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Selection of Antiepileptic Drugs in Older People

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Opinion statement

Elderly people are one of the fastest-growing populations in the United States, and the incidence of epilepsy in older people is much higher than in other population subgroups. This age group is the most vulnerable because of the increased incidence of multiple medical comorbidities, including stroke. The diagnosis of epilepsy is extremely challenging and often delayed in this age group because of an atypical presentation. Seizures are manifest through extremely vague complaints, such as episodes of altered mental status or memory lapses. Once the diagnosis is established by careful history taking and diagnostic testing, anticonvulsants are the mainstay of treatment. The choice of anticonvulsants in elderly patients requires careful evaluation of medical comorbidities, which vary on an individual basis. This subgroup also is more susceptible to adverse effects because of the physiologic changes in the body due to older age, which affect the pharmacokinetics of most anticonvulsants. The ideal drug in this age group should have linear pharmacokinetics, fewer adverse effects, minimal or no drug–drug interactions, no enzyme induction/inhibition, a long half-life, and minimal protein binding, and should be cost-effective. As such, there is no ideal drug for this patient population, although both older- and newer-generation anticonvulsants are

used for long-term treatment. Most newer anticonvulsants have the advantage of a favorable pharmacokinetic profile, minimal or no drug–drug interactions, and fewer adverse events, as well as being well tolerated. The older anticonvulsants still are widely used, because the newer anticonvulsants are much more expensive.

Introduction

The incidence of epilepsy is highest in the elderly population because of their medical comorbidities, especially cerebrovascular disease [1, 2]. In a report of their 3-year observational study, Paradowski and Zagrajek [3] described seizures in the elderly as mostly partial in nature and typically the consequence of vascular brain damage. The diagnostic criteria in these patients should include an electroencephalogram (EEG). The routine EEG may show insignificant findings, and evidence of interictal epileptiform abnormalities is less in the elderly than in younger age groups [4]. Prolonged inpatient video-EEG recording or ambulatory EEG should be included in the workup of elderly patients because it has more yield in establishing the diagnosis [5].

Treatment

- Treatment decisions in older patients require consideration of complex age-related physiologic changes, use of concomitant medications, and comorbidities. The most common underlying etiology of acute symptomatic seizures and epilepsy is stroke, with seizures occurring in 4 %-6 % of patients typically within 24 h of stroke onset. Seizures can be misdiagnosed in this population because their clinical presentation often differs from those in younger adults. In the elderly, presenting complaints can be vague with complaints of confusion, altered mental status, or memory problems as opposed to focal clonic seizures, versive seizures, and bilateral asymmetric tonic seizures in younger patients. Comorbidities in elderly patients with seizures may complicate the interpretation of diagnostic tests. Treatment decision in the elderly require considering complex age-related physiologic changes, use of concomitant medications, and comorbidities. These decisions are especially important because older individuals are more likely than younger patients to have recurrent seizures. In the elderly, pharmacokinetics of antiepileptic drugs (AEDs) are more complex because of lower protein binding, impaired hepatic metabolism, altered volume of distribution, decreased renal elimination, and decreased enzyme inducibility. Ideally, an AED would be fully absorbed with linear pharmacokinetics, with clearance unaffected by renal impairment, and would not interact with other medications. Correcting the underlying etiology is the ideal treatment of an acute seizure with clear precipitating cause. The use of AED therapy should be reserved for patients with epilepsy as opposed to acute symptomatic seizures. With efficacious newer and older

AEDs with different advantages and disadvantages, the prognosis is generally good for elderly patients with epilepsy [6].

- The rates of seizure freedom do not differ much between older and newer anticonvulsants. Newer agents are preferred because they have favorable pharmacokinetic profiles and fewer side effects. In the first of three randomized, double-blind trials in older people newly diagnosed with epilepsy published by Brodie and colleagues, lamotrigine was found to be much better tolerated and as effective as carbamazepine [7]. In Saetre et al who used a controlled-release instead of a standard formulation of carbamazepine with an identical study design with the same treatment schedule found that the difference between lamotrigine and carbamazepine was almost completely negated. The median lamotrigine levels in these two studies were similar (2.2 vs 2.3 mg/L), but the median carbamazepine dose was different (6.9 mg/L standard CBZ vs 5.1 mg/L controlled-release CBZ). They also found that gabapentin can also be used as an alternative [8]. Rowan et al conducted an 18-center, randomized, double-blind, double dummy, parallel study to determine the tolerability and efficacy of lamotrigine and gabapentin compared to carbamazepine in older patients with epilepsy. The study took place in 1998 at 18 Veterans Affairs Medical Centers and included patients 60 years or older (mean age=72 years), had multiple medical conditions, and took seven comedications on average. A total of 593 elderly subjects with newly diagnosed seizures were randomly assigned to either GBP 1500 mg/day, LTG 150 mg/day, or CBZ 600 mg/day and were treated for 12 months. The mean plasma levels remained stable throughout the trial and were GBP 8.67±4.83 μg/mL, LTG 2.87±1.60 μg/mL, and CBZ 6.79±2.92 μg/mL. The most common cause of early terminations were subjects on LTG 44.2 %, GBP 51 %, or CBZ 64.5 % (P=0.0002). LTG was significant paid to CBZ (P<0.0001), and Gabapentin (GBP) vs CBZ (P=0.008). CBZ was the most common AED discontinued for adverse events (CBZ 31 %, GBP 21.6 %, LTG 12.1 %). Two-paired comparisons were significant: LTG vs CBZ (P<0.0001) and LTG vs GBP (P=0.015). At 12 months, there were no significant differences in the seizure free rate. The authors concluded that in terms of addressing the main limiting factor in patient retention, adverse drug reaction, patients receiving lamotrigine or gabapentin did better and had similar seizure control. Initial therapy for older patients with newly diagnosed seizures should consider these two medications first [9].
- The goal of treatment of epilepsy in older patients should be complete control of seizures with enhanced quality of life using a modest dose of a single AED and a multidisciplinary approach to minimize the effects of epilepsy [10].
- Anticonvulsants of choice in elderly in special circumstances.

Osteoporosis and AED use in the elderly

The literature review conducted by Meier and Kraenzlin showed association between epilepsy and fracture risk [11]. Even though people with epilepsy have a 2 6 times great risk of fractures than the general population, only 35 % of fractures are directly attributable to seizure activity [12]. Cumulative duration of AED exposure increases the risk of fracture significantly. Patients using nonenzyme-inducing AEDs have a more pronounced risk than patients using EIAEDs [13, 14]. One study by Souverein et al showed that the increased fracture risk with AED use was modest—the odds ratio was 1.18 for carbamazepine, 1.79 for phenobarbital, 1.14 for oxcarbazepine, 1.15 for valproate, and 1.27 for clonazepam [13]. Vestergaard et al found that the fracture risk was not significantly increased with lamotrigine, primidone, tiagabine, ethosuximide, topiramate, and vigabatrin [15]. The increased fracture risk is complicated by the epilepsy itself and the bone depleting effect of AEDs contributing independently. Low bone density in adults has been found at multiple sites, including femoral neck, lumbar spine, and calcaneus. All age groups and both genders are affected by AED-associated bone loss. Coppola et al's study of 96 children and adolescents, showed 58 % (N=56) were found to have reduced bone density with clinical osteopenia in 75 % and osteoporosis in 25 % [16]. Ensrud et al found in their longitudinal study that in elderly women older than 64 years with epilepsy that AEDs lead to accelerated bone loss at the proximal femur and with continued use increase the risk of hip fracture by 29 % over 5 years [17]. Vestergaard et al found that the observed increase in relative fracture rate (RR 2.18; 95 % CI 1.94 2.45) was higher than expected based on the BMD values (RR 1.2 1.3). Thus, something was contributing to the higher fracture risk in addition to AED use [15].

Cytochrome P450 EIAEDs are more commonly associated with a negative impact on bone. It has been proposed that CYP450 inducing AEDs, including phenobarbital, phenytoin, carbamazepine, and oxcarbazepine, upregulate the enzymes responsible for the metabolism of vitamin D, resulting in conversion of 25 (OH) vitamin D into inactive metabolites. This decrease in 1,25 (OH)2 vitamin D leads to reduced calcium absorption, with consecutive secondary hyperparathyroidism, increased bone resorption, and accelerated bone loss. Most classic AEDs reduce BMD, including benzodiazepines, carbamazepine, phenytoin, phenobarbital, and valproic acid, in addition to the newer AEDs gabapentin and oxcarbazepine. Several studies have shown that reduced levels of 25(OH) D are associated with enzyme-inducing AEDs use [17–22]. In a longitudinal study by Pack and associates, women on a year of AED monotherapy with phenytoin, carbamazepine, lamotrigine, or valproic acid were found to have significant bone loss at the femoral neck in phenytoin treated patients, but patients treated with carbamazepine or lamotrigine had no such changes [19]. All patients are recommended to receive prophylactic administration of calcium and vitamin D. BMD measurement is recommended for patients with long-term AED exposure, especially for patients treated with EIAEDs and those with a high risk of fractures. Patients with a high fracture risk can be potential candidates for bisphosphonate therapy [11].

Dose adjustment in hepatic dysfunction in the elderly

Dosage reduction of benzodiazepines, lamotrigine, clobazam, tiagabine, or rufinamide is needed in elderly with hepatic dysfunction. Risk of intoxication is high with benzodiazepines, clobazam and considerable in phenytoin, valproic acid, phenobarbital and tiagabine because of decreased protein binding. The drug levels should be checked periodically in addition to dose reduction for prevent risk of intoxication [23].

Dose adjustment in renal dysfunction in the elderly

Elderly with end stage renal disease on dialysis requires dose adjustments of their anticonvulsants. Significant removal by dialysis is seen in patients on phenobarbital, gabapentin, topiramate, levetiracetam (50 %), and lacosamide. Lamotrigine, felbamate, and rufinamide are moderately removed by dialysis.

Slight reduction is needed with phenobarbital, primidone, and rufinamide whereas moderate

Reduction of dosage should be done in patients on felbamate (by one-half), topiramate, gabapentin, oxcarbazepine, zonisamide, levetiracetam, clobazam, and lacosamide (if ESRD). Risk of intoxication is high with phenobarbital and primidone and considerable with topiramate and oxcarbazepine [23].

Anticonvulsants of choice in the management of elderly with psychiatric comorbidities

Older anticonvulsants, carbamazepine and valproate, have been found to be effective in acute mania and also in bipolar disorder. The antiglutamergic mechanism of action is associated with anxiolytic and antidepressant properties of these drugs [24].

Among the newer anticonvulsants, lamotrigine has shown improvement in mood in several open clinical trials [25–27]. Lamotrigine has also been found efficacious in depression and hypomania [28]. Trileptal also has mood-stabilizing properties but limited use in elderly because of the risk of hyponatremia [24].

Drug induced seizures in elderly—role of anticonvulsants

Franson et al conducted a literature review of medications that are most commonly associated with inducing seizures in the elderly population. Seizures can be exacerbated by inadequate maintenance of anticonvulsant levels because of toxicity, sudden withdrawal, or by indirect action of other hormones or medications. This is partially due to the elderly being more likely to be confused or misuse medications. Also, drug drug interactions such as interactions of multiple antiepileptics may decrease efficacy because of enzyme inhibition, autoinduction, or autoinhibition. Reduction of hepatic metabolism by drugs that inhibit the hepatic microsomal enzyme system, such as cimetidine, ciprofloxacin, erythromycin, and high dose allopurinol, can lead to increased serum concentration. Psychotropic medications like antipsychotics and antidepressants can induce seizures. Antipsychotic medication

use can cause seizures in 1 % of patients receiving them at the recommended dosages and lowers the seizure threshold. Atypical antipsychotics can have even high rates, such as clozapine, which is associated with a 2.8 % risk of seizures and can climb to 4.4 % 14 % with doses of >600 mg/day. Newer antipsychotics like risperidone have a 0.3 % incidence of seizure activity. The incidence of seizures secondary to antidepressant use ranges from <0.1 % to 4.0 % depending on the type (tricyclics: regular usage <1.0 %/with overdose 3.4 %; second generation antidepressants: with overdose 36.4 %, SSRIs have a relative lack of seizure potential, MAOIs 0 %-0.012 %).

Nonpsychotropic medications such as B-lactam antibiotics, aminoglycosides, metronidazole, quinolones, and isoniazid have had reports of seizures in elderly patients receiving them. Up to 3 % of retirement home residents receiving amantadine for influenza A virus infection have reported seizures. Patients with theophylline toxicity, on therapeutic dose, or low serum concentration have reports of seizures. In a case series of 12 patients age 55 85 with theophylline-induced seizures, at seizure onset serum theophylline concentrations ranged from 14 35 mg/L. Histamine H2 antagonists, levodopa, and thiazide derivatives had also been associated with seizures. Abrupt discontinuation of medications may result in generalized seizures, most commonly, barbiturates and alcohol followed by benzodiazepines. Typically, generalized seizures occur between 7 and 30 hours after someone who consumes large amounts of alcohol stops. Ideal treatment involves prevention with a benzodiazepine, typically chlordiazepoxide. Similarly, patients taking high doses of benzodiazepines for a long period of time are at risk for seizures after abruptly discontinuing. This is even more common in short half-life, high potency agents, and in those taking higher than recommended doses. The seizures tend to be generalized, nonfocal with tonic-clonic activity, and are typically self-limiting. Treatment of medication-induced seizures should begin with ascertaining if there has been a history of epilepsy. After a first seizure in a patient at a therapeutic drug concentration, they should be observed closely and have lab studies including drug screening. This also is the recommended treatment for those arriving to the hospital after having several convulsive seizures and stable vital signs. Patients presenting in status epileptics should be immediately treated. In the event of a drug-induced seizure, AED treatment should be short-term [29].

Anticonvulsant withdrawaloption or not in elderly

The anticonvulsants medications in elderly can be withdrawn if they fulfill the criteria of the normal EEG and MRI brain. They should have normal physical examination, and video EEG monitoring should be considered to see if there were any interictal EEG abnormalities. The patients should be made aware of the risk of recurrent seizures which is 10 %–70 %. The pros and cons of withdrawal should be discussed in length with the patients and benefits should outweigh the risks (eg, the risk of falls and fractures) [30].

Begley et al conducted a retrospective review to estimate the lifetime and annual cost of epilepsy in the United States in 1995 and found that patients with intractable epilepsy had the highest direct and indirect costs [31]. In this review, we discuss both older and newer anticonvulsants of importance in the treatment of epilepsy in the elderly population (Table 1).

Table 1. Summary of older and newer anticonvulsants used in elderly population

Drug	Main drug interactions	Elimination	Standard dosage	Cost	Main adverse effects
Older AEDs					
Carbamazepine	Enzyme inducer	Hepatic	Start 100 mg/day and then titrate to 400 mg twice daily	Inexpensive	Hyponatremia, tremors, cardiotoxicity, sexual dysfunction, possible bone loss, and weight gain.
Phenytoin	Enzyme Inducer (nonlinear kinetics)	Hepatic	200 mg daily. Increase in 30 mg increments if needed	Inexpensive	Ataxia, Osteoporosis blood dyscrasias, rash, and hepatotoxicity
Valproic acid	Enzyme inhibitor	Hepatic	250 mg three times daily	Moderate	Encephalopathy, weight gain, hair loss, and tremor
Phenobarbital	Enzyme inducer	Hepatic	Initial dose 50 mg daily	Inexpensive	Sedation, cognitive slowing, and drowsiness
Newer AEDs					
Gabapentin	None	Renal	300 mg three times daily	Moderate	Weight gain, myoclonus, pedal edema, fatigue, and dizziness
Lamotrigine	Nonenzyme inducing	Hepatic	150 mg twice daily	Expensive	Rash (Dose dependent), Insomnia, tremor ataxia, vomiting, somnolence, dizziness, and tremor
Levetiracetam	None	Renal and Hepatic	500 mg twice daily	Expensive	Psychosis, agitation, somnolence, and dizziness
Tiagabine	Nonenzyme inducing	Hepatic	32 mg/day	Expensive	Dizziness, encephalopathy.
Topiramate	Enzyme inducer	Renal	100 mg twice daily	Expensive	Word finding difficulties, paresthesias, weight loss, renal stones, and closed angle glaucoma(rare).
Zonisamide	Nonenzyme inducing	Hepatic and renal	100 mg twice daily	Expensive	Somnolence, renal stones, weight loss, ataxia, and agitation.
Pregabalin	None	Renal	300 mg twice daily	Expensive	Dizziness, ataxia, nausea and drowsiness, weight gain, and edema.

Adapted from references [6, 10, 32, 33••, 37].

Pharmacologic treatment

First-generation anticonvulsants

Phenytoin

Phenytoin inhibits the repeated activation of voltage-dependent sodium channels and the reduction of glutamate in neuronal synapses, resulting in anticonvulsant activity [32].

Standard dosage Phenytoin may be started a dose of 100 mg per day and increase to target dose over 3–7 days to 200 mg once daily in elderly [33••]. If older people have dysphagia, phenytoin have liquid or chewable formulations. Phenytoin also has

	extended release formulations, which can reduce the risk of peak-dose side effects, and make compliance easier with once daily dosing.
Contraindications	Hypersensitivity to phenytoin or other hydantoin medications [34].
Main drug interactions	Drugs that inhibit the cytochrome P450 enzymes CYP2C9 and CYP2C19 may inhibit the metabolism of phenytoin, increasing the drug's half-life. Phenytoin decreases levels of tricyclic antidepressants and calcium channel blockers (diltiazem, verapamil). It also interacts with warfarin and with diabetes and arthritis medications [32].
Main side effects	Phenytoin dosing should be followed closely in elderly patients, as the drug is highly protein-bound and these patients tend to have lower albumin levels, which may result in higher unbound AED levels than the predicted total AED level, leading to toxicity even at therapeutic levels [35]. Long-term phenytoin treatment may result in osteoporosis and osteomalacia. Gingival hyperplasia occurs in about 50 % of patients as the result of long-term therapy with the drug [32].
Special points	In a Veterans Administration cooperative study of older AEDs, such as carbamazepine, phenytoin, phenobarbital, and primidone, carbamazepine and phenytoin yielded the most success in the treatment of partial seizures [5]. Studies on phenytoin kinetics in elderly patients found a decrease in maximum volume (V_{max}) with age; therefore, lower dosages should be used in this population [32]. There is an increased risk of confusion, ataxia, and sedation in these patients [36].
Cost-effectiveness/cost	Phenytoin 100-mg extended-release (ER) capsule (generic): total daily dose, 300 mg=three capsules per day; average monthly cost, USD $27 [37].

Carbamazepine

	Carbamazepine blocks the repeated activation of voltage-dependent neuronal sodium channels and reduces the release of glutamate, thus, stabilizing the neuronal membrane [38].
Standard dosage	The starting dosage of carbamazepine is 100 mg/day, which can be titrated to a maximum of 400 mg twice daily [38, 39]. Carbamazepine is also available in liquid and chewable formulations, and extended release formulation is also available if needed.
Contraindications	Hypersensitivity, tricyclic antidepressant use, history of bone marrow suppression, concomitant use, or use within 14 days of monoamine oxidase inhibitors, concurrent use with nefazodone, concomitant use of delavirdine, or other nonnucleoside reverse transcriptase inhibitors [40].
Main drug interactions	Changes in nonglycated albumin increase free carbamazepine concentrations and, thus, increase the pharmacologic effects of the drug and risks of drug interactions [38]. Carbamazepine decreases the levels of tricyclic antidepressants, calcium channel blockers (diltiazem and verapamil), and warfarin [41].
Main side effects	Elderly patients have reported nausea, headaches, dizziness, diplopia, ataxia, hyponatremia, osteoporosis, and osteomalacia [40].
Special points	Carbamazepine clearance in elderly people on long-term therapy was shown to be 30 % to 40 % lower than in younger people. Lower daily dosing in the elderly is highly encouraged [32]. Carbamazepine results in greater impairment of attention compared with gabapentin [42].
Cost-effectiveness/cost	Average monthly cost, USD $15 [37].

Valproic acid

	Although the exact mechanism of action of valproic acid (VPA) is debated, studies have shown that VPA has a role in increasing the release of γ-aminobutyric acid (GABA) concentrations in the brain through multiple enzyme systems, such as GABA transaminase, α-ketoglutarate dehydrogenase, and succinic semialdehyde dehydrogenase. Other theories suggest a possible reduction in excitatory neurotransmission, modification of monoamines, or weak inhibition of voltage-gated sodium channels [43].
Standard dosage	250 mg three times a day. Higher dosages may be required in patients receiving hepatic enzyme–inducing drugs. Depakote ER, an extended release formulation, can also be used in elderly, which can reduce the risk of peak-dose side effects, and make compliance easier with once daily dosing. If older people have dysphagia, depakote has a liquid formulation [44].
Contraindications	Liver disease [32].
Main drug interactions	VPA increases carbamazepine and amitriptyline concentrations. It displaces phenytoin and diazepam from plasma protein-binding sites, resulting in increased clearance and low plasma concentrations. Patients receiving warfarin may experience a transient increased anticoagulant effect. Felbamate, stiripentol, isoniazid, fluoxetine, aspirin, and chlorpromazine increase the concentration of VPA; therefore, lower VPA dosages are necessary [44]. Valproate leads to a decrease in lamotrigine clearance by 50 %. In these instances, the dose of lamotrigine must be lowered significantly, starting at 25 mg every other day [45].
Main side effects	Dizziness, impaired coordination, ataxia, and cognitive impairment are some of the central nervous system (CNS) symptoms associated with VPA. Other side effects include weight gain, gingival hyperplasia, hair loss, tremors, thrombocytopenia, and pancreatitis [32].
Special points	The effectiveness of VPA has been well established from studies performed largely in younger adults, which showed that VPA is as effective as carbamazepine, phenytoin, and phenobarbital in treating partial-onset and generalized tonic–clonic seizures [44]. Parkinsonism and cognitive decline tend to reverse once the medication is discontinued [46].
Cost-effectiveness/cost	VPA 250-mg capsule (generic): total daily dose, 750 mg=three capsules per day; average monthly cost, USD $41 [37].

Phenobarbital

	Phenobarbital, a barbiturate, inhibits the GABA receptor, prolongs the opening of the chloride channels, and enhances inhibition. It also blocks excitatory responses to glutamate. The end result is hyperpolarization of the brain's neurons [38].
Standard dosage	30–50 mg once daily at bedtime initially, with a possible increase after 10–15 days [33••]. Phenobarbital is also available in liquid which can be used in elderly with dysphagia.
Main drug interactions	Phenobarbital induces hepatic enzymes and increases the metabolism of drugs metabolized by CYP2C, CYP3A, and uridine 5′-diphospho-glucuronosyltransferase (UGT). VPA inhibits the glucuronidation of phenobarbital, leading to increases in phenobarbital plasma concentrations. Felbamate inhibits the metabolism of phenobarbital by blocking CYP2C19. VPA and felbamate should be monitored closely or reduced when given with phenobarbital as an added therapy [32].

Main side effects	Phenobarbital use in the elderly may lead to sedation, ataxia, and idiosyncratic problems such as connective tissue disturbance, rash, and hepatitis. It also may cause osteomalacia, sexual dysfunction, and folate deficiency [12, 32].
Special points	Phenobarbital is not the preferred first-line treatment of epilepsy in the elderly; however, it is an inexpensive option prescribed occasionally [32].
Cost-effectiveness/cost	Generic 64.8-mg tablets, 60 tablets per month; cost, USD $19.50 [37].

Second-generation anticonvulsants

Lamotrigine

	Lamotrigine causes presynaptic blockade of sodium-dependent channels and inhibits glutamate release [38].
Standard dosage	Initially, 25 mg/day for 2 weeks, then 50 mg/day for 2 weeks. The dosage may be increased by 50 mg/day every 1–2 week to a target dose of 150 mg twice daily. For elderly who are taking hepatic enzyme–inducing AEDs, lamictal is usually started at 25 mg twice a day. The amount can be increased by 50 mg per day every 2 weeks as long as it is tolerated and provided there are no troublesome side-effects. The AEDs that require these higher dosages of lamictal are carbamazepine phenytoin , phenytoin and phenobarbital [33••]. For elderly taking valproate the initial dose should be 12.5 25 mg every other day, with increases in dosage of 25 mg per day every 2 weeks if required and tolerated , to a target dose of 150 200 mg daily [45].
Contraindications	Hypersensitivity to the drug or ingredients used in its preparation, severe liver, and kidney disease [23].
Main drug interactions	Lamotrigine interacts with VPA and may increase the risk of skin rash, dizziness, double vision, and blurred vision in patients receiving carbamazepine [32, 47].
Main side effects	The most common side effects are CNS related and include dizziness, asthenia, somnolence, and headache. There also is an increased frequency of rash, including Stevens–Johnson syndrome, which is related to the rate of titration, initial dosage, and concomitant use of VPA [47].
Special points	Lamotrigine was shown to be better tolerated and to have fewer CNS side effects, although discontinuation due to the development of skin rashes was twice as frequent with amotrigine than phenytoin. In a subgroup of patients with poststroke seizures, carbamazepine was relatively better tolerated than lamotrigine [48].
Cost-effectiveness/cost	200-mg tablet; USD $287 for a 30-day supply [37].

Levetiracetam

	The mechanism of action of levetiracetam is unknown. However, levetiracetam binds to the synaptic vesicle protein SV2A, which has been linked to epilepsy in animal models. Binding at this site may modulate synaptic transmission through alteration of vesicle fusion [49•].
Standard dosage	500 mg/day or 1000 mg/day initially, increased if indicated after 2 weeks [33••]. The advantage of levetiracetam is also that it is also available in liquid formulations which can be used in elderly with dysphagia. Extended

	release formulation is also available for once a dosing making compliance easier in elderly population.
Main drug interactions	Levetiracetam is less susceptible to clinically significant drug interactions because it is not bound to plasma protein and is not metabolized by CYP350 enzymes [32].
Main side effects	Levetiracetam has several CNS-related side effects, including somnolence, dizziness, asthenia, and headache; however, it is not associated with any cognitive dysfunction [38].
Special points	Levetiracetam has been shown to be efficacious in patients with refractory partial seizures, with a response rate of 42 %, and up to 8 % of the patients become seizure-free. Aggression and mood lability were the most common reasons for withdrawal [50•]. An observational study with a sample of 491 patients with a mean age of 71 revealed a rather small percentage of patients with mental slowing (3.2 %) and confusion (1.6 %) [51••].
Cost-effectiveness/cost	Expensive (particularly intravenous); 30-day supply of 500 mg BID is $125 [37].

Tiagabine

	Tiagabine is a potent enhancer of GABA action by specifically inhibiting GABA reuptake into presynaptic neurons, making endogenously produced GABA more available for postsynaptic inhibitory effects [52].
Standard dosage	4–8 mg/day initially.The drug may be titrated in adults at weekly increments of 4–8 mg/day until a clinical response is elicited or up to 32 mg/day when divided into several doses [6, 53].
Contraindications	Hypersensitivity to the drug and its ingredients.
Main drug interactions	Concomitant use of enzyme-inducing anti-epileptic drugs would decrease the level of tiagabine. Tiagabine showed no drug interactions with theophylline, warfarin, or digoxin [38].
Main side effects	Dizziness, asthenia, somnolence, nausea, nervousness, tremor, difficulty concentrating, and abdominal pain [32].
Special points	Although weakness associated with tiagabine has been severe enough to cause falls, this effect is mostly dose-dependent and reversible. Elderly patients may be at increased risk for falls while on this drug; a lower starting dose and titration administered with food and close monitoring will decrease this adverse effect [32].
Cost-effectiveness/cost	USD $208 for a 30-day supply [37].

Topiramate

	Topiramate blocks voltage-dependent sodium channels, enhances the activity of GABA at a nonbenzodiazepine site on GABA(A) receptors, and antagonizes an NMDA–glutamate receptor. It also weakly inhibits carbonic anhydrase in the CNS [54].
Standard dosage	25 mg/day initially, increased in 25-mg or 50-mg increments every 2 weeks [33••].
Main drug interactions	Topiramate increases phenytoin plasma levels by weak inhibition of CYP2C19 enzymes. In return, it also is susceptible to enzyme-inducing AEDs. Its plasma concentration and half-life are decreased by 40 % with

	concurrent use of carbamazepine and phenytoin. It also has been shown to decrease the levels and concentration of digoxin [32].
Main side effects	Topiramate may cause anorexia and bodyweight loss, which may be pronounced, and renal calculi due to its inhibition of carbonic anhydrase in the kidney [32, 38]. Topiramate has caused deficits in working memory and verbal fluency [55]. There have been concerns regarding decline in driving skills, such as divided attention, field of view, and visual scanning [56, 57]. Although some of these difficulties have been observed even with low dosages, they are reversible once medication is discontinued.
Cost-effectiveness/cost	Expensive; 60 100-mg tablets per month cost USD $240 [37].

Gabapentin

	Gabapentin exerts its pharmacologic action by binding to voltage-dependent calcium channels and inhibiting calcium currents, resulting in attenuation of neurotransmitter release [58].
Standard dosage	Initial target dose for titration of gabapentin is 300 mg TID; 300 mg may be given the first day, followed by 300 mg twice daily the second day, 300 mg three times a day on the third day, and then increased if needed to 1800 mg/day in three divided doses [59, 60]. Gabapentin is also available in a liquid formulation.
Main drug interactions	Gabapentin undergoes few drug interactions, but antacids and cimetidine lower its bioavailability. It is recommended that gabapentin and antacid doses be separated by a minimum of 2 h [32].
Main side effects	Somnolence, dizziness, ataxia, and fatigue are among the most common adverse effects. Increases in bodyweight also have been noted. Gabapentin is thought to have fewer cognitive side effects in elderly patients [42, 61].
Special points	A randomized crossover study comparing gabapentin and carbamazepine in healthy elderly persons showed that both AEDs have a modest detrimental influence on cognition. However, patients on gabapentin had significantly fewer cognitive effects than those on carbamazepine [42].
Cost-effectiveness/cost	Moderate; 30-day supply of gabapentin 300 mg three times daily is USD $118.80 [37].

Zonisamide

	Zonisamide exerts its pharmacologic action by blocking voltage-sensitive sodium and T-type calcium channels [62].
Standard dosage	50 mg/day initially; may be increased to 100 mg/day in 1 week. The dosage may be increased further by 50 mg/day every 1–2 weeks or by 100 mg/day after 2 weeks. The maximum recommended dose of zonisamide is 200 mg BID [33••].
Contraindications	Sulfonamide allergy.
Main drug interactions	Zonisamide has not been shown to induce or inhibit microsomal monooxygenase systems, but hepatic inducers such as phenytoin, phenobarbital, and carbamazepine increase its metabolism, resulting in a reduced half-life [32].
Main side effects	Zonisamide has several CNS-related side effects, such as somnolence, ataxia, and dizziness, which may be reduced with dose titration over

	several weeks. Kidney stones are another main side effect. Stevens–Johnson syndrome also has been reported with zonisamide use [32].
Cost-effectiveness/cost	100 mg capsules . USD $123 for a 30-day supply [37].

Epilepsy surgery

Forty percent to 100 % of patients with epilepsy achieve seizure remission after surgery. For patients with refractory mesial temporal lobe epilepsy, surgery is the most effective option. Some patients have less optimal results, including those undergoing extratemporal surgery and those with nonlesional epilepsy [63, 64].

Complications	Memory impairment and focal neurologic deficits, such as visual field loss, are the most common complications[63, 64].
Cost-effectiveness/cost	Expensive over the short term but highly cost-effective in the long term.

Vagal nerve stimulation

In patients with chronic refractory epilepsy, vagal nerve stimulation is effective in reducing seizure frequency. A 50 % or greater reduction in seizure frequency is seen in 40 % of patients with implants. Patients also have an improved quality of life, possibly because of a reduction in required AED dosage [65–67].

Complications	Dysphonia, dysphagia, and throat pain/dysesthesias are the most common complications.
Cost-effectiveness/cost	Expensive over the short term but highly cost-effective in the long term.

Modified diet

The ketogenic diet is a high-fat, low-carbohydrate regimen that through ketone bodies and/or glucose restriction, may mediate direct anticonvulsant effects. A modified Atkins diet or other low-glycemic diet may be adjunctive epilepsy therapy because of the difficulty in complying with the strict ketogenic diet [68, 69].

Additional complications	In patients with cardiovascular or mitochondrial disease, the ketogenic diet is contraindicated. Patients on the ketogenic diet are at risk for hyperlipidemia.
Cost-effectiveness/cost	Inexpensive.

Compliance with Ethics Guidelines

Conflict of Interest
Batool F. Kirmani, Diana Mungall Robinson, Adeline Kikam, Ekokobe Fonkem, and Daniel Cruz 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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