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Comparison of FDA-Approved Antiepileptic Drugs

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Prior to 1990, six major antiepileptic drugs (AEDs) were available for treating all forms of epilepsy. These agents include carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid. These conventional agents have been used as monotherapy and in combined regimens in newly diagnosed and refractory cases, yet 20% to 30% of epileptic patients are refractory to these drugs. Also, complex pharmacokinetic parameters, need for monitoring, drug interactions, teratogenic potential, troublesome side effects, and adverse impact on patient quality-of-life provide challenges for patients and clinicians alike.¹⁴

Since 1990 the FDA has approved several new AEDs. These include gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, and felbamate. These newer agents have fewer safety and tolerability problems and are easier to use. Even though they are more expensive than the older AED's, their expense may be offset by their potential benefits.¹⁴⁻¹⁷ Among the newer agents, only oxcarbazepine is approved for use as monotherapy for the treatment of newly diagnosed patients. Lamotrigine and oxcarbazepine are also approved as monotherapy for refractory partial epilepsy. All of the eight newer AEDs (gabapentin, lamotrigine, felbamate, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide) are approved for refractory partial epilepsy as add-on therapy.

Recently, the American Academy of Neurology (AAN) and the American Epilepsy Society (AES) presented guidelines for use of these newer agents. Tiagabine, levetiracetam, and zonisamide are not yet recommended for monotherapy by the FDA or in these guidelines.^{15,16}

Comparison of FDA-Approved Antiepileptic Drugs

Drug	FDA Labeled Indications	Dosage Range ^{18,19} Daily Cost*	Serious Adverse Effects ^{15,16,19}	Significant Drug Interactions ^{19,20}	Comments ²⁰
Carbamazepine <i>(Tegretol)</i>	<ul style="list-style-type: none"> Partial seizures with complex symptomatology Generalized tonic-clonic seizures (grand mal), mixed seizure patterns¹ 	<ul style="list-style-type: none"> Adults: 800 mg initially to 1,200 mg daily maximum, increasing at weekly intervals by 200 mg Children: varies by age per weight \$1.40 per day 	Syncope, blood dyscrasias, visual difficulties, hepatitis, rash, Stevens-Johnson syndrome, pancreatitis	Calcium channel blockers, clarithromycin, clozapine, contraceptives, cyclosporin, CYP3A4 inhibitors, danazol, diclofenac, doxycycline, erythromycin, haloperidol, imatinib, isoniazid, lamotrigine, mebendazole, methadone, nefazodone, phenytoin, propofol, propoxyphene, protease inhibitors, quinidine, SSRIs, warfarin	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ Therapeutic range: 4 to 12 mcg/mL Liver function tests should be performed at baseline and periodically
Ethosuximide <i>(Zarontin)</i>	<ul style="list-style-type: none"> Generalized absence, Control of absence (petit mal) epilepsy² 	<ul style="list-style-type: none"> Adults: 500 mg initially to 1,500 mg daily maximum, increase by 250 mg every 4 to 7 days as tolerated Children: 3 to 6 years, 15 mg (maximal initial dose: 250 mg) to 40 mg/kg/day maximum, titrate every 4 to 7 days as tolerated \$6.55 per day 	Blood dyscrasias, lupus, Stevens-Johnson syndrome, aggression	Azole antifungals, clarithromycin, diclofenac, isoniazid, nefazodone, nicardipine, propofol, protease inhibitors, quinidine, telithromycin	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ Usual therapeutic range: 40 to 100 mcg/mL Liver function tests should be performed at baseline and periodically

More . . .

Drug	FDA Labeled Indications	Dosage Range ^{18,19} Daily Cost*	Serious Adverse Effects ^{15,16,19}	Significant Drug Interactions ^{19,20}	Comments
Phenobarbital	<ul style="list-style-type: none"> Generalized onset myoclonic Partial onset, generalized onset tonic-clonic¹⁹ 	<ul style="list-style-type: none"> Adults: 120 mg to 180 mg daily (oral) Children: varies by age per weight \$0.24 per day 	Rash, Stevens-Johnson syndrome, blood dyscrasias, angioedema	Azole antifungals, calcium channel blockers, chloramphenicol, clomipramine, contraceptives, cyclosporin, disopyramide, doxycycline, gemfibrozil, isoniazid, lamotrigine, methadone, methoxyflurane, modafinil, non-nucleoside reverse transcriptase inhibitors, omeprazole, quinidine, telithromycin, ticlopidine, tricyclic antidepressants, warfarin	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ Therapeutic range: 15 to 40 mcg/mL
Phenytoin (Dilantin)	<ul style="list-style-type: none"> Partial onset (psychomotor) seizure Generalized onset tonic-clonic³ 	<ul style="list-style-type: none"> Adults: Loading dose needed for initiation, then 4 mg initially to 6 mg/kg/day maximum Children: varies by age per weight \$0.80 per day 	Hepatotoxicity, blood dyscrasias, rash, Steven's Johnson syndrome, osteomalacia, lupus, lymphoma	Azole antifungals, calcium channel blockers, carbamazepine, chloramphenicol, cimetidine, contraceptives, cyclosporine, disopyramide, disulfiram, doxycycline, felbamate, flurbiprofen, gemfibrozil, HMG-CoA reductase inhibitors (select), ibuprofen, indomethacin, isoniazid, lamotrigine, mefenamic acid, modafinil, nucleoside reverse transcriptase inhibitors, pioglitazone, piroxicam, quinidine, rifabutin, rifampin, sirolimus, SSRIs, ticlopidine, warfarin, telithromycin, warfarin, non-phenobarbital	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ Therapeutic range: 10 to 20 mcg/mL (free levels: 1 to 2 mcg/mL)
Primidone (Mysoline)	<ul style="list-style-type: none"> Partial onset Generalized onset tonic-clonic, grand mal, psychomotor, focal seizures⁴ 	<ul style="list-style-type: none"> Adults: 100 mg initially to 2,000 mg maximum daily, increase by 100 to 125 mg increments every 3 days as tolerated Children: varies by age per weight \$3.90 per day 	Thrombocytopenia, anemia, dyspnea, lupus-like syndrome	Lamotrigine, quinidine	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ Adjust dose in renal impairment Therapeutic range: 5 to 12 mcg/mL

Drug	FDA Labeled Indications	Dosage Range ^{18,19} Daily Cost*	Serious Adverse Effects ^{15,16,19}	Significant Drug Interactions ^{19,20}	Comments
Valproic Acid (<i>Depakene</i>)	<ul style="list-style-type: none"> Generalized absence Generalized onset myoclonic Partial onset Generalized onset tonic-clonic, complex partial seizures, absence seizures (simple and complex)⁵ 	<ul style="list-style-type: none"> Adults: 10 mg initially to 60 mg/kg/day maximum, increase by 5 to 10 mg/kg/day weekly as tolerated Children: not recommended due to hepatotoxicity \$7.52 per day 	Hepatotoxicity, pancreatitis, blood dyscrasias, rash, Stevens-Johnson syndrome, hyperammonemia, anaphylaxis, psychosis	Felbamate, lamotrigine, macrolide antibiotics	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ Therapeutic range: 50 to 100 mcg/mL Liver function tests should be performed at baseline and at frequent intervals especially during the first 6 months
Felbamate (<i>Felbatol</i>)	<ul style="list-style-type: none"> Monotherapy or adjunctive treatment for partial seizures in adults Adjunctive treatment in generalized or partial seizures associated with Lennox-Gastaut syndrome in children. Note: not for first line treatment^{**6} 	<ul style="list-style-type: none"> Adults: 1,200 mg initially to 3,600 mg maximum daily Children: 15 initially to 45 mg/kg/day maximum Titrate with increases at two week intervals <ul style="list-style-type: none"> \$11.99 per day 	Aplastic anemia, liver failure	Azole antifungals, calcium channel blockers, contraceptives, diclofenac, isoniazid, macrolide antibiotics, nefazodone, phenytoin, propofol, protease inhibitors, quinidine, valproic acid	<ul style="list-style-type: none"> For refractory epilepsy¹⁴⁻¹⁶ Monitor liver function enzymes and bilirubin at baseline and every 1 to 2 weeks
Gabapentin (<i>Neurontin</i>)	<ul style="list-style-type: none"> Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years of age Adjunctive therapy in the treatment of partial seizures in pediatric patients age 3 to 12 years⁷ 	<ul style="list-style-type: none"> Adults: 300 mg initially to 3,600 mg maximum daily Children: 10 mg initially to 50 mg/kg/day maximum Titrate and increase slowly as tolerated <ul style="list-style-type: none"> \$15.60 per day 	Aggression	None	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ FDA unapproved indication: newly diagnosed partial/mixed seizures as monotherapy (Level A)^{***} Slow titration minimizes adverse effects Serum level monitoring not needed

Drug	FDA Labeled Indications	Dosage Range ^{18,19} Daily Cost*	Serious Adverse Effects ^{15,16,19}	Significant Drug Interactions ^{19,20}	Comments
Lamotrigine (<i>Lamictal</i>)	<ul style="list-style-type: none"> Adjunctive therapy for partial seizures in adults and pediatric patients (≥ 2 years of age) Adjunctive therapy for the generalized seizures of Lennox-Gastaut syndrome in adult and pediatric patients (≥ 2 years of age) Conversion to monotherapy in adults with partial seizures receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as single AED⁸ 	<ul style="list-style-type: none"> Adults: as monotherapy, 50 mg initially to 500 mg maximum daily Children: as monotherapy 0.3 mg initially to 8 mg/kg/day maximum Titrate and increase dose gradually every two weeks as tolerated <ul style="list-style-type: none"> \$15.83 per day 	Rash (including Stevens Johnson and toxic epidermal necrolysis), hypersensitivity reactions including hepatic and renal failure, disseminated intravascular coagulation, arthritis	Barbiturates, carbamazepine, contraceptives, phenytoin, primidone, quinidine, valproic acid	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ FDA unapproved indication: newly diagnosed partial/mixed seizures as monotherapy (Level A)^{***}, newly diagnosed absence seizures in children as add-on (Level B)^{***} Serum level monitoring not needed
Levetiracetam (<i>Keppra</i>)	<ul style="list-style-type: none"> Adjunctive therapy in the treatment of partial onset seizures in adults⁹ 	<ul style="list-style-type: none"> Adults: 500 mg initially to 3,000 mg maximum daily Children: no recommended doses however, clinical trials have used 10 mg initially to 60 mg/kg/day maximum Titrate and increase at two week intervals as tolerated <ul style="list-style-type: none"> \$12.40 per day 	Psychosis, blood dyscrasias, suicide attempts	None	<ul style="list-style-type: none"> For refractory epilepsy¹⁴⁻¹⁶ Serum level monitoring not needed
Oxcarbazepine (<i>Trileptal</i>)	<ul style="list-style-type: none"> Monotherapy or adjunctive therapy in partial seizures in adults and children aged 4 to 16¹⁰ 	<ul style="list-style-type: none"> Adults: 300 mg initially to 2,400 mg maximum daily, increase at 3 to 7 day intervals as tolerated Children: 8 mg/kg/day (maximum initial dose 600 mg daily) increasing by 8 to 10 mg/kg/day as tolerated at 3 to 7 day intervals <ul style="list-style-type: none"> \$14.66 per day 	Hyponatremia, rash	Contraceptives	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ Monitor serum sodium during first 3 month and more frequently with hyponatremic drugs Level monitoring not needed

Drug	FDA Labeled Indications	Dosage Range ^{18,19} Daily Cost*	Serious Adverse Effects ^{15,16,19}	Significant Drug Interactions ^{19,20}	Comments
Tiagabine (<i>Gabitril</i>)	<ul style="list-style-type: none"> Adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures¹¹ 	<ul style="list-style-type: none"> Adults: 4 mg to 56 mg daily, starting at 4 mg and increasing by 4 to 8 mg at weekly intervals Children: 12 years and >: 0.25 mg/kg/day initially with increments of 0.25 to 5 mg/kg/day maximum at two to four week intervals up to 1 to 2 mg/kg/day \$8.60 per day 	Nonconvulsive status epilepticus, stupor	Azole antifungals, calcium channel blockers, diclofenac, isoniazid, macrolide antibiotics, nefazodone, propofol, protease inhibitors, quinidine	<ul style="list-style-type: none"> For refractory epilepsy¹⁴⁻¹⁶ Monitor complete blood counts, renal function tests, liver function tests, and routine blood chemistry periodically Serum level monitoring not needed
Topiramate (<i>Topamax</i>)	<ul style="list-style-type: none"> Adjunctive therapy for adults and pediatric patients ages 2-16 years with partial onset seizures, or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome¹² 	<ul style="list-style-type: none"> Adults: 25 mg initially to not more than 1,600 mg daily with dose increases of 25 mg weekly as tolerated Children: 1 mg initially to 9 mg/kg/day maximum with 1 to 3 mg/kg/day increases made weekly as tolerated \$39.18 per day 	Nephrolithiasis, open angle glaucoma, hypohidrosis, depression, psychosis, metabolic acidosis	Contraceptives	<ul style="list-style-type: none"> For newly diagnosed, new-onset, and refractory epilepsy¹⁴⁻¹⁶ FDA unapproved indication: newly diagnosed partial/mixed seizures as monotherapy (Level A)^{***}, refractory partial epilepsy as monotherapy (Level A)^{***} Adjust dose in renal impairment Slow titration minimizes adverse effects Monitor serum bicarbonate at baseline and periodically Serum level monitoring not needed

Drug	FDA Labeled Indications	Dosage Range ^{18,19} Daily Cost*	Serious Adverse Effects ^{15,16,19}	Significant Drug Interactions ^{19,20}	Comments
Zonisamide (<i>Zonegran</i>)	<ul style="list-style-type: none"> Adjunctive therapy in the treatment of partial seizures in adults¹³ 	<ul style="list-style-type: none"> Adults: 100 mg initially to 600 mg daily maximum, titrate in 100 mg increments at two week intervals Children: 2 mg initially to 8 (possibly 12) mg/kg/day maximum titrated at two week intervals as tolerated \$12.60 per day 	Rash, renal calculi, hypohidrosis	Azole antifungals, calcium channel blockers, diclofenac, isoniazid, macrolide antibiotics, nefazodone, propofol, protease inhibitors, quinidine	<ul style="list-style-type: none"> For refractory epilepsy¹⁴⁻¹⁶ Levels of 20 to 30 mcg/mL associated with efficacy Serum level monitoring not needed Monitor renal function

* Daily cost is based on maximum adult dosage (70 kg). Cost information is approximate as of the time this chart was prepared. It is based on manufacturer stated internet website prices, observed retail pharmacy prices, and www.drugstore.com listings. Actual selling prices may differ.

** Use only if patients unresponsive to standard drug and where risk/benefit ratio supports use.⁶

*** American Academy of Neurology (AAN) and the American Epilepsy Society (AES) Level A or B Use Recommendations. These evidence-based guidelines provide recommendations for use based on at least one prospective, randomized controlled clinical trial (RCT) with defined requirements (Level A) or at least one prospective matched group cohort study, lesser RCT, or at least three controlled trials (Level B).^{15,16}

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