

Pharmacologic Decision-making in the Treatment of Focal Epilepsy— A Critical Comparison of Antiepileptic Drugs

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Abstract

Physicians who treat patients with epilepsy must balance many factors when selecting the appropriate treatment for an individual patient, including seizure type, concomitant antiepileptic drug (AED) therapy, age, comorbid conditions, and even insurance coverage. Optimal management of seizures is further complicated by a continuously increasing pool of AEDs. As seizure type is a main factor in AED selection, this review will provide an evidence-based guide for physicians treating focal epilepsy. This includes a summary of efficacy, safety, and tolerability data from randomized clinical trials as well as findings related to rational polypharmacy, drug–drug interactions, comorbidities, drug administration (titration, dosing, formulation), US Food and Drug Administration (FDA)-approved indications, and cost. Following the review are four case reports that provide real-life examples of clinical challenges physicians face, particularly when dealing with special populations, which highlight the decision-making process entailed when determining the best course of treatment for patients with epilepsy.

Keywords

Epilepsy, antiepileptic drug, focal seizures, treatment decisions, enzyme inducers, effectiveness, cost

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Epilepsy is a general term used to describe a collection of common, chronic conditions of recurrent and unpredictable seizures. While seizures in newly diagnosed patients are often controlled with a single antiepileptic drug (AED),¹ the estimated 30–40 % of patients who are resistant to monotherapy could benefit from a combination of two or more carefully selected AEDs.^{2,3} The reasons for AED treatment failures are as complex as the disease itself and likely depend, at least partly, on initial treatment decisions.⁴

Prior to the recent influx of nearly two dozen AEDs to the pharmacopeia, treatment choices in epilepsy were fairly straightforward, but arguably limited. Today, the decision as to which AED to administer can be a daunting task given the sheer number of AEDs available, lack of head-to-head drug comparisons, and the staggering array of patient-specific variables that physicians must consider when choosing an appropriate treatment regimen. Among the many factors that can affect response to AEDs are the type of seizure, disease stage, prior and current AED

therapy, age, concomitant medications, and comorbid conditions. Given the serious nature of epilepsy and the complexity of the drugs currently available to treat it, prescribing AEDs using only a trial-and-error approach may not be the best strategy. Thus, a more sophisticated method for treatment decisions is desirable in order to meet individual patient needs and to optimize patient outcome.

Not all AEDs are effective for both focal (partial-onset) and generalized seizures, and one of the most important factors in choosing an AED is the type of seizure and epilepsy syndrome being treated.⁵ While focal seizures overall are successfully managed with the recently approved AEDs, an important subset of patients remain refractory to treatment.⁵ Almost all of the second- and third-generation AEDs have been approved based on their efficacy and safety as adjunctive treatment for focal seizures.^{6,7} Thus, most of the data available for comparative evaluations of the newer AEDs are from trials in which patients were already taking at least one AED (with or without concurrent use of vagus nerve stimulation).

This review will consider evidence that can affect treatment decisions for focal epilepsies. Generalized epilepsies and treatment decisions for generalized seizures (including absence, myoclonic, and tonic-clonic seizures, as well as Lennox-Gastaut or West syndromes) will not be discussed.

What to Compare—What Matters When We Choose an Antiepileptic Drug?

Randomized clinical trials (RCTs) are designed to assess the efficacy, tolerability, and safety of a particular drug compared with placebo within the strict confines of an *a priori*-defined study design. As such, results from drug trials can fail to answer common clinical questions.^{8,9} While efficacy is naturally the most important factor when choosing an AED, it exists in partnership with many other factors, all of which can contribute to drug effectiveness—how a treatment works under ordinary conditions, administered by the typical practitioner to the typical patient. To guide treatment decisions, physicians need some indication as to how efficacious one AED can be compared with another (or in combination with another) while being mindful of patient- and drug-specific variables that can influence treatment success, including safety and tolerability, drug–drug interactions, dosing, and cost.

Rational Polytherapy

The explosion of a variety of new AEDs to the market in recent years has renewed interest in combination therapy for epilepsy, particularly for patients who are not adequately controlled with a single AED. Though monotherapy is considered the standard of care for patients with newly diagnosed epilepsy, treatment with two or more AEDs has been shown to be effective in patients who do not achieve adequate seizure control following sequential monotherapy.¹⁰ The term ‘rational polytherapy’ (or ‘polypharmacy’) has been used to describe the careful selection of drug combinations intended to improve overall treatment effect without added drug toxicity.¹¹ In practice, implementing rational polytherapy can be quite challenging as evidence from prospective trials designed to identify optimal AED combinations is lacking. However, given the roughly 200 two-drug combinations and >1,000 three-drug combinations that are possible with currently available AEDs, prospective comparative efficacy trials are impractical and cost-prohibitive.¹¹ Most of what is currently known about particular AED combinations has been derived from clinical experience or gleaned from retrospective and post hoc exploratory analyses.

The decision to add a drug to a treatment regimen rather than pursue sequential monotherapy can have several advantages, including the potential for synergistic effects. Because of the successful combination of drugs with differing mechanisms of action (MOA) for a number of other diseases (e.g., Alzheimer’s disease, HIV, diabetes), a similar approach for epilepsy seems logical, and one would expect greater likelihood of synergistic effects when combining AEDs with different MOAs. While clinical and preclinical evidence suggests that drug effectiveness can be increased by combining a sodium-channel blocking AED with a drug that enhances GABAergic neurotransmission, the only AED combination that has shown a synergistic effect to date is lamotrigine (LTG) combined with valproate (VPA).^{2,12,13} Moreover, the efficacy of two or more sodium-channel blocking AEDs combined may not be more efficacious than each drug alone.² Complicating an MOA-based treatment strategy is the fact that most AEDs do not have a single known MOA, with several AEDs having affinity for several molecular targets (e.g., VPA, topiramate [TPM], and gabapentin [GBP]). Such ‘multi-target’ AEDs may, however, be advantageous for patients suffering from several types of seizures with multiple underlying disease mechanisms, but their use in specific AED combinations for focal seizures is difficult to determine given the limited data.

Although synergistic effects are difficult to ascertain, combinations of AEDs with differing MOAs have shown positive effects in patients with focal seizures. In a post hoc exploratory analysis, efficacy of lacosamide (LCM, a sodium-channel blocking AED) in combination with either non sodium-channel blocking AEDs (SCB-) or sodium-channel blocking AEDs (SCB+) was evaluated.¹⁴ Sodium-channel blocking AEDs were defined as carbamazepine (CBZ), LTG, oxcarbazepine (OXC), or phenytoin (PHT). At the highest approved dose of LCM, the median percent reduction from baseline in seizure frequency was numerically higher in the SCB- group versus the SCB+ group (63 % versus 39 %), although both groups did demonstrate significant improvement versus placebo.¹⁴ In a retrospective examination of AED combinations used most frequently, superior efficacy (seizure freedom for ≥12 months, measured head-to-head) was found for LTG combined with VPA and for CBZ combined with TPM over other AED combinations or monotherapy:¹⁵

- LTG+VPA > VPA or LTG monotherapy;
- LTG+VPA > CBZ+VPA; VPA+GBP; CBZ+VPA+PHT; and
- CBZ+TPM > CBZ monotherapy.

Patients in this study were developmentally disabled and the types of seizures were heterogeneous (including Lennox-Gastaut syndrome and primary generalized seizures); therefore, though compelling, these results are difficult to extrapolate to the adjunctive treatment of patients with focal seizures.

Lastly, a recent study corroborates that combining AEDs with different MOAs results in overall better effectiveness.¹⁶

Until evidence-based guidelines are available to recommend specific AED combinations, physicians must carefully consider the available data for the many factors that are discussed below when determining an appropriate adjunctive AED for patients with focal epilepsy.

Efficacy Seizure Reduction

Primary efficacy endpoints in RCTs measure seizure reduction from baseline by determining the 50 % responder rate (the proportion of patients

Table 1: Newer Antiepileptic Drugs for Adjunctive Treatment of Patients With Focal Epilepsy

Drug/Brand Name (Approval)	Maximum Approved Dose	Seizure Reduction From Baseline for Maximum Approved Dose, median %				Responder Rate for Maximum Approved Dose, ^a % patients				Seizure Freedom for Maximum Approved Dose, ^b % patients			
		Drug	PBO	Diff	Ref	Drug	PBO	Diff	Ref	Drug	PBO	Diff	Ref
Eslicarbazepine/Aptiom® (2013)	1,200 mg/day (qd)	35 ^{c,d}	16 ^{c,d}	19	17	41 ^{d,e}	22 ^{d,e}	19	17	4.2 ^{c,d}	1.2 ^{c,d}	3	18–20
Gabapentin/Neurontin® (1993)	1,800 mg/day (600 mg tid)	32	6	26	21	26	8	18	22		NR		
Lacosamide/Vimpat® (2008)	400 mg/day (200 mg bid)	37 ^{c,d}	18 ^{c,d}	19	23	40 ^d	23 ^d	17	23	3.3 ^{c,d}	0.9 ^{c,d}	2.4	24–26
Lamotrigine/Lamictal® (1994)	500 mg/day (in 2 divided doses)	36	8	28	27	34	18	16	28		NR		
Levetiracetam/Keppra® (1999)	3,000 mg/day (1500 mg bid)	39 ^{c,f}	7 ^{c,f}	32	29, 30	41 ^{c,f}	14 ^{c,f}	27	29, 30	8.2 ^{c,f}	0.5 ^{c,f}	7.7	29, 30
Oxcarbazepine/Trileptal® (2000)	1,200 mg/day (600 mg bid)	40	8	32	31	41	13	28	32	10	0.6	9.4	32
Perampanel/Fycompa™ (2012)	12 mg/day (qd)	27.2	12.8	14.4	33	35	19	16	34	4.1	1.0	3.1	33
Pregabalin/Lyrica® (2005)	600 mg/day (200 mg tid or 300 mg bid)	44 ^{c,d}	0 ^{c,d}	45	35	47 ^{c,d}	10 ^{c,d}	37	36–38	12	1.0	11	36
Tiagabine/Gabitril® (1998)	56 mg/day (in 2–4 divided doses)	36	3	33	39	30	4	26	39		NR		
Topiramate/Topamax® (1996)	400 mg/day (200 mg bid)	45 ^{c,f}	8 ^{c,f}	37	40	41 ^{c,f}	15 ^{c,f}	26	40	8.7	0	8.7	41
Zonisamide/Zonegran® (2000)	400 mg/day (200 mg bid)	40	9	31	42	42	22	20	42	6.1	2.8	3.3	43

Data reported from a single trial, unless otherwise noted. ^aPercentage of patients with ≥ 50 % seizure reduction from baseline. ^bDuring maintenance phase (range 8–24 weeks). ^cCalculated weighted averages from multiple studies. ^dAveraged from three studies. ^eValues estimated from graph. ^fAveraged from two studies. bid = twice daily; Diff = difference; NR = not reported in prescribing information or published pivotal trials; Ref = reference; PBO = placebo; tid = three times daily.

with at least a 50 % reduction in seizure frequency, a primary endpoint typically required by the European Medicines Agency (EMA) or the median percent reduction from baseline in seizure frequency (a usual US Food and Drug Administration [FDA]-required primary outcome). A comparison of the median percent reductions in seizure frequency for newer AEDs commonly used as adjunctive treatment for focal seizures reveals a small range of differences in efficacy (see *Table 1*). Vigabatrin (VGB) (Sabril®) and ezogabine (EZG)/retigabine (Potiga®/Trobalt®) are considered ‘last resort’ drugs, and are therefore not included in *Table 1*.^{17–43} VGB is indicated as adjunctive therapy only in patients with complex partial seizures who are unresponsive to treatment with other AEDs and for whom the risk for vision loss with VGB treatment outweighs the perceived benefits.⁴⁴ EZG has also been linked with retinal abnormalities, potential vision loss, and blue skin discoloration;⁴⁵ it is currently unknown if the skin discoloration or retina pigmentation changes are reversible.⁴⁶

The efficacy of the newer AEDs for refractory focal seizures has been compared in recently published systematic reviews and meta-analyses (see *Table 1*).^{47,48} Costa et al. found significant differences in responder rates (primary outcome) compared with placebo among patients with refractory focal seizures treated with OXC, LTG, TPM, GBP, pregabalin (PGB), levetiracetam (LEV), tiagabine (TGB), zonisamide (ZNS), eslicarbazepine (ESL), or LCM; results were the same when the efficacy analysis was adjusted for baseline risk.⁴⁷ Similar results were found by Gao et al.⁴⁸ in a comparative analysis of adjunctive ESL, EZG, carisbamate (CAR), LCM, brivaracetam (BRV), and perampanel (PMP) versus placebo in patients with refractory focal seizures.

In the absence of head-to-head trials, indirect comparisons of AED efficacy can be used to guide clinical decisions. Results from a random-effects meta-analysis (based on relative measurements of treatment effect) showed significant differences in responder rates favoring TPM over the pooled net effect of the other AEDs; the least efficacious AEDs were GBP and LCM.⁴⁷ When adjusted for baseline risk, TPM and LEV were most efficacious, while GBP and TGB were least efficacious. Gao et al.⁴⁸ used a similar methodology to indirectly compare responder rates among the AEDs tested and found that ESL and BRV were the most efficacious; however, at the time of this publication BRV has not received FDA approval.⁴⁸

Though it may be convenient to take these results at face value, such indirect comparisons can be complicated by many factors. In a systematic review and meta-analysis evaluating the possible effects of methodological differences in trial design and analyses on AED efficacy comparisons, it was determined that indirect efficacy comparisons are confounded by several factors, including length of efficacy evaluation, the trial phase used to determine responder rate (entire treatment phase [titration + maintenance] versus maintenance period), and the statistics used to calculate responder rate (last observation carried forward [LOCF] versus completer).⁴⁹ Thus, results from such indirect efficacy comparisons should be approached with caution, and other factors must be considered when making treatment decisions.

Seizure Freedom

The ultimate goal of AED treatment is seizure freedom. Seizure freedom is often reported as the proportion of seizure-free patients or the proportion of seizure-free days during treatment. Since the analysis of seizure freedom is

Table 2: Incidence ($\geq 15\%$ for Any Drug) of Treatment-emergent Adverse Events Associated With Newer Antiepileptic Drugs for Adjunctive Therapy

Preferred Term % drug/PBO	ESL (800– 1,200 mg/day) n=825	GBP ^a n=543	LCM (200– 400 mg/day) n=741	LEV ^a n=769	LTG ^a n=711	OXC (600– 1,200 mg/day) n=334	PMP (4–12 mg/day) n=858	PGB (150– 600 mg/day) n=670	TGB ^a n=494	TPM (200– 400 mg/day) n=183	ZNS ^a n=269
Nervous System											
Asthenia	2/2		2/1	15/9		4/5	2/1		20/14	6/1	
Ataxia	5/2	12/6	6/2	3/1	22/6	13/5	4/0	15/4	5/3	16/7	6/1
Dizziness	24/9	17/7	25/8	9/4	38/13	29/13	32/9	32/11	27/15	25/15	13/7
Headache	14/9		13/9	14/13	29/19	30/23	12/11				10/8
Nervousness		2/2		4/2		3/1			10/3	16/6	2/1
Somnolence	14/8	19/9	7/5	15/8	14/7	24/12	15/7	22/11	18/15	29/12	17/7
Digestive System											
Nausea	13/5		10/4		19/10	20/10	6/5		11/9	10/8	9/6
Vomiting	8/3		8/3		9/4	19/5	3/3		7/3		
General Disorders/Body as a Whole											
Fatigue	5/4	11/5	7/6			13/7	9/5			15/13	8/6
Eye Disorders/Special Senses											
Diplopia	10/2	6/2	9/2	2/1	28/7	22/5	2/1	9/4		10/5	6/3

Adverse events presented in respective prescribing information (PI) are those that occurred with an incidence $\geq 2\%$ and greater than placebo;^{17,22,23,27,31,34,35,39,40,42,52} blank cells indicate data not reported in PI; **BOLD** indicates highest relative incidence among the antiepileptic drugs included in this comparison. ^aDoses not specified in PI, reported for all approved doses combined. ESL = eslicarbazepine; GBP = gabapentin; LCM = lacosamide; LEV = levetiracetam; LTG = lamotrigine; OXC = oxcarbazepine; PBO = placebo; PGB = pregabalin; PI = prescribing information; PMP = perampanel; TGB = tiagabine; TPM = topiramate; ZNS = zonisamide.

not standard, nor has it been a primary endpoint in most clinical trials to date, any comparisons of seizure freedom rates among AEDs can be misleading and may be difficult due to methodological differences. With these caveats in mind, seizure freedom rates among several AEDs have been compared using a 'pragmatic intent-to-treat (ITT)' approach.⁵⁰ Gazzola et al. found that seizure freedom rates (proportion of seizure-free patients) among those treated with OXC, GBP, LTG, LEV, PGB, and ZNS were low, ranging from $\leq 1.0\%$ (ZNS, LTG) to 6.4% (LEV).⁵⁰ Using an LOCF approach, seizure freedom rates in the same trials were found to be falsely inflated, serving as an example of the complexity and difficulty of such comparisons.⁵⁰ Of the newer AEDs for which seizure freedom is reported in the pivotal trials, PGB has the highest rate versus placebo, followed by OXC, TPM, and LEV (see *Table 1*).

In the same random-effects meta-analysis described above, seizure freedom rates (available for 32 of 63 studies) showed no significant differences among the AEDs tested, but all AEDs had a more favorable response than placebo. By combining indirect and direct evidence from eight head-to-head trials, comparisons of seizure freedom rates favored TPM over LTG, while no differences were detected between LTG and either PGB or LEV.⁴⁷ An additional meta-analysis found seizure freedom rates favoring all AEDs over placebo, with outcomes favoring LCM over ESL, EZG, CAR, BRV, and PMP.⁴⁸ Again, differences in parameters and assumptions can limit the ability to show a clinically meaningful difference in seizure freedom rates among the AEDs.

Taken together, direct and indirect comparisons indicate few if any differences in efficacy of one newer AED over another, underscoring the importance of other factors that contribute to drug effectiveness and treatment success.

Safety and Tolerability

Though efficacy varies little among the newer third- and second-generation AEDs—and is similar to the first generation AEDs (e.g., VPA, CBZ)⁵¹—the

newer AEDs are often advantageous with respect to tolerability, having fewer side effects, and a lower risk for drug–drug and hypersensitivity interactions than older AEDs.⁷

Adverse Events

The potential for adverse events (AEs) with a particular AED may be a strong differentiating factor when making treatment decisions. Most AEs are manageable, only requiring dose adjustments or a change in drug formulation, e.g., from immediate-release to XR. Overall, the newer AEDs have few worrisome side effects. AEs most commonly associated with the newer AEDs are neurological or gastrointestinal effects, including dizziness, ataxia, somnolence, and nausea (see *Table 2*).

In addition to the common AEs identified in *Table 2*, select 'Warnings and Precautions' that may further distinguish one AED over another are listed in *Table 3*. Patients treated with ESL have had drug reaction with eosinophilia and systemic symptoms (DRESS), also known as multiorgan hypersensitivity; kidney stones can occur with TPM and ZNS; LEV⁵² and PMP have been linked to psychiatric symptoms and behavioral issues; cognitive dysfunction or depression and mood problems have been reported with TPM; and weight gain with PGB, PMP, and GBP may be a differentiating factor. Not listed in *Table 3* (since it appears in the prescribing information [PI] for each AED and would therefore not be a distinguishing factor) are suicidality and the potential for increased seizure frequency with rapid withdrawal. Two of the newer AEDs also carry black box warnings on their labeling for rare and idiosyncratic reactions: LTG for serious skin rashes (including Stevens-Johnson syndrome and toxic epidermal necrolysis); PMP for life-threatening psychiatric and behavioral reactions (including aggression, hostility, irritability, anger, and homicidal ideation).⁵³

In the random-effects meta-analysis, six pre-specified AEs were compared among the newer AEDs: ataxia, headache, dizziness, fatigue, nausea, and somnolence. Overall, few differences between AEDs were found:

Table 3: Select Warnings and Precautions Identified in Prescribing Information^a

Drug/Brand Name	Warnings and Precautions
Eslicarbazepine/Aptiom [®]	Anaphylactic reactions and angioedema DRESS/multi-organ hypersensitivity Serious dermatologic reactions Drug-induced liver injury
Gabapentin/Neurontin [®]	Behavioral problems, hostility (including aggressive behaviors) in pediatrics Thought disorders (including concentration problems and change in school performance) in pediatrics Hyperkinesia (primarily restlessness and hyperactivity) in pediatrics DRESS/multi-organ hypersensitivity
Lacosamide/Vimpat [®]	Dizziness and ataxia Caution for patients with known cardiac conduction problems, severe cardiac disease, or who are taking drugs known to prolong the QT interval
Lamotrigine/Lamictal [®]	Serious rash/rash-related death Fatal or life-threatening multi-organ hypersensitivity Blood dyscrasias Aseptic meningitis
Levetiracetam/Keppra [®]	Psychiatric symptoms: psychotic symptoms, irritability, and aggressive behavior Somnolence and fatigue
Oxcarbazepine/Trileptal [®]	Hyponatremia Anaphylactic reactions and angioedema Serious dermatologic reactions Psychomotor slowing, difficulty with concentration, and speech or language problems Ataxia and gait disturbances Hematologic events
Perampanel/Fycompa [®]	Hostility and aggression Dizziness and gait disturbance Falls
Pregabalin/Lyrica [®]	Angioedema Hypersensitivity reactions (hives, dyspnea, and wheezing) Peripheral edema Weight gain
Tiagabine/Gabitril [®]	Impaired concentration, speech or language problems, and confusion Binding in the eye and other melanin-containing tissues Serious rash
Topiramate/Topamax [®]	Kidney stones Cognitive dysfunction or depression/mood problems Acute myopia and secondary angle closure glaucoma (can lead to permanent vision loss if left untreated) Visual field defects Oligohidrosis and hyperthermia Metabolic acidosis Hyperammonemia
Zonisamide/Zonegran [®]	Kidney stones/effect on renal function Potentially fatal reaction to sulfonamides, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, and aplastic anemia/other blood dyscrasias Oligohidrosis and hyperthermia in pediatrics Depression and psychosis Psychomotor slowing, difficulty with concentration, and speech or language problems (particularly word-finding) Creatine phosphokinase elevation and pancreatitis

BOLD indicates boxed warnings as well as adverse events that require frequent/careful monitoring or discontinuation of drug. ^aSee appropriate prescribing information for complete information on warnings and precautions for each drug. ^{17,22,23,27,31,34,35,39,40,42,52} DRESS = drug reaction with eosinophilia and systemic symptoms.

Ataxia: no difference
Headache: ↑LCM
Dizziness: ↑PGB

Fatigue: ↑TPM, ↓LTG
Nausea: ↑OXC, ↓GBP, ↓LEV
Somnolence: ↑OXC, ↓TGB

withdrawals due to AEs with LEV; no differences among the other AEDs were detected.⁴⁷

Drug–Drug Interactions and Comorbidities

In addition to AE incidence, patient withdrawal due to AEs for a particular AED can be a good indicator of tolerability. Withdrawals due to AEs were greater than placebo for all AEDs.⁴⁷ Comparison of each AED to the pooled effect of the others revealed significantly fewer

important factors to consider when making treatment decisions for the patient with focal epilepsy are the risk for drug–drug interactions and the presence of comorbid conditions. AEDs are among the most complex class of drugs in terms of pharmacokinetic properties and are

Table 4: Known Drug Interactions^a With Newer Antiepileptic Drugs

Drug/Brand Name	Enzyme Inducer	Drugs that Change Antiepileptic Drug Plasma Levels	Drugs that Are/May Be Affected by Antiepileptic Drugs
Eslicarbazepine/Aptiom [®]	Yes ^b	CBZ, PB, PHT reduce ESL concentration	CBZ Ethinylestradiol/levonorgestrel PHT Statins S-warfarin
Gabapentin/Neurontin [®]	No	Cimetidine decreases mean apparent oral clearance of GBP by 14 % Hydrocodone increases GBP AUC by 14 % Maalox reduces the bioavailability of GBP by 20 % Morphine increases mean GBP AUC by 44 % Naproxen increases GBP absorption by 12–15 %	Hydrocodone Norethindrone
Lacosamide/Vimpat [®]	No	None	Ethinylestradiol
Lamotrigine/Lamictal [®]	No	CBZ, PB, PHT, and rifampin decrease LTG concentration by 40 % Oral contraceptives decrease LTG concentration by 50 % VPA increases LTG concentration more than twofold	Levonorgestrel VPA
Levetiracetam/Keppra [®]	No	None	None
Oxcarbazepine/Trileptal [®]	Yes ^b	CBZ decreases MHD ^c concentration by 40 % PB decreases MHD ^c concentration by 25 % PHT decreases MHD ^c concentration by 30 % Verapamil decreases MHD ^c concentration by 20 % VPA decreases MHD ^c concentration by 18 %	Cyclosporine Ethinylestradiol/levonorgestrel Felodipine PB PHT
Perampanel/Fycopma [®]	No	CBZ reduces PMP AUC by 67 % Ketoconazole increases PMP AUC by 20 % OXC reduces PMP AUC by 50 % PHT reduces PMP AUC by 50 % Rifampin and St John's wort can reduce PMP levels TPM reduces PMP AUC by 20 %	Alcohol/ CNS depressants Levonorgestrel Midazolam OXC
Pregabalin/Lyrica [®]	No	None	None
Tiagabine/Gabitril [®]	No	CBZ, PHT, and PB increase TGB clearance by 60 % VPA increases free TGB concentration by 40 % <i>in vitro</i>	VPA
Topiramate/Topamax [®]	Yes ^b	CBZ decreases TPM concentration by 40 % LTG decreases TPM concentration by 13 % PHT decreases TPM concentration by 48 % VPA decreases TPM concentration by 14 %	Alcohol/CNS depressants Amitriptyline Diltiazem Ethinylestradiol Glyburide Hydrochlorothiazide Lithium Metformin PHT VPA
Zonisamide/Zonegran [®]	No	PHT, CBZ, and PB increase metabolism/clearance and decrease the half-life of ZNS	None

^aData reported in prescribing information. ^{17,22,23,27,31,34,35,39,40,42,52} ^bInduces oral contraceptives. ^cData reported for oxcarbazepine (OXC) monohydroxy derivative (MHD), active metabolite. AUC = area under the plasma concentration-time curve; CBZ = carbamazepine; ESL = eslicarbazepine; GBP = gabapentin; LEV = levetiracetam; LTG = lamotrigine; PB = phenobarbital; PGB = pregabalin; PHT = phenytoin; PMP = perampanel; TGB = tiagabine; TPM = topiramate; VPA = valproate; ZNS = zonisamide.

some of the leading medications responsible for drug–drug interactions.⁵⁴ Risk for drug interactions are especially high in the elderly, as most elderly epilepsy patients take an average of seven prescription medications.⁵⁵

As a group, the newer AEDs are less likely to cause adverse drug interactions because most do not induce the CYP450 enzyme system, the main culprit of drug–drug interactions (see *Table 4*). Induction of hepatic CYP isozymes increases drug metabolism as well as the metabolism of endogenous compounds, including free fatty acids, steroids, vitamin D, and prostaglandins.^{54,56,57} Concerns have been raised regarding older, commonly prescribed enzyme-inducing AEDs (CBZ, PHT, and phenobarbital

[PB]) due to their effects in reducing the action of many classes of drugs, such as statins, oral contraceptives, analgesics, antiarrhythmics, and immunosuppressants.⁵⁶ Treatment with older AEDs therefore has the potential for serious consequences in patients with comorbid conditions such as psychiatric disorders, HIV/AIDS, cancer, and diabetes.

French and Gidal explored the effects of newer AEDs on drug serum concentrations of older AEDs and vice versa.⁵⁴ This study and the data reported in specific PIs showed that most newer AEDs (GBP, LTG, LEV, OXC, PGB, TGB, TPM) have no effect on the drug plasma concentrations of older AEDs (CBZ, PB, PHT, primidone, VPA), with the exception of an increase

Table 5: Indications, Formulations, and Cost of Newer Antiepileptic Drugs

Drug/Brand Name	Indication for Adjunctive Focal (Partial-Onset) Seizures	Other Indications	Maximum Approved Dose ^a	Type of Formulation (Strengths)	Cost ^b Brand	Generic	No. Daily Tablets or Capsule to Reach Maximum Dose Brand	Generic
Immediate-release Formulations								
Eslicarbazepine/ Aptiom [®]	Adult patients	NONE	1,200 mg/day	Tablets (200, 400, 600, 800 mg)	\$1,294.71	NA	2	NA
Gabapentin/ Neurontin [®]	Patients ≥3y	Postherpetic neuralgia (adults)	1,800 mg/day (600 mg tid)	Tablets (600, 800 mg) Capsules (100, 300, 400 mg) Oral solution (250 mg/5 ml)	\$483.02	\$21.52	3	3
Lacosamide/ Vimpat [®]	Tablets, oral solution (≥17y) Injection for IV use (≥17y)	Monotherapy for POS (≥17y)	400 mg/day (200 mg bid)	Tablets (50, 100, 150, 200 mg) Oral solution (10 mg/ml) Single-use vial (200 mg/20 ml)	\$652.57	NA	2	NA
Lamotrigine/ Lamictal [®]	Patients ≥2y	Adjunctive therapy for PGTC and LGS (≥2y) Conversion to monotherapy for POS (≥16y) in patients with CBZ, PB, PHT, primidone, or VPA monotherapy Bipolar I disorder (≥18y) to delay mood episodes in patients treated for acute mood episodes with ST	500 mg/day (in 2 divided doses)	Tablets (25, 100, 150, 200 mg) Chewable dispersible tablets (2, 5, 25 mg) Orally disintegrating tablets (25, 50, 100, 200 mg)	\$850.95	\$18.90	3	3
Levetiracetam/ Keppra [®]	Injection for IV use (≥16y) Tablets, oral solution (≥1 month)	Adjunctive therapy for myoclonic seizures (≥12y with JME) Adjunctive therapy PGTC (≥6y with IGE)	3,000 mg/day (1,500 mg bid)	Tablets (250, 500, 750, 1,000 mg) oral solution (100 mg/ml) Single-use vial (500 mg/5 ml)	\$1,039.53	\$51.82	4	4
Oxcarbazepine/ Trileptal [®]	Patients ≥2y	Monotherapy for partial seizures (≥4y)	1,200 mg/day (600 mg bid)	Tablets (150, 300, 600 mg) Oral suspension (60 mg/ml)	\$598.62	\$27	2	2
Pregabalin/ Lyrica [®]	Adult patients	Neuropathic pain associated with DPN Postherpetic neuralgia Fibromyalgia Neuropathic pain associated with spinal cord injury	600 mg/day (300 mg bid or 200 mg tid)	Capsules (25, 50, 75, 100, 150, 200, 225, 300 mg) Oral solution (20 mg/ml)	\$272.00 (bid) \$398.35 (tid)	NA	2 (bid) 3 (tid)	NA
Perampanel/ Fycompa [®]	Patients ≥12y	NONE	12 mg/day	Tablets (2, 4, 6, 8, 10, 12 mg)	\$617.46	NA	1	NA
Tiagabine/ Gabitril [®]	Patients ≥12y	NONE	56 mg/day (in 2–4 divided doses)	Tablets (2, 4, 12, 16 mg)	\$1,357.66	\$963.69	5	14 ^c
Topiramate/ Topamax [®]	Patients ≥2y	Adjunctive therapy for PGTC and LGS (≥2y) Initial monotherapy for POS and PGTC (≥2y) Prophylaxis for migraine headaches (adults)	400 mg/day (200 mg bid)	Tablets (25, 50, 100, 200 mg) Sprinkle capsules (15, 25 mg)	\$808.26	\$15.22	2	2
Zonisamide/ Zonegran [®]	Adult patients	NONE	400 mg/day (200 mg bid)	Capsules (25, 50, 100 mg)	\$725.75	\$28.80	4	4
Extended-release Formulations								
Lamotrigine/ Lamictal [®] XR [™]	Patients ≥13y	Adjunctive therapy for PGTC (≥13y) Conversion to monotherapy for POS patients receiving treatment with a single AED (≥13y)	250 mg/day ^d 400 mg/day ^e 600 mg/day ^f	XR tablets (25, 50, 100, 200, 250, 300 mg)	\$603.43 ^d \$885.68 ^e \$1,345.99 ^f	\$215.54 ^d \$312.62 ^e \$465.19 ^f	1 2 2	1 2 2
Levetiracetam/ Keppra XR [®]	Patients ≥12y	NONE	3,000 mg/day	XR tablets (500, 750 mg)	\$1,044.37	\$82.54	4	4
Oxcarbazepine/ Oxtellar XR [™]	Patients ≥6y	NONE	2,400 mg/day	XR tablets (150, 300, 600 mg)	\$1,070.84	NA	4	NA
Topiramate/ Qudexy [™] XR	Patients ≥2y	Monotherapy for POS or PGTC (≥10y) Adjunctive therapy for PGTC or LGS (≥2y)	400 mg/day	XR capsules, intact or sprinkle (25, 50, 100, 150, 200 mg)	NA	NA	2	NA
Topiramate/ Trokendi XR [™]	Patients ≥6y	Monotherapy for POS and PGTC (≥10y) Adjunctive therapy for PGTC or LGS (≥2y)	400 mg/day	XR capsules (25, 50, 100, 200 mg)	\$1206.96	NA	2	NA

Unless otherwise noted, data reported in the prescribing information.^{17,22,23,27,31,34,35,39,40,42,52,74–78} ^aAdjunctive therapy for focal (partial-onset) seizures. ^bUS dollars; lowest cost for fewest tablets or capsule needed to reach maximum approved daily dose per 30 days. Data from www.GoodRx.com⁸⁰ using Chicago-area zipcode, 60601. Accessed on June 18, 2014. ^cGeneric only available in 2 or 4 mg tablets. ^dFor patients taking VPA. ^eFor patients NOT taking CBZ, PHT, PB, primidone, or VPA. ^fFor patients taking CBZ, PHT, PB, primidone, and NOT VPA. DPN = diabetic peripheral neuropathy; IGE = idiopathic generalized epilepsy; JME = juvenile myoclonic epilepsy; LGS = Lennox-Gastaut Syndrome; PGTC = primary generalized tonic-clonic seizures; POS = partial-onset seizures; ST = standard therapy; XR = extended release; y = year.

in PHT and decrease in CBZ with ESL, increases in PB and PHT with OXC, a decrease in VPA with LTG, decrease in VPA with TGB, and a possible increase in PHT and decrease in VPA with TPM.^{17,39,40,54} Conversely, drug plasma levels of many of the newer AEDs were decreased by the addition of older AEDs. None of the older AEDs had an effect on GBP, LEV, or PGB.⁵⁴

Overall, VPA had the least effect on newer AED drug plasma concentrations⁵⁴; however, when combined with LTG, dose adjustments may be required since VPA increases LTG plasma concentrations by decreasing LTG clearance (see Lamictal® PI for specific dosing recommendations of LTG in combination with various AEDs²⁷). The effect of drugs that are known to change plasma levels of the newer AEDs, and a list of drugs that are affected by the newer AEDs as reported in the PIs, are provided in *Table 4*.

Since newer AEDs are equivalent or nearly equivalent in efficacy⁵⁸ without the risks associated with the older enzyme-inducing AEDs, prudence dictates that newer AEDs be used preferentially, reserving enzyme-inducing AEDs as a last resort.

Pregnancy

The choice of AED for women of child-bearing age was once thought to be crucial given the known effects of VPA on fetal cognition⁵⁹ and the increased risk for malformations with AED use, especially if the fetus is exposed during organogenesis. While the overall risk for malformations with AEDs are double that of untreated pregnancies and tripled when AEDs are combined (particularly when VPA is one of them),⁶⁰ recent results from AED pregnancy registries reveal that most newer AEDs can be taken with relatively low risk to the developing fetus. In a recent comparative safety analysis of pregnant women enrolled in the North American AED Pregnancy Registry between 1997 and 2011, VPA led to a higher risk for neural tube defects, cardiac defects, hypospadias, and oral clefts, and TPM was associated with cleft lip (1.4 % of infants).⁶¹ The risk for major malformations was low for ZNS (0 %), LEV (2.4 %), and LTG (2.0 %); moderate with TPM (4.2 %); and highest with VPA (9.3 %).⁶¹ All of the newer AEDs are Pregnancy Category Class C drugs with the exception of TPM, which is a Class D drug and should be used during pregnancy only when there is a clear benefit that outweighs the potential harm to the fetus.⁴⁰

Effectiveness—The Balance Between Efficacy and Tolerability

Retention rates (proportion of patients remaining on treatment) can indicate the long-term tolerability and effectiveness of a particular drug. Long-term retention rates of the newer AEDs have been reported in numerous publications. Overall, 1-year retention rates were greatest in patients treated with LTG (79 %⁶² and 40 %–60 %⁶³), LEV (60 %–75 %),^{62,63} and TPM (40 %–60 %).⁶³ The greatest 2-year retention rates found were in patients treated with OXC (85 %)⁶⁴ and LTG (74 %).⁶⁵ Three-year retention was highest with LTG (74 %) followed by TPM (64 %), GBP (42 %), and TGB (38 %).⁶⁶

Drug Administration—Titration, Dosing, and Drug Formulations

One of the most important reasons for low drug effectiveness is patient non-adherence to their treatment regimen.⁶⁷ Patients that are not fully adherent to their AED treatment regimen have increased seizures and higher rates of morbidity and mortality.^{68–70} Poor adherence depends on several factors, including length of titration, dosing frequency,

and drug formulation (tablet, capsule, liquid). There is little difference among AEDs in the time to reach steady-state/maintenance dose (~4 weeks) with the exception of LTG and TPM, both requiring up to 8 weeks titration depending on dose-escalation strategy. In general, increased dosing frequency means reduced treatment adherence. In a systematic review,⁷¹ patient adherence was significantly greater with once-daily drug dosing versus three- and four-times daily dosing; a significant difference in adherence also was found in favor of twice-daily dosing versus four-times daily dosing, while no difference was detected between once- and twice-daily dosing.

Most patients prefer to take fewer daily doses of any medication. Extended-release (XR) or controlled-release (CR) drug formulations can simplify treatment and improve adherence by reducing dosing frequency,⁷² though the overall number of daily tablets or capsules may not differ greatly from immediate-release (IR) AEDs that need to be dosed more frequently (see *Table 5*). XR AEDs can alleviate breakthrough seizures and AEs caused by fluctuating plasma concentrations and peak-dose toxicity⁷³ and may be preferable over IR formulations in patients who take drugs for other conditions. Newer AEDs that are available as XR formulations include LEV, LTG, OXC, and TPM.^{74–78}

Intravenous (IV) formulations of AEDs are important during seizure emergencies—such as acute repetitive seizures, status epilepticus, and prolonged seizures. Both LCM and LEV are available as an IV formulation, though neither is technically approved for use in seizure emergencies. AEDs that are available as a liquid/syrup/oral solution (GBP, LEV, LCM, OXC, PGB), a chewable or orally disintegrating tablet (LTG), or a capsule that can be sprinkled onto food (TPM, Qudexy™ XR) are useful options for patients with swallowing difficulties.

Food and Drug Administration Indications, Off-Label Use, Generics, and Cost

Several of the newer AEDs are approved for indications other than the typical ‘adjunctive therapy for focal seizures,’ including TPM, GBP, OXC, LTG, and LEV. These ‘multi-use’ AEDs could be advantageous (and cost-effective) for patients with mixed seizure types and for those with comorbid conditions, such as bipolar disorder (LTG), postherpetic neuralgia (GBP and PGB), neuropathic pain or fibromyalgia (PGB), and migraine (TPM; see *Table 5*).

AEDs are prescribed for off-label use more than any other drug class (74 % versus 60 % for antipsychotics and 41 % for antibiotics).⁷⁹ Off-label prescribing is legal and is acknowledged by the FDA as an integral part of the practice of medicine. Of course, as also outlined by the FDA, off-label prescribing should be based ‘on scientific rationale and on sound medical evidence ... maintain[ing] records of the product’s use and effects.’ AEDs can be used off-label within epilepsy and outside of epilepsy. Examples of off-label use outside of epilepsy include CBZ and OXC (bipolar disorder), GBP (pain associated with many disorders), PGB and TGB (anxiety), TPM (essential tremor), ZNS, and TPM (obesity). Example of off-label use within epilepsy would include monotherapy, primary generalized epilepsy, and use in children.

Use of generic AEDs, when available, can offer tremendous cost savings to patients⁸⁰ (see *Table 5*), but it is important to understand that AEDs are

unlike other drug classes in that small differences between formulations can have serious consequences, including breakthrough seizures and toxic side effects.⁸¹ Additionally, as generics only have to show bioequivalence to the branded drug, pharmacokinetic differences among generic products may also have serious consequences. Experts in the field recommend maintaining patients on a single generic manufacturer to minimize generic switching and the associated repercussions.^{82,83} The American Academy of Neurology (AAN) supports the use of the newer AEDs, but opposes generic substitution without attending physician approval. The AAN also opposes legislation requiring physicians to seek authorization prior to drug dispensing.⁸¹

The Bottom Line—What Really Differentiates and What Helps Clinicians Choose a Drug?

In the absence of large, observational studies to determine the long-term effectiveness of individual AEDs, clinicians must approach treatment decisions with a full perspective, considering and comparing the many factors that contribute to treatment success for an individual patient. The overall differences in efficacy among the newer AEDs—and between newer and older AEDs—do not clearly separate one drug from another. This is true for other drug classes (such as anxiolytics, antidepressants, and antipsychotics) and also largely for neurostimulation (vagal nerve stimulation, deep brain stimulation, and responsive neurostimulation). Based on currently available data and systematic analyses, other factors that do not clearly distinguish one new AED over another are pregnancy category, cost, and FDA-approved indications. Factors that may be helpful in choosing a specific AED for a particular patient include the type of dosing and formulation, as well as the titration schedule. A factor that clearly differentiates one AED from another is the presence of certain comorbid conditions. Additional differentiating factors include the potential for drug–drug interactions, safety, and tolerability with the newer AEDs being more desirable than the older, enzyme-inducing AEDs. Therefore, clinicians should first consider one of the newer AEDs (IR or XR) when making adjunctive treatment choices for patients with focal epilepsy.

Making Treatment Choices—Illustrative Cases from Our Practice

In order to provide real-life examples of the clinical challenges noted above, particularly for specialized populations, below are case reports from our practices that detail our thought processes in determining diagnosis and best course of treatment for these individual patients.

Case 1. Episodes in Pediatric Patient

Presentation

A previously healthy 6-year-old boy fell asleep at his desk while at school. His teacher woke him up, but he was disoriented. He felt numbness and tingling in the left side of his face, realized he had dropped a pen, went to pick it up and fell out of his chair. While on the ground, the teacher described him to be rigid, in a fetal position with clenched hands and teeth. His eyes were rolled up, and he was drooling. This lasted approximately 3 minutes, and he returned to baseline within 30 minutes. He was seen at a local Emergency Department where a head computed tomography (CT), a comprehensive metabolic panel and urine toxicology screen were all normal. He was discharged without medications, with a diagnosis of a new onset seizure.

Approximately 5 weeks later, he had a second event at home. While playing with his brother, his left arm went numb, and within seconds, his left arm, left hand, and left leg were twitching. The episode lasted 1 minute, during which he remained conscious but was very tired following the event.

The perinatal, developmental, medical, and family histories were unremarkable. Upon neurologic exam, mental status, cranial nerves, motor and sensory exam, deep tendon reflexes, coordination, and gait were all normal. A routine electroencephalogram (EEG) showed right centroparietal spike and slow waves with no tangential dipole and no activation with drowsiness or sleep. Brain magnetic resonance imaging (MRI) was normal.

Diagnosis and Treatment

This child was diagnosed with epilepsy of unknown etiology, characterized by focal seizures. Although some of the features suggest a benign syndrome such as Benign Childhood Epilepsy with CentroTemporal Spikes, the lack of activation of epileptiform discharges during drowsiness and sleep make this diagnosis less likely.

AED therapy was recommended, and after reviewing a few options, including potential side effects and availability of different formulations, OXC was selected, with the drug titrated over 3 weeks to 30 mg/kg day, divided into two daily doses.

The patient continued to have typical seizures and OXC was increased to 45 mg/kg/day. Seizures continued to occur and a switch to LEV monotherapy was attempted without success. As the dose of OXC was reduced, seizures became more frequent. Eventually, OXC and LEV combination therapy improved seizure frequency by 50 %.

Discussion

The availability of a child-friendly formulation is an important consideration in the treatment of pediatric epilepsy, as many children are not able to swallow even moderately sized tablets. The AEDs selected in this case are available as an oral suspension (OXC), and as an oral solution (LEV). Other formulations suitable for most young children are chewable tablets, orally disintegrating tablets and sprinkle capsules. If possible, a child-friendly, XR formulation should be considered, in order to decrease the risk for dose-related side effects, especially the ones affecting the central nervous system (sedation, dizziness, uncoordination, etc.) and the gastrointestinal system (stomach discomfort, nausea, vomiting, etc.) The selection of a formulation that is easy to take (and give by caregivers) with the fewest daily doses possible, will likely increase adherence to the prescribed treatment. As it was recently reported, early adherence to treatment could be an important factor in improving seizure outcomes.⁸⁴ When possible, monotherapy should be attempted. Yet, if the use of polytherapy is required to improve seizure control, the fewest number of combination drugs should be sought, as this will likely result in a lower risk for side effects.⁸⁵

Case 2. Sleep Terror, Diagnosis and Treatment in the Elderly

Presentation

While traveling through Peru, a male patient (61 years) woke up completely disoriented, which was initially attributed to sunstroke. While driving some weeks later, his arms then body suddenly started trembling, leaving him frightened and disoriented for several minutes. Similar events occurred

over the next 3 months, several times per month. Consequently, he had sleep difficulties, experiencing sleep terrors and memory problems, which occurred up to three times per night.

The patient did not suffer from other diseases except arterial hypertension, and no family history of neurologic diseases. Upon neurologic examination, cerebral nerves, movement, sensory function, coordination, and reflexes were normal. However, the patient complained of increasing memory impairments and several episodes of amnesia occurring within the last year. He also provided audio tape recordings demonstrating night-time screaming lasting about 20 seconds.

Differential workup concerning non-epileptic sleep terror, psychogenic pseudo seizures, and epileptic seizures was performed. A long-term video EEG polygraphic recording, including electrocardiogram (ECG) and sleep polysomnography, was collected. During video-EEG-monitoring, interictal theta waves were recognized temporal right. During an attack, open eyes, distorted face, gestural hyperkinetic movements of all extremities, oral automatisms (smacking with lips), tachycardia, and goose bumps occurred. The EEG showed nonrapid eye movement (NREM 2) sleep and flattening as well as muscle artifacts. The attack duration was 18 seconds followed by a fast reorientation.

MRI showed normal findings in the gray and white matter. No marked decrease or increase of metabolism was noted via fludeoxyglucose-positron emission tomography (FDG-PET). An ictal single-photon emission computed tomography (SPECT) was performed and showed focal hyperperfusion in the right amygdala region. The magnetic resonance spectroscopy (MRS) investigation indicated a decrease of N-acetyl aspartate (NAA) in the amygdala region right. The analysis of the cerebral spinal fluid was normal.

Diagnosis and Treatment

Considering all investigation results, mesial temporal lobe epilepsy of unknown origin was diagnosed.

Treatment was started with LEV. After slow titration up to 1,000 mg LEV, seizure frequency was reduced by 70 %. Due to skin allergy fears, LTG was not used, but a low dose of TPM up to 100 mg/d added; LEV in combination was reduced to 500 to 1,000 mg/d. Under this combination therapy the patient reported further improvement.

Discussion

When selecting AEDs for elderly patients, drugs with missing or low interaction potential should be considered because most epilepsy patients are treated with other drugs.⁸⁶ Comorbidities with cognitive, emotional, or sleep disturbances also influence AED selection. In this respect, LEV and LTG are well tolerated in terms of cognitive function. If irritation occurs, the dosage of LEV must be reduced. To avoid cognitive impairment, a low dose of TPM (50 to 100 mg) can be helpful. With adherence problems, once-daily dosage of AEDs may be easier controlled by nurses. In elderly patients, once-daily evening administration of VPA or once-daily morning administration of LTG (in order to avoid sleep difficulties) was used.

Due to slow titration rate and problems falling asleep, LTG was not used as first monotherapy. CBZ and OXC were avoided with regard to enzyme induction and risk for hyponatremia in the elderly.

Case 3. Distinction Between Focal and Idiopathic Generalized Epilepsy

Presentation

A 36-year-old right-handed woman developed her first seizure 1 month before presentation to the epilepsy clinic. She felt odd, then lost consciousness, turned her head to the left, became stiff, and shook all over. She was taken to the emergency room where she had another episode. She turned her head to the left as if following something, stiffened, and had generalized jerking activity. Five days later, she had two more attacks, one of which was witnessed by her mother who noted versive head turning to the right before generalized jerking activity. She was already on PGB for fibromyalgia and she had increased her PGB dose just before the first seizure episode. Following her third seizure she was started on LEV, 750 mg twice a day, and PGB was removed. There was no recurrence of seizures initially. EEG was normal in waking, drowsiness, and sleep, and MRI was normal. She was seizure free for 21 months, then seizures recurred, initially after missing 2 days of LEV, but then while taking it regularly. She had approximately one convulsive seizure every 4 to 6 months. She also developed smaller seizures, starting approximately 3 years after her first major seizure. These were precipitated by stress. She called them 'partial seizures' and described them as going into a dream state during which she could hear people talking but could not tell what they were saying. She estimated two to three occurrences per month. These seizures continued despite increasing the dose of LEV to 2,500 mg per day. Video-EEG in the Epilepsy Monitoring Unit recorded two generalized tonic-clonic seizures that started on EEG with generalized 4–5 Hz spike-and-wave discharges (see *Figure 1*). She also had a cluster of generalized absence seizures associated with generalized 3–4 Hz spike-and-wave discharges (see *Figure 2*). LTG was then added, titrated to 100 mg bid, and LEV was reduced to 1,000 mg bid due to some jitteriness. She had no recurrence of generalized tonic-clonic seizures; however, 6 months later she reported small episodes of losing her conversation for a few seconds. We increased LTG to 300 then 400 mg per day. She has remained seizure free for at least 2 years.

Diagnosis and Treatment

The patient was diagnosed with idiopathic generalized epilepsy (IGE) with generalized absence and generalized tonic-clonic seizures. Versive head turning may have suggested focal onset, but is not unusual in primary generalized tonic-clonic seizures.⁸⁷ What the patient called partial seizures probably represented generalized absence seizures. IGE usually starts before age 20 but may occasionally start later, up to 5.7 % after age 30 in one study.⁸⁸ The diagnosis of generalized epilepsy helped in choosing a medication appropriate for generalized epilepsy, and avoiding medications that are specific for focal epilepsy.⁸⁹

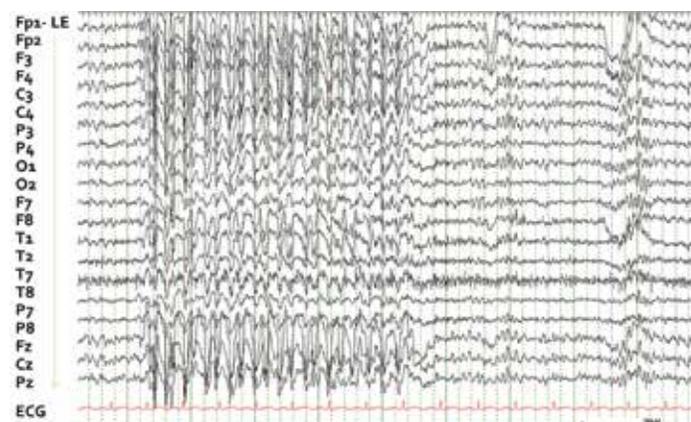
Discussion

The distinction between focal epilepsy and IGE is important for the appropriate choice of AED therapy. In particular, some AEDs have the potential to precipitate or exacerbate some generalized seizure types such as myoclonic or absence seizures. This has been reported for CBZ, OXC, GBP, PGB, TGB, and VGB, all of which should be avoided in the treatment of IGE. The clinical distinction of focal and generalized seizures can be straightforward in some instances and challenging in others, requiring recording of seizures on EEG and video.

Figure 1: Generalized Electroencephalogram Onset for the First Generalized Tonic-Clonic Seizure



Figure 2: Generalized 3 Hz Spike-and-wave Discharge Associated with a Generalized Absence Seizure



Case 4. Limbic Simple Partial Seizures with Cardiovascular Masking

Presentation

A 39-year old man presented with a 16-year history of stereotypical episodes. He reported sudden onset of shortness of breath, with difficulty speaking, followed by bilateral eye ‘fluttering’ movements, with no change in consciousness during events. Duration was typically 10–15 seconds. At onset, symptoms occurred once or twice a year, but subsequently increased in frequency to daily, sometimes occurring five times per day, often awakening him from sleep.

Ten years after onset of symptoms, he underwent extensive cardiac workup including 24-hour Holter monitor, which resulted in pacemaker placement, which had no effect on his symptoms, and was subsequently

deactivated 1 year after placement. Before presentation at age 39, he was not treated with antiepileptic medications.

There was no history of febrile seizures or significant head trauma. The patient was the product of a normal pregnancy and delivery with normal developmental milestones.

Diagnosis and Treatment

Video EEG monitoring showed approximately 10 seizures per day, with associated signs of inattentiveness documented by inability to consistently follow simple commands, which often progressed to bilateral eyelid fluttering and mouthing movements. After the events, he was immediately conversant, and able to accurately recall his symptoms. With all events, there was a stereotypical associated bradycardia to 30–40 beats per minute, which began approximately 5 to 6 seconds after symptom onset, lasting 5 seconds before resolving. There were no inter-ictal epileptiform discharges. There were associated ictal EEG changes, with some events showing diffuse, 7–8 Hz activity at the end of the event. Head CT was normal. MRI was contraindicated because of his pacemaker.

The patient started CBZ, titrating to a dose of 600 mg twice daily, with complete resolution of symptoms. He has remained seizure free for years since initiation of CBZ.

Discussion

This case represents an atypical presentation of simple partial epileptic seizures of limbic origin. Clinical historical factors favoring the diagnosis of epilepsy include the similarity and duration of symptoms during repetitive events. While ictal EEG changes helped in confirming the epileptic etiology of symptoms, they did not localize the origin of seizures. Ictal signs and symptoms suggest origin in the limbic system, with associated difficulty breathing, mouthing automatisms, and bradycardia. The anterior cingulate gyrus, which regulates many autonomic motor functions, represents a possible region of seizure onset. Localization to the cingulate gyrus is also supported by the associated bilateral peri-orbital facial movements, because the M3 facial movement center projects bilaterally to the upper quadrant of the face, and is located in the anterior cingulate region.⁹⁰ While typical semiology for anterior cingulate-onset seizures includes hypermotor activity, a subset of subjects with atypical anterior cingulate includes only simple motor seizures. Scalp EEG changes often are non-localizing, and ictal patterns can be widespread.⁹¹

Importantly, the case highlights the involvement of the cardiovascular system in seizures. The patient’s diagnosis was delayed for many years because of the initial diagnostic focus on cardiovascular symptoms. Investigation of other associated symptoms eventually led to testing with video EEG monitoring, and confirmation of epileptic seizures. Given the lack of interictal EEG abnormalities, capturing the symptoms during video EEG monitoring was important for diagnosis. While diagnosis was delayed, his response to treatment was prompt. Like most patients with epileptic seizures, his seizures came under good control with antiepileptic medication treatment. ■

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