138 highly refractory patients [34]. RFN was significantly better than placebo in median percent reduction in total seizures (32.7% vs 11.7%; P=0.0015) and median "drop attack" tonic–atonic seizures (42.5% reduction vs 1.4% increase). An extension trial showed maintained response rates during the last 6 months and 12 months of the study (data on file, Eisai Inc., Woodcliff Lake, NJ). Its mechanism of action is theorized to be prolongation of the inactive state of sodium channels.

RFN also was more effective than placebo in a multicenter clinical trial of refractory partial seizures in which 3,200 mg/d was given as adjunct therapy [35]. In

addition, nonblinded studies suggest positive effects on myoclonic and absence seizures [36].

RFN has a time to maximum concentration (T_{max}) of 4–6 h, reaching a bioavailability of ≥85%. Absorption is improved in the fed state. The half-life elimination is 6–10 h. Hepatic hydrolysis by carboxylesterases to an inactive metabolite is the main mechanism, with less than 4% excreted as the parent compound. Protein binding is clinically insignificant. With the exception of PHT levels increasing 21% in children, the effect size of RFN on other AEDs may be clinically insignificant.

VPA increases steady-state RFN plasma levels in a dose-dependent manner, whereas coadministration of PHT, PRM, and PB decreases RFN plasma concentrations by up to 46% in children, 32% in adolescents, and 25% in adults, and coadministration of CBZ results in decreases of about 20%. Vigabatrin (VGB) coadministration also reduces RFN levels.

There is little to no effect on cytochrome P-450 (CYP) enzymes at standard dosing; however, mild induction of CYP3A4 can reduce ethinyl-estradiol and norethindrone levels, although the clinical relevance is unknown. Female patients of childbearing age should be warned of the potential reduced effectiveness of contraception.

Somnolence and vomiting are common adverse events, as are headache, dizziness, fatigue, nausea, diplopia, and tremor. The observed degree of QT shortening on electrocardiography (ECG) is without known clinical risk, but RFN should be avoided in patients with familial short QT syndrome, and caution must be exercised with other medications that can shorten the QT interval. Developmental toxicity was seen in animal studies; however, the potential for teratogenicity in humans is unknown. RFN is considered pregnancy category C.

For children aged 4 years and older, the recommended initial starting dosage is 10 mg/kg per day in divided doses. The daily dosage may be increased by 10 mg/kg every other day until the target dosage of 45 mg/kg per day or 3,200 mg/d, whichever is less. In adults, the recommended starting dosage is 400–800 mg/d, given twice daily, and may be increased as quickly as 400–800 mg/d every other day until the maximum dosage of 3,200 mg/d is reached, although this rapid titration has been difficult for some patients to manage.

Lacosamide

Lacosamide (LCM) was released in mid-2009, as the FDA finalized its categorization as a schedule V controlled substance. It has a novel mechanism on the sodium channel, functionally enhancing its slow inactivation state, theoretically limiting rapid sequential firing. It also modulates CRMP-2, although it is unknown whether this will have clinical impact. One clinical trial found that adjunct use of LCM significantly reduced partial-onset seizure frequency at 200 mg/d (35.3%) and 400 mg/d (44.9%) versus placebo (25.4%) [37], and another study found reductions at 200 mg/d (26%), 400 mg/d (39%), and 600 mg/d (40%) [38] versus placebo (10%). The highest dosage, 600 mg/d, did not offer significantly greater benefits and caused more adverse events, so this dosage was not included in the product labeling.

LCM is rapidly and completely absorbed, with plasma levels peaking between 1 h and 4 h following oral administration [39]. The elimination half-life is 13 h, primarily through the kidney, and protein binding is less than 15%. There are no known drug–drug interactions with other AEDs.

The starting dosage is 50 mg twice daily and is increased by 50 mg twice daily each week to the target dosage of 200 mg twice daily. Some patients cannot tolerate the target dosage. Dizziness, headache, diplopia, somnolence, fatigue, ataxia, tremor, and nausea were reported as ≥10% in some clinical trials. A dose-related increase in PR interval on ECG may occur (4.2–4.6 ms at 400 mg/d).

The intravenous (IV) formulation is FDA approved for use as a substitution for the oral form when medically necessary. The IV formulation is indicated when oral mediation cannot be taken or may not be well absorbed, but its availability lends itself to intensive care where it has been used off-label to treat refractory status epilepticus [40]. Research is ongoing into its effect on chronic pain and anxiety.

Vigabatrin

In August 2009, VGB was given orphan drug status by the FDA for use in infantile spasms and as adjunctive therapy for adult patients with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss. VGB is an analogue of γ-aminobutyric acid (GABA) but is not an agonist. Instead, it irreversibly inhibits GABA transaminase, thereby increasing GABA levels. Visual loss may be a result of its efficient transport to the retina. Once detected, the loss is permanent. In 30% or more of adult patients, progressive bilateral concentric visual field constrictions occur, often from the normal of 90° to 65°, but the range is from mild to as severe as 10° of visual fixation. There are some reports of central retinal damage and loss of visual acuity. There is no safe period beyond which retinal damage will not continue to occur.

As part of the FDA approval, the medication must be obtained from a central pharmacy that requires physician registration and patients must undergo quarterly visual assessments by an ophthalmologist, which includes electro-

retinograms in a percentage of patients, some whom require anesthesia. VGB should be withdrawn as early as possible if substantial clinical benefit is not observed; guidelines are 2–4 weeks for infantile spasms and 3 months in adult patients.

Lamotrigine XR

LTG was approved in the United States in 1995 for use as add-on therapy in partial seizures with or without secondary generalization. There have been further indications to include: adjunct use in partial seizures and Lennox-Gastaut syndrome (chewable tabs) to as young as 2 years old, as monotherapy conversion from valproate or enzyme-inducing medications in partial epilepsy, and for bipolar I disorder. In June 2009, the extended-release formulation (LTG-XR) was approved.

LTG-XR tablets are enteric coated to delay the drug's absorption until gastric emptying and also use a matrix formulation to limit the rate of dissolution for approximately 12–15 h. This agent was more effective than placebo as an adjunct in once-daily dosing in a double-blinded study [41]. Pharmacokinetic studies in an open-label study switching patients (n=44) from immediate-release LTG (LTG-IR) to LTG-XR showed a similar area under the curve (AUC) for 0–24 h, except in those taking concomitant inducing agents, in whom the AUC was 21% lower in those receiving the XR formulation [42]. This study showed a decrease in the peak-to-trough fluctuation in those on LTG-XR, and that T_{max} increased from 1–1.5 h in the LTG-IR group to between 4 h and 11 h in the LTG-XR group, depending on whether patients were on inducing or inhibiting agents. The XR formulation may help avoid peak dose adverse events.

In studies using LTG-IR, the increased rate of glucuronidation with higher estrogen and other sex hormones leads to significant reductions in LTG plasma levels; therefore, frequent monitoring of serum levels is now advised during pregnancy. Use of oral contraceptives induces its metabolism, with cessation of these agents associated with an 84% increase in LTG in plasma within 1 week of the change [43], suggesting that deinduction of LTG glucuronidation is faster than that of CYP.

Levetiracetam XR

LVT is indicated as adjunctive therapy in the treatment of a) partial-onset seizures with or without secondary generalization in adults and children aged 4 years and older with epilepsy, b) myoclonic seizures in adults and adolescents aged 12 years and older with juvenile myoclonic epilepsy, and c) primary generalized tonic–clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy. LVT-IR was approved in 1999 for adults as adjunctive therapy; it is available in an oral solution and an IV form. LVT-XR was FDA approved in late 2008 based on a multinational comparison study [44]. It uses a matrix system to control the release, increasing T_{max} from just under an hour to 4 h, with an AUC comparable with that of LVT-IR [45]. The T_{max} can be extended further with intake of a high-fat, high-calorie meal. Behavioral issues such as irritability have not been formally compared with those in LVT-XR, although they were reported in 6% of 77 patients in a placebo-controlled trial [46], a rate lower than the accumulated rate of 13.5% in clinical trials and postmarketing trials of LVT-IR. Continued seizures were a factor in developing negative mood, as some patients who were seizure-free on LVT-IR reported a positive change in mood [47]. In other studies, discontinuation of LVT-IR because of behavioral abnormalities was statistically associated with a faster titration rate, a history of psychiatric disorder, a diagnosis of symptomatic generalized epilepsy, learning disabilities, status epilepticus, and febrile convulsions. Concomitant use of LTG may improve these symptoms. In children, an early study using pyridoxine at 100–200 mg/d also showed some potential to alleviate behavioral abnormalities [48]. LVT showed promise in a placebo-controlled trial for chronic pain in multiple sclerosis [49].

Comparison with First-Generation Medications

Notably, the first-generation medications, including PB, PHT, PRM, CBZ, and VPA, all significantly affect the liver enzymes. Although the newer medications are not clearly more efficacious against seizures, they generally are better tolerated [6, 7]. The potential problems of chronic enzyme induction include loss of bone density and significant elevation of cardiac disease markers [50].

Conclusions

A wide variety of AEDs are now available. Figure 1 and Table 3 demonstrate the thought process involved in choosing among them. For partial seizures, virtually any agent (except ethosuximide) may be considered. For the idiopathic generalized epilepsies, only broad-spectrum agents would be expected to treat all seizure types. The next major factor in choosing a medication is tolerability. The most successful medication in terms of seizure freedom and long-term retention is one that a patient finds tolerable at the very least, and at best, goes unnoticed. Matching the "personality" of the medication to the personality of the patient may lead to better successes. Underlying mood disorders and the wish for weight gain or loss are the most common issues that arise, with tendencies of the medications noted in Table 1. However, using TPM or ZNS in patients with a tendency for chronic headache and PGB or

GBP in those with chronic pain or anxiety may be effective for the population with epilepsy. Another key to compliance is the dosing schedule. Once-daily dosing is convenient for patients with busy lives and is becoming common with the addition of XR formulations of older medications.

The shift in attention to tolerability includes the chronic adverse effects of AEDs. The first-generation medications cannot be considered first line because of their associations with osteoporosis and their tendency to increase cholesterol and other assays with negative cardiovascular connotations.

The Pregnancy Registry remains our best hope for determining the true risks of congenital malformations, perinatal complications, and neurodevelopment with use of the various AEDs. For now, it seems clear that VPA should be avoided as monotherapy and most definitely in polytherapy. It is important to define the risks, but it also is worthwhile to stress the positive: WWE have a nearly 95% chance of having a perfectly healthy baby.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. LaRoche SM, Helmers SL: The new antiepileptic drugs: scientific review. JAMA 2004, 291:605–614.
2. Marson AG, Al-Kharusi AM, Alwaidh M, et al.: The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007, 369:1016–1026.
3. Marson AG, Appleton R, Baker GA, et al.: A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial. Health Technol Assess 2007, 11:iii–iv, ix–x, 1–134.
4. Montouris G, Abou-Khalil B: The first line of therapy in a girl with juvenile myoclonic epilepsy: should it be valproate or a new agent? Epilepsia 2009, 50(Suppl 8):16–20.
5. Panayiotopoulos CP, Obeid T, Tahan AR: Juvenile myoclonic epilepsy: a 5-year prospective study. Epilepsia 1994, 35:285–296.
6. Marson AG, Al-Kharusi AM, Alwaidh M, et al.: The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. Lancet 2007, 369:1000–1015.
7. Rowan AJ, Ramsay RE, Collins JF, et al.: New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology 2005, 64:1868–1873.
8. • French JA, Kanner AM, Bautista J, et al.: Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004, 62:1261–1273. *Along with Part I by the same authors [9•], this article reviews the evidence-based data for the use of AEDs in specific clinical situations. Although often there is a lack of high-quality published data to support the use of medications that have had good anecdotal results, this review lists and rates the evidence available for most of the modern AEDs*.
9. • French JA, Kanner AM, Bautista J, et al.: Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004, 62:1252–1260. *This is the first part of a two-part article by the same group*.
10. Glauser T, Ben-Menachem E, Bourgeois B, et al.: ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006, 47:1094–1120.
11. Kwan P, Brodie MJ: Effectiveness of first antiepileptic drug. Epilepsia 2001, 42:1255–1260.
12. Kanner AM, Balabanov AJ: The use of monotherapy in patients with epilepsy: an appraisal of the new antiepileptic drugs. Curr Neurol Neurosci Rep 2005, 5:322–328.
13. Kwan P, Brodie MJ: Epilepsy after the first drug fails: substitution or add-on? Seizure 2000, 9:464–468.
14. • Liow K, Barkley GL, Pollard JR, et al.: Position statement on the coverage of anticonvulsant drugs for the treatment of epilepsy. Neurology 2007, 68:1249–1250. *Neurologists should know about this statement by the American Academy of Neurology.*
15. •• Gidal BE, Tomson T: Debate: substitution of generic drugs in epilepsy: is there cause for concern? Epilepsia 2008, 49(Suppl 9):56–62. *This is an excellent review of both sides of the argument*.
16. Patsalos PN, Berry DJ, Bourgeois BF, et al.: Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008, 49:1239–1276.
17. Chiou CC, Yang LC, Hung SI, et al.: Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. J Eur Acad Dermatol Venereol 2008, 22:1044–1049.
18. Newell BD, Moinfar M, Mancini AJ, Nopper AJ: Retrospective analysis of 32 pediatric patients with anticonvulsant hypersensitivity syndrome (ACHSS). Pediatr Dermatol 2009, 26:536–546.
19. Arif H, Buchsbaum R, Weintraub D, et al.: Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology 2007, 68:1701–1709.
20. Hirsch LJ, Arif H, Nahm EA, et al.: Cross-sensitivity of skin rashes with antiepileptic drug use. Neurology 2008, 71:1527–1534.
21. Franciotta D, Kwan P, Perucca E: Genetic basis for idiosyncratic reactions to antiepileptic drugs. Curr Opin Neurol 2009, 22:144–149.
22. •• Hesdorffer DC, Kanner AM: The FDA alert on suicidality and antiepileptic drugs: fire or false alarm? Epilepsia 2009, 50:978–986. *The authors discuss insights into the process by which the FDA alert came about, some criticisms of it, and, most importantly, constructive suggestions to integrate into clinical practice*.
23. Shneker BF, Cios JS, Elliott JO: Suicidality, depression screening, and antiepileptic drugs: reaction to the FDA alert. Neurology 2009, 72:987–991.

24. •• Verrotti A, Coppola G, Parisi P, et al.: Bone and calcium metabolism and antiepileptic drugs. Clin Neurol Neurosurg 2010, 112:1–10. *This is a succinct review of bone metabolism and a summary of data for the effects of each AED on bone health*.
25. Coppola G, Fortunato D, Auricchio G, et al.: Bone mineral density in children, adolescents, and young adults with epilepsy. Epilepsia 2009, 50:2140–2146.
26. Meador K, Reynolds MW, Crean S, et al.: Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008, 81:1–13.
27. McVearry KM, Gaillard WD, VanMeter J, Meador KJ: A prospective study of cognitive fluency and originality in children exposed in utero to carbamazepine, lamotrigine, or valproate monotherapy. Epilepsy Behav 2009, 16:609–616.
28. •• Harden CL, Hopp J, Ting TY, et al.: Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): I. obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009, 50:1229–1236. *This three-part series should be reviewed by all clinical neurologists because it represents the current standard of care for using AEDs before, during, and after pregnancy.*
29. Harden CL, Meador KJ, Pennell PB, et al.: Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): II. teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009, 50:1237–1246.
30. Harden CL, Pennell PB, Koppel BS, et al.: Management issues for women with epilepsy—focus on pregnancy (an evidence-based review): III. vitamin K, folic acid, blood levels, and breast-feeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Epilepsia 2009, 50:1247–1255.
31. Chen YH, Chiou HY, Lin HC, Lin HL: Affect of seizures during gestation on pregnancy outcomes in women with epilepsy. Arch Neurol 2009, 66:979–984.
32. Crawford P: Epilepsy and pregnancy. Seizure 2002, 11(Suppl A):212–219.
33. Tomson T, Palm R, Kallen K, et al.: Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. Epilepsia 2007, 48:1111–1116.
34. Glauser T, Kluger G, Sachdeo R, et al.: Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology 2008, 70:1950–1958.
35. Brodie MJ, Rosenfeld WE, Vazquez B, et al.: Rufinamide for the adjunctive treatment of partial seizures in adults and adolescents: a randomized placebo-controlled trial. Epilepsia 2009, 50:1899–1909.
36. Kluger G, Kurlemann G, Haberlandt E, et al.: Effectiveness and tolerability of rufinamide in children and adults with refractory epilepsy: first European experience. Epilepsy Behav 2009, 14:491–495.
37. Halasz P, Kalviainen R, Mazurkiewicz-Beldzinska M, et al.: Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. Epilepsia 2009, 50:443–453.
38. Ben-Menachem E, Biton V, Jatuzis D, et al.: Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia 2007, 48:1308–1317.
39. Doty P, Rudd GD, Stoehr T, Thomas D: Lacosamide. Neurotherapeutics 2007, 4:145–148.
40. Tilz C, Resch R, Hofer T, Eggers C: Successful treatment for refractory convulsive status epilepticus by parenteral lacosamide. Epilepsia 2010, 51:316–317.
41. Naritoku DK, Warnock CR, Messenheimer JA, et al.: Lamotrigine extended-release as adjunctive therapy for partial seizures. Neurology 2007, 69:1610–1618.
42. Tompson DJ, Ali I, Oliver-Willwong R, et al.: Steady-state pharmacokinetics of lamotrigine when converting from a twice-daily immediate-release to a once-daily extended-release formulation in subjects with epilepsy (The COMPASS Study). Epilepsia 2008, 49:410–417.
43. Christensen J, Petrenaite V, Atterman J, et al.: Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. Epilepsia 2007, 48:484–489.
44. Richy FF, Banerjee S, Brabant Y, Helmers S: Levetiracetam extended release and levetiracetam immediate release as adjunctive treatment for partial-onset seizures: an indirect comparison of treatment-emergent adverse events using meta-analytic techniques. Epilepsy Behav 2009, 16:240–245.
45. Ulloa CM, Towfigh A, Safdieh J: Review of levetiracetam, with a focus on the extended release formulation, as adjuvant therapy in controlling partial-onset seizures. Neuropsychiatr Dis Treat 2009, 5:467–476.
46. Peltola J, Coetzee C, Jimenez F, et al.: Once-daily extended-release levetiracetam as adjunctive treatment of partial-onset seizures in patients with epilepsy: a double-blind, randomized, placebo-controlled trial. Epilepsia 2009, 50:406–414.
47. Helmstaedter C, Fritz NE, Kockelmann E, et al.: Positive and negative psychotropic effects of levetiracetam. Epilepsy Behav 2008, 13:535–541.
48. Major P, Greenberg E, Khan A, Thiele EA: Pyridoxine supplementation for the treatment of levetiracetam-induced behavior side effects in children: preliminary results. Epilepsy Behav 2008, 13:557–559.
49. Rossi S, Mataluni G, Codeca C, et al.: Effects of levetiracetam on chronic pain in multiple sclerosis: results of a pilot, randomized, placebo-controlled study. Eur J Neurol 2009, 16:360–366.
50. Mintzer S, Skidmore CT, Abidin CJ, et al.: Effects of antiepileptic drugs on lipids, homocysteine, and C-reactive protein. Ann Neurol 2009, 65:448–456.