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EPILEPSY (E WATERHOUSE, SECTION EDITOR)

Treating Epilepsy in the Setting of Medical Comorbidities

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Opinion statement

Treatment of epilepsy in patients with medical comorbidities can be challenging. Comorbidities can affect medical management and quality of life. In this review, we discuss treatment options in patients with epilepsy and medical comorbidities. In our opinion, the best way to manage patients with medical comorbidities and epilepsy is to accurately recognize and diagnose medical comorbidities, and to have adequate knowledge and familiarity with antiepileptic drug (AED) metabolism, dosing, side effects, and drug interactions. We believe the trend should move toward using the newer generation of AEDs given their generally reduced rate of adverse effects and interactions. The primary goal of therapy is seizure freedom without side effects.

Introduction

The following review discusses current recommendations for treating epilepsy in patients with medical comorbidities such as obesity, diabetes, obstructive sleep apnea (OSA), polycystic ovarian syndrome (PCOS), coronary artery disease (CAD), hyperlipidemia, nephrolithiasis, liver and kidney

disease, migraine, and depression. Although the primary decision regarding antiepileptic drug (AED) choice should be based on seizure type, secondary AED recommendations have been suggested in the setting of various medical comorbidities (See Table 1).

Treatment considerations

Obesity

- Epilepsy patients struggle with obesity because of less physical activity, adverse effects of AEDs, and poor emotional well-being [1].
- Topiramate combined with phentermine was approved in 2012 as an adjunct to a reduced-calorie diet and exercise for chronic weight management in obese or overweight adults with one weight-related comorbidity, such as hypertension, type 2 diabetes mellitus, or dyslipidemia

Table 1. Second line AED considerations in patients with medical comorbidities

Medical comorbidity	AEDs: consider using	AEDs: consider avoiding	Other non-AED treatment options
Obesity	Topiramate, zonisamide (generalized and focal seizures) Ethosuximide (absence seizures)	Valproic acid, gabapentin, pregabalin	Aerobic exercise
PCOS	Lamotrigine, levetiracetam	Valproic acid, gabapentin, pregabalin, tiagabine	
OSA	Topiramate, zonisamide (may promote weight loss)	Benzodiazepines, ezogabine	Continuous positive airway pressure
Diabetes	Topiramate, zonisamide (may promote weight loss	Valproic acid	Glucophage, low-carbohydrate diet, vitamin D3
Nephrolithiasis		Topiramate, zonisamide, ketogenic diet	Hydration, oral potassium citrate
CAD		Ketogenic diet, valproic acid, tiagabine	Omega 3 fatty acid Vitamin D3
Liver disease	Levetiracetam, gabapentin, topiramate	Benzodiazepines, carbamazepine, ethosuximide, phenytoin, phenobarbital, tiagabine, felbamate	
Kidney disease		Gabapentin, topiramate, lacosamide, levetiracetam (all can be used with adjusted dosing and proper monitoring)	
Migraine	Topiramate, valproic acid, gabapentin, levetiracetam, tiagabine, zonisamide, lamotrigine (migraine aura)	Lacosamide, rufinamide, tiagabine	VNS (vagus nerve stimulator)
Depression	Lamotrigine, Oxcarbazepine, valproic acid	Perampanel, levetiracetam Carbamazepine (If on concurrent MAOI)	Cognitive behavioral therapy (CBT), ECT, VNS, Physical exercise

[2]. This combination leads to significant weight loss accompanied by significant improvements in cardiovascular risk factors, including blood pressure, lipid, and inflammatory biomarker levels, as well as reductions in medication use [3•].

- Zonisamide, felbamate, and rufinamide are reported to cause some weight loss.
- Lamotrigine, oxcarbazepine, and levetiracetam are considered weight neutral.
- Valproic acid, gabapentin, pregabalin, and vigabatrin are associated with weight gain.

Diabetes mellitus

- Anti-GAD antibodies may form the basis of a possible link between epilepsy and type 1 diabetes mellitus [4]. In approaching patients with both diabetes and epilepsy, weight management is the most important therapeutic intervention [5].
- Topiramate stimulates insulin-mediated glucose uptake through the central nervous system [6].
- Valproic acid should be avoided given the known side effect of weight gain.

Obstructive sleep apnea

- Individuals with epilepsy more frequently have sleep apnea, especially if they have diabetes [7, 8]. OSA in turn may exacerbate epilepsy by causing sleep deprivation (a precipitating factor for seizures), hypoxemia, and decreased cerebral blood flow [9]. Treatment of OSA in patients with epilepsy improves seizure control [10, 11].
- OSA in patients with epilepsy should be treated aggressively as treatment reduces the seizure frequency, increases overall quality of life, and improves neurocognitive measures and cardiovascular risk factors [12].

Polycystic ovarian syndrome

- Epilepsy and AEDs may have complex interactions with the reproductive system such as reducing fertility and resulting in earlier menopause [13, 14].The prevalence of PCOS independent of AED treatment in women with temporal lobe epilepsy is 10 % to 25 % [15].
- Valproic acid causes PCOS and fertility problems. It is best avoided in women of childbearing potential.

Coronary artery disease and hyperlipidemia

- Seizures in the setting of drug resistant epilepsy may contribute to cardiac disease. A study demonstrated that over 40 % of patients with refractory partial epilepsy (9 out of 22) had ST segment changes at the end of a seizure [16].

- The ketogenic diet can cause worsening hyperlipidemia and coronary artery disease [17].
- There are interactions between anticonvulsants and other classes of medications that can lead to hyperlipidemia, such as valproic acid and quetiapine (presumably through inhibition of CYP3A4) [18].

Nephrolithiasis

- Nephrolithiasis is a known side effect of the ketogenic diet and carbonic anhydrase inhibitors.
- Topiramate, zonisamide, and the ketogenic diet have been shown to cause nephrolithiasis in epilepsy patients. This side effect can be possibly avoided by instruction regarding proper hydration, avoidance of hot temperatures, and the use of oral potassium citrate, which has been shown to significantly decrease the prevalence of stones [19] .

Liver disease

- Liver disease influences drug disposition by decreasing hepatic blood flow, the loss of function of hepatocytes, and decreasing protein synthesis [20]. The liver produces albumin, to which some AEDs are extensively bound. An alteration in the ability of the liver to synthesize proteins decreases the amount of bound drug and increases the drug's free fraction that can sometimes lead to drug toxicity.
- Levetiracetam is the most recommended therapeutic alternative in the acute phase of status epilepticus in patients with liver disease as it is not hepatically metabolized [21, 22].
- Chronic benzodiazepines should be avoided in liver disease as the drug can accumulate [23]. They should only be used as needed, especially in acute situations such as status epilepticus.
- Valproic acid can cause liver damage, especially in those with underlying liver disease.
- Chronic treatment options: Mild hepatic impairment does not necessitate an AED dose adjustment [24]. AEDs such as gabapentin, levetiracetam, and topiramate with low levels of protein binding and limited hepatic metabolism are preferred [24] . However, in the presence of severe liver disease, it is advisable to reduce the target dose of levetiracetam by 50 % and the target dose of topiramate by 30 %. Carbamazepine, lamotrigine, phenytoin, phenobarbital, tiagabine, and oxcarbazepine are metabolized in the liver and require caution and dose adjustment [25]. Valproic acid, felbamate and, to a lesser extent, phenytoin are associated with hepatic toxicity and should be avoided in patients with pre-existing liver disease [26].

Renal disease

- Renal impairment alters protein binding and glomerular filtration rate, resulting in increased levels of some AEDs.

- Renal insufficiency disturbs the pharmacokinetics of AEDs extensively eliminated by the kidneys, leading to increased half-life and drug accumulation [27]. Initial and target doses of renally excreted drugs like gabapentin, topiramate, lacosamide, and levetiracetam should be lowered [27]. For highly protein-bound AEDs like valproic acid and phenytoin, measurement of free drug levels should be considered.
- Hemodialysis efficiently removes water-soluble AEDs that are not highly protein-bound and have a small volume of distribution [28]. Thus, supplemental doses of phenobarbital, ethosuximide, lacosamide, and levetiracetam may be required after dialysis. AEDs that are mainly eliminated by the liver, such as benzodiazepines, carbamazepine, ethosuximide, phenytoin, tiagabine, and valproic acid are recommended in renal impairment and hemodialysis [28].
- The target dose of renally excreted drugs will be lower than in patients with normal renal function, but the goal of therapy is seizure freedom without side effects. Thus, medication doses do not need to be adjusted if patients are doing well and are without side effects.

Migraine

- Migraine and epilepsy coexist as migraines may cause epilepsy by inducing brain ischemia; epilepsy may cause migraines by activating the trigeminovascular system [29].
- When selecting drugs for migraine prophylaxis in an epilepsy patient, anticonvulsants with efficacy for both migraine and epilepsy should be considered. These include valproic acid, topiramate, gabapentin, levetiracetam, tiagabine, and zonisamide [30–33]. Lamotrigine has been reported to be effective for treatment of migraine aura but not headache [34]. Reduction in migraine frequency has been observed in some patients with comorbid epilepsy treated with the vagus nerve stimulator (VNS) [35].

Depression

- Depression negatively impacts the quality of life of patients with epilepsy and diagnosis is important; both conditions increase the risk of developing the other [36].
- In selecting an antidepressant to be used in a patient with epilepsy, consideration should be made with regard to the prominent depressive symptoms exhibited by the patient, drug-drug interactions with the antiepileptic drugs, and the potential for seizure activity. Selective serotonin reuptake inhibitors are generally considered first line of treatment because of their safety, tolerability, and side effect profile. Electroconvulsive therapy treats those with severe depression and epilepsy who are unable to take antidepressants. Cogni-

tive, behavioral, and interpersonal therapy may improve quality of life.

Treatment options in patients with epilepsy and medical comorbidities

Medications

Benzodiazepines

Clobazam, clonazepam, diazepam, lorazepam, and midazolam are commonly used benzodiazepines in the treatment of epilepsy, status epilepticus, and alcohol withdrawal seizures. Benzodiazepines are gamma-aminobutyric acid type A ($GABA_A$) receptor agonists.

Standard dosage

Clonazepam: The initial oral dose is 1.5 mg/day divided into three doses. The dose may be increased every 3 days as needed up to a maximum dose of 20 mg/day.
Clorazepate: The recommended initial dose is 7.5 mg three times daily and may be increased by 7.5 mg on a weekly basis as needed. The maximum dose is 90 mg/day.
Diazepam: The recommended oral dose ranges from 2 10 mg administered two to four times daily. The recommended parenteral dose is 2-20 mg administered IM or IV.
Lorazepam: The recommended dose is 2 6 mg/day orally in divided doses. For treatment of status epilepticus the recommended dose is 0.1 mg/kg given intravenously at a rate of 2 mg/minute. If seizures recur, another 4 mg dose may be given.

Contraindications

Acute narrow angle glaucoma, respiratory insufficiency and OSA.

Main drug interactions

Use with opioid analgesics, ketorolac, meclizine, or zolpidem can worsen central nervous system (CNS) depression. Concurrent use of amitriptyline and diazepam may result in psychomotor deficits (decreased reaction time, decreased vigilance). Concurrent use of St. John's Wort and benzodiazepines may result in reduced benzodiazepine effectiveness [37].

Common and serious side effects

Respiratory and CNS depression if used in high doses or with other depressant medications such as barbiturates.

Carbamazepine

Carbamazepine is effective for the treatment of partial and secondarily generalized tonic clonic seizures. It acts to stabilize the inactivate state of voltage-gated sodium channels. Anticonvulsant activity principally involves limitation of seizure propagation by reduction of post-tetanic potentiation of synaptic transmission. This medication demonstrates sedative, anticholinergic, antidepressant, muscle relaxant, antiarrhythmic, antidiuretic, and neuromuscular transmission-inhibitory actions.

Standard dosage

200 mg orally twice daily for the first week may increase by adding up to 200 mg/day in three or four divided doses at weekly intervals to a target dose of

	800 1200 mg/day. The generally maximum dose is 1200 1600 mg. The usual therapeutic plasma level is 4 to 12 mcg/mL [38].
Contraindications	Bone marrow depression, simultaneous use of MAO inhibitors or hypersensitivity to tricyclic compounds.
Main drug interactions	Use with nefazadone, fluoxetine, simvastatin, contraceptives, topiramate, amitriptyline, and tramadol may result in reduced efficacy and/or a risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma) [37]. Use with monoamine oxidase inhibitors may result in an increased risk of serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes) [37]. Use with hydrocholorthiazide may result in hyponatremia [37]. Macrolide antibiotics increase carbamazepine levels.
Common and serious side effects	Serious carbamazepine-associated hepatotoxicity can occur as a hypersensitivity reaction in the form of hepatitis with hepatocellular necrosis. This usually occurs within 3 4 weeks after the initiation of therapy and is independent of serum carbamazepine levels. Other side effects include toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), aplastic anemia and agranulocytosis [37]. These reactions are more common in people who carry the human leukocyte antigen (HLA) allele HLA-B*1502, seen almost exclusively in people of Asian ancestry.
Special points	Carbamazepine is extensively metabolized by the liver, and its metabolism is sensitive to decreased hepatic function but not to changes in hepatic blood flow [39]. CBC, hepatic, 25-OH vitamin D, and renal function tests should be checked periodically.

Ethosuximide

Ethosuximide is a T-type calcium channel blocker and an effective treatment for absence seizures.

Standard dosage	5 00 mg/day adjusted by 250-mg increments every 4 to 7 days to desired therapeutic effect. The usual average daily dose is 20 30 mg/kg [40].
Main drug interactions	Ethosuximide plasma concentrations may be reduced by carbamazepine, fosphenytoin, ginkgo, orlistat, phenobarbital, or phenytoin.
Common and serious side effects	Weight loss, abnormal liver, and/or renal function tests, GI upset, nausea, headache, and depression have been reported.
Special points	Because of extensive liver metabolism, significant impairment of liver function may decrease the clearance of ethosuximide.

Ezogabine

Ezogabine is a potassium channel opener that is used for the treatment of partial epilepsy.

Standard dosage	100 mg orally three times daily for 1 week increase dosage by no more than 50 mg three times daily (150 mg/day) at 1-week intervals to the usual maintenance dose of 200 to 400 mg orally three times daily [41].
Main drug interactions	Concurrent use with lamotrigine, orlistat, carbamezapine, phenytoin, and digoxin may alter drug concentrations.
Common and serious side effects	Blue skin discoloration confusion, dizziness, blurred vision, double vision, tremor, and fatigue.

Special points	Given the black box warning of vision loss, ezogabine should be used in refractory cases in which benefits of treatment outweigh the risk of vision loss. Baseline and periodic eye exams are recommended.

Felbamate

Felbamate is a broad-spectrum antiepileptic medication that is effective against both partial and generalized seizures. It modulates $GABA_A$ receptors and blocks N-Methyl-D-aspartic acid (NMDA) glutamate receptors. Felbamate is eliminated via hepatic and renal metabolism. It inhibits the cytochrome P450 (CYP) system, resulting in significant interactions with other AEDs.

Standard dosage	1200 mg/day orally in three to four divided doses may increase dosage in 600-mg increments every 2 weeks to 3600 mg/day if clinically indicated [42].
Contraindications	Blood dyscrasia or hepatic dysfunction.
Main drug interactions	Felbamate affects clopidogrel (reduced efficacy), warfarin (increased risk of bleeding), and citalopram (increased QT prolongation). Use with valproic acid or clobazam results in increased valproic acid or clobazam concentrations. Use with carbamazepine may result in decreased carbamazepine or felbamate effectiveness. Concurrent use of felbamate with phenytoin or phenobarbital may result in increased phenytoin or phenobarbital concentrations.
Common and serious side effects	nausea, SJS, weight loss, aplastic anemia, hepatic failure, and depression.
Headache	
Special points	Patients with impairment of liver and kidney function would be expected to have reduced metabolism and clearance of felbamate respectively. Hepatic function tests and CBC should be checked at baseline and periodically.

Gabapentin

Gabapentin is effective for partial seizures and secondarily generalized tonic-clonic seizures. Gabapentin interacts with cortical voltage-sensitive calcium channels and increases the synaptic concentration of GABA. It is renally excreted. The Food and Drug Administration (FDA) originally approved it for focal seizures but it is currently used more often for chronic neuropathic pain than epilepsy.

Standard dosage	300 mg orally three times a day may increase up to 1800 mg/day (divided into three doses). Dosages up to 4800 mg/day (divided into four doses) have been well-tolerated.
Main drug interactions	Morphine (increase in gabapentin concentrations) hydrocodone (decreased bioavailability of hydrocodone).
Common and serious side effects	Hypertension, blood glucose fluctuations, and weight gain [24, 25].
Special points	Gabapentin clearance decreases in proportion to the decrease in creatinine clearance in patients with renal insufficiency. It is recommended to restrict the total dose of gabapentin to 600 mg, 300 mg, and 150 mg per day when the creatinine clearance is 30 60 , 15 30, and <15 mL/min, respectively. A

loading dose of gabapentin 200–300 mg following each 4 hours of hemodialysis is recommended.

Lacosamide

Lacosamide is an effective treatment for partial onset seizures. In vitro electrophysiologic studies have shown that lacosamide selectively enhances slow inactivation of voltage-gated sodium channels, which results in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing.

Standard dosage
- 50 mg orally twice daily; increase weekly by 100 mg/day given in two divided doses up to 200 400 mg/day.
- 50 mg IV twice daily; increase weekly by 100 mg/day given in two divided doses up to 200 400 mg/day; infuse over 30 60 minutes [43].

Main drug interactions Ketorolac (reduced lacosamide effectiveness).

Common and serious side effects Cardiac arrhythmia, nausea, vomiting, headache, depression, and fatigue.

Special points In patients with liver disease, lacosamide levels may increase by 50 % 60 % and dose titration should be carried out with caution. The maximum suggested dose in mild to moderate liver impairment is 300 mg/day. Lacosamide is not recommended for use in patients with severe liver impairment. Lacosamide levels increase in patients with mild to moderate renal impairment. For patients with severe renal impairment (creatinine clearance of ≤30 mL/min) and in patients with end stage renal disease, a maximum dose of 300 mg/day is recommended.

Lamotrigine

Lamotrigine is a sodium channel blocker, among other possible mechanisms, and is an effective treatment both for focal and generalized epilepsies. It is rapidly absorbed and has an oral bioavailability of 98 %. The protein binding of lamotrigine is 55 %. It primarily undergoes hepatic metabolism.

Standard dosage 25 mg/day orally for 2 weeks, then 50 mg/day for 2 weeks may increase dosage by 50 mg/day every 1 to 2 weeks to the usual maintenance dose of 200 400 mg/day in two divided doses [44]. Dose will need to be adjusted in presence of valproic acid (reduced lamotrigine dose) and enzyme inducing drugs such as phenytoin carbamazepine, and phenobarbital (increased lamotrigine dose).

Main drug interactions With escitalopram, there is an increased risk of myoclonus. Decreased lamotrigine plasma concentrations are seen with oral contraceptives, acetaminophen, primidone, and rifampin. Lamotrigine toxicity is more likely when taken with sertraline and valproic acid.

Common and serious side effects Hypotension, SJS, hyponatremia, nausea, vomiting, loss of appetite, headache, somnolence, depression.

Special points Dose needs to be adjusted in the setting of liver disease, which should be based on therapeutic response rather than serum levels. The elimination half-life of lamotrigine is increased by approximately 50 % in patients with renal insufficiency and so the dose of lamotrigine may need to be reduced in these patients [45]. Lamotrigine levels can drop significantly during

pregnancy, and dose adjustments may be necessary to maintain therapeutic effect.

Levetiracetam

Levetiracetam is effective for partial and generalized epilepsy. It is rapidly and almost completely absorbed; 66 % of levetiracetam is excreted renally as unchanged drug.

Standard dosage 500 mg orally or IV infused over 15 minutes twice daily increase daily dosage by 1000 mg/day every 2 weeks to reach a recommended dose of 3000 mg/day [46] .

Main drug interactions Reduced levetiracetam effectiveness can be seen when taken with ginko, evening primrose, ketorolac, or orlistat.

Common and serious side effects Somnolence, hostile behavior, irritability, depression.

Special points Levetiracetam dose is adjusted in the setting of renal insufficiency as follows:
Cl_{cr} >80 mL/minute/1.73 m^2: 500 1500 mg every 12 hours
Cl_{cr} 50-80 mL/minute/1.73 m^2: 500 1000 mg every 12 hours
Cl_{cr} 30-50 mL/minute/1.73 m^2: 250 750 mg every 12 hours
Cl_{cr} <30 mL/minute/1.73 m^2: 250 500 mg every 12 hours
A supplemental dose of 250 500 mg of levetiracetam following dialysis is recommended [47].

Phenytoin

Despite significant chance of toxicity and pharmacokinetic misadventure phenytoin remains one of the most commonly used drugs for treating secondarily generalized tonic clonic seizures and status epilepticus. Phenytoin is highly (>90 %) protein-bound and is extensively metabolized by the liver.

Standard dosage Usual maintenance dose is 300 400 mg/day (4 5 mg/kg/day)[48]. Higher doses may be needed in infrequent cases where patients more rapidly metabolize the drug. In status epilepticus an IV loading dose of 20 mg/kg is given at a rate not exceeding 50 mg/min. The fosphenytoin prodrug, dosed in an equal amount of "phenytoin equivalents (PE)", can be given at a rate up to 150 mg/min. In less urgent settings phenytoin can be orally loaded.

Contraindications Do not use with delavirdine, rilpivirine, Adams-Stokes syndrome, AV block, SA block ,or sinus bradycardia.

Main drug interactions Phenytoin has more than 360 drug interactions as it is a strong CYP3A4 inducer that can result in decreased drug concentrations of CYP3A4 substrates such as atorvastatin. Phenytoin toxicity can result if combined with medications such as nortriptyline. Phenytoin can lower the level of corticosteroids.

Common and serious side effects Cardiac arrhythmia, SJS, hyperglycemia, nausea, vomiting, hepatotoxicity, ataxia, tremor, nystagmus, delusions.

Special points Phenytoin beneficially elevates HDL in some reports [37]. Use of phenytoin in liver disease can result in phenytoin toxicity [49]. CBC, 25-OH vitamin D and liver function tests should be checked periodically. Phenytoin does not obey linear kinetics and small changes in dose, absorption, protein binding

or clearance can result in large, at times clinically significant, changes in plasma concentration.

Perampanel

Perampanel is an adjunct therapy for partial onset seizures and has been commercially available in the United States since January 2014. It is the first noncompetitive α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist approved by the FDA [50].

Standard dosage 2 mg orally once daily at bedtime may increase dosage by 2 mg/day once weekly to 4 8 mg orally once daily at bedtime maximum recommended daily dose 12 mg (will need to adjust dose if used with concomitant enzyme-inducing AED) [51].

Main drug interactions Carbamazepine increases perampanel clearance.

Common and serious side effects Backache, abnormal gait, ataxia, dizziness, headache, somnolence, irritability, mood disorder, aggressive behavior, homicidal/suicidal thoughts.

Primidone

Primidone interacts with voltage-gated sodium channels and can be used for both partial and generalized seizures. Primidone is also metabolized to phenobarbital, which mediates chloride ion influx through $GABA_A$ receptors.

Standard dosage Maintenance dose is 250 mg orally three to four times a day (max dose 2 g/day).

Main drug interactions Primidone reduces the concentration of drugs metabolized by CYP3A4. Concurrent use with valproic acid, barbiturates or benzodiazepines may result in severe central nervous system depression.

Common and serious side effects Ataxia, vertigo, granulocytopenic disorder, megaloblastic anemia, and thrombocytopenia.

Special points CBC and comprehensive metabolic panel should be checked every 6 months [52].

Rufinamide

Rufinamide is FDA approved to treat Lennox-Gastaut syndrome. Randomized controlled trials have also shown effect against partial-onset seizures.

Standard dosage 400 800 mg/day orally in two divided doses increase by 400 800 mg/day every 2 days to a maximum dose of 3200 mg/day in two equally divided doses [53].

Contraindications Familial Short QT syndrome may increase risk of sudden death and ventricular arrhythmias by shortening the QT interval [53].

Main drug interactions Rufinamide used with oral contraceptives may result in reduced efficacy of the contraceptive. Concurrent use with lamotrigine and carbamazepine results in decreased plasma concentrations of lamotrigine and carbamazepine. Rufinamide used with phenytoin or phenobarbital may result in increased phenytoin or phenobarbital concentrations. When used with primidone, the combination may result in decreased rufinamide concentrations.

Common and serious side effects	Shortened QT interval, nausea/vomiting, ataxia, dizziness, headache, somnolence, blurred vision, double vision, fatigue, suicidal behavior.

Tiagabine

Tiagabine, a GABA reuptake inhibitor, is an effective add on treatment for partial seizures with or without secondary generalization. It is 96 % bound to albumin and is extensively metabolized by the hepatic CYP3A4 isoenzyme [54].

Standard dosage	4 mg orally once a day may increase dosage by 4 8 mg/day at weekly intervals to a maximum dose of 56 mg/day (given in two to four divided doses) [37].
Main drug interactions	Tiagabine's effectiveness can be reduced by concomitant use of carbamazepine, evening primrose, ginko, ketorolac, orlistat, phenobarbital, phenytoin, or primidone.
Common and serious side effects	Hypertension, SJS, nausea, vomiting, migraine, depression, dysmenorrhea, and insomnia.
Special points	Liver disease is shown to attenuate tiagabine's metabolism and it is advised to reduce the dosage to minimize neurotoxicity. Tiagabine is discouraged in patients with severely impaired liver function [55].

Topiramate

Topiramate is used mainly in focal epilepsy, primary generalized tonic-clonic seizures, Lennox Gastaut syndrome and migraine prophylaxis. It blocks voltage-gated sodium channels, inhibits kainate-type glutamate receptors, decreases L-type voltage-sensitive calcium currents, increases the opening of GABA mediated chloride channels, inhibits carbonic anhydrase, and increases potassium conductance.

Standard dosage	25 50 mg orally once daily may increase by 25 50 mg/day at 1-week intervals to the usual maintenance dose of 200 400 mg/day [56].
Contraindication	specific to Trokendi or Qudexy XR form of topiramate Recent alcohol use (within 6 hours prior to or 6 hours after use) and metabolic acidosis with concomitant metformin use [56].
Main drug interactions	Reduced oral contraceptive efficacy increased risk of nephrolithiasis (when taken with acetazolamide).
Common and serious side effects	Nephrolithiasis, metabolic acidosis, weight loss, confusion, depression, glaucoma, fatigue, change in taste, and open angle glaucoma.
Special points	Prior to dosing a baseline serum bicarbonate level is recommended especially in patients at high risk for renal impairment (older age, or comorbid diabetes mellitus, hypertension, or autoimmune disease). A reduction in the dosing rate for topiramate is recommended for patients with moderate or severe renal impairment. Topiramate has been found to improve insulin sensitivity, result in weight loss and make favorable changes in lipids and glucose metabolism [57, 58]. Incidence of kidney stones may be reduced through an increase in fluid intake and avoidance of concomitant treatment with the ketogenic diet.

Valproic acid

Valproic acid has a broad spectrum of activity against both focal and generalized epilepsies. The anticonvulsant effect of valproic acid is mediated at

multiple levels: potentiation of GABA, inhibition of NMDA receptor mediated excitation, and blockade of voltage-dependent sodium currents [16].

Standard dosage 10 15 mg/kg/day orally (give in two to three divided doses if total daily dose exceeds 250 mg), may increase dosage 5 10 mg/kg/day at 1-week intervals to achieve optimal clinical response [59].

Contraindications Hepatic disease, POLG1 mitochondrial disease, pregnant women, and urea cycle disorders [26, 60].

Main drug interactions Use with amitriptyline may result in increased risk of serotonin syndrome. Use with nortriptyline may result in increased serum nortriptyline levels. Use with warfarin may result in an increased risk of bleeding.

Common and serious side effects Pancreatitis, hepatotoxicity, teratogenic potential, weight gain, depression, insomnia, and PCOS [61].

Special points Postpubertal females are particularly at risk of valproic acid induced weight gain. In addition, this drug is also said to cause various metabolic derangements, PCOS, and alteration in reproductive and endocrine function [62, 63]. There is also evidence that valproic acid causes hyperinsulinemia by interfering with insulin metabolism in the liver, not explained just by obesity, thus increasing propensity toward metabolic syndrome [64]. Baseline and periodic monitoring of liver function tests, CBC and platelets is recommended.

Zonisamide

Zonisamide is a broad-spectrum antiepileptic drug with efficacy against partial and generalized seizures.

It has a prolonged half-life, making once-daily dosing possible. The drug is about 40 % protein-bound. It is about 70 % metabolized by the liver, with reduction by CYP3A4 accounting for about 50 % and N-acetylation accounting for 20 % of the metabolites [65].

Standard dosage 100 mg/day orally, may increase dosage by 100 mg/day every 2 weeks to the usual effective dosage range of 100 600 mg/day in one to two divided doses.

Contraindications Hypersensitivity to sulfonamides.

Main drug interactions With metformin, there is increased risk of lactic acidosis.

Common and serious side effects Somnolence, agranulocytosis, headache, depression, nephrolithiasis, altered taste, and nausea/vomiting.

Special points Zonisamide is cleared by both the renal and hepatic routes [66]. The clearance of zonisamide has been shown to decrease with decreasing creatinine clearance but no specific guidelines for dosage reductions in renal insufficiency have been reported. Weight loss was initially observed as a side effect in the trials that led to its approval for use in epilepsy 400 mg of zonisamide per day is an effective dose for weight reduction. [67, 68].

Diet and lifestyle

- A low carbohydrate diet (Atkins Diet, ketogenic diet) can improve both seizure control and glycemic control [69]. The main side effect of these diets is hyperlipidemia (increase in LDL, VLDL, total cholesterol, triglyceride levels; decrease in HDL), and they are thus contraindicated in

those with hyperlipidemia or coronary artery disease.

- Vitamin D3 is being studied for a role in preventing oncological and cardiovascular disease, infections, and diabetes. Vitamin D3 deficiency is prevalent in epilepsy patients. AEDs such as phenobarbital, phenytoin, carbamazepine, primidone, and valproic acid can cause decreased bone mineral density [70]. A single oral dose of vitamin D3 40,000–200,000 IU, followed by 2000–2600 IU daily, can help normalize vitamin D deficiency. Improvement in seizure control in patients with drug resistant epilepsy is being studied [71]. If not taken in excess, complications are rare.
- Lifestyle management for effective seizure control includes medication adherence, adequate sleep, proper nutrition and reduction in stress [72]. We also recommend moderation in alcohol and caffeine, and no stimulant "energy drinks."

Physical therapy

Specific therapy Aerobic exercise.

Usage Should be tailored to each individual (could include one hour of treadmill three times a week or strength training). Activities of high injury risk should be avoided in patients with incompletely controlled seizures.

Special points
- Physical activity may improve mood, quality of life, health, learning, memory, and could provide a neuroprotective effect [73•].
- Studies have shown that physical exercise is not a seizure-inducing factor [73•].

Complementary and alternative medicine

Specific therapy Meditation, yoga, biofeedback, relaxation.

Usage Studies have shown that Sahaja yoga, 20 minutes of meditation daily, biofeedback (in which patients become aware of a normally unconscious body function such as heart rate to gain control over it), and muscle relaxation (in which a progressive muscle relaxation technique is used to relax muscles especially at the onset of seizures) can result in a reduction of seizure frequency [74].

Special points Although not many randomized controlled trials exist, evidence exists for a beneficial effect of yoga and meditation [74], through a proposed multifaceted effect on biological and physiological function. Biofeedback and muscle relaxation have also been shown to reduce seizure frequency and can be a helpful adjunct to traditional treatment.

Surgery

Standard procedure Epilepsy surgery provides the best chance for seizure freedom in well-selected patients, but it is limited to those in whom an epileptogenic focus can be localized and safely resected. For example, temporal lobectomy is indicated for those who have drug resistant mesial temporal epilepsy with hippocampal sclerosis.

Contraindications Multiple epileptogenic foci, seizures from eloquent cortex, no identifiable epileptogenic focus [75].

Complications Hemiparesis, vision loss, language, or memory impairment, postoperative bleed or infection, depression.

Special points Despite technological advances and accumulation of evidence regarding its effectiveness epilepsy surgery is significantly underutilized, resulting in worse outcomes, increased morbidity and mortality, and increased healthcare costs in the population of patients with drug resistant epilepsy [75].

Vagus nerve stimulator (VNS)

Usage Intended for those with drug resistant epilepsy, this device therapy involves delivering intermittent electrical stimulation to the cervical portion of the left vagus nerve [76]. In the pivotal clinical trial, a 24.5 % median seizure reduction compared with baseline was observed in the treatment group [77]

Complications Hoarseness, shortness of breath, pain at stimulation site.

Special points In addition to decreasing seizure frequency, an improvement in mood and migraines have been witnessed in patients treated with VNS, even in those with little or no change in seizure frequency [35, 76].

Responsive neurostimulation

Standard procedure The responsive neurostimulator (RNS) device is implanted and secured into the skull. Two intracranial electrodes (depth or strip electrodes) are placed over the epileptogenic site and connected to the stimulator. The programmable device detects seizure activity and delivers a responsive electrical stimulation to the cortex in an attempt to disrupt the seizure activity [78•]. The pivotal trial showed a 37.9 % median seizure reduction compared with baseline in the blinded phase, and a 53 % median seizure reduction at the end of the 2-year open label phase [79].

Complications Intracranial hemorrhage, pain at the implant site, infection at the implant site and paresthesias [75].

Special points RNS has been recently approved by the FDA and is indicated for patients with drug resistant localizable partial seizures not otherwise candidates for resection surgery, originating from no more than two foci, especially in areas of eloquent cortex or in those who have failed prior surgical resections.

Conclusions

The last two decades have seen an explosion in options for the treatment of epilepsy, including the approval of a number of new medications, some of which have novel mechanisms of action compared with the older generation of drugs. Although the newer drugs are not generally more effective than the older drugs, the advantage for most lies in their safety profile—fewer drug interactions, more predictable pharmacokinetics, less hepatic metabolism effects, and less acute and chronic toxicity. Moreover, with many of the newer epilepsy medications now off patent, cost is not as great a barrier to efficacious therapy as it once was.

With these therapeutic options comes the opportunity to tailor therapy to the specific needs of the individual patient. Consideration of medical comorbidities is an important part of this decision. An accurate diagnosis of the epilepsy syndrome and seizure types, coupled with knowledge of the patient's medical history and recognition of the properties of the medications under consideration, can lead to improved outcomes. Complementary and alternative medical measures can also help. For patients who prove refractory to medical management, referral to a comprehensive epilepsy center for consideration of surgical and device therapy is indicated.

Compliance with Ethics Guidelines

Conflict of Interest
Nivedita Jerath, Dronacharya Lamichhane, Madhu Jasti, Vinusha Yarlagadda, Eduardo Zilli, Yara Nazzal, and Mark Granner declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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