A Summary of Antiseizure Medications Available in the United States: 4th Edition

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Introduction: The current review summarizes the most commonly used antiseizure medications (ASMs) available for prescription in the United States and is an update to the AES 2018[1] and 2020 summaries. Information on rarely prescribed ASMs may be found elsewhere.[2] Tables 1-3 present the major pharmacologic properties of commonly used ASMs to assist clinicians with providing care for persons with epilepsy and to facilitate the training of healthcare professionals.

Background: Two and one-half decades ago, the choice of ASMs was relatively limited. Beginning in August 1993 in the United States, the first new ASM in approximately 15 years was approved by the US Food and Drug Administration (FDA). Since then, a panoply of ASMs have been approved. The vast majority of these ASMs are in new drug classes, and many have novel mechanisms of action. Furthermore, most of the newer ASMs have pharmacokinetic properties that are different from those of older ASMs.

Target Audience: Now that more than 30 ASMs are available in the United States, it can be challenging for epileptologists, neurologists, pharmacists, nurses, trainees, and other healthcare professionals to quickly access and cross-reference information needed in clinical practice to optimally select and use these medications. The American Epilepsy Society Treatments Committee provides this summary as a tool to help meet this need. It is the sincere hope of the authors and the American Epilepsy Society that providers will find this document to be a beneficial reference tool in the advanced care of people with epilepsy.

Sources: Data for these summaries were obtained in January 2024 from the most recent FDA-approved prescribing information (PI) for each ASM available in the FDA's searchable database, Drugs@FDA: FDA-Approved Drugs.[3] Additional notes:

- Among PIs for all ASMs approved since 1993, the PIs for carbamazepine, divalproex, and phenytoin were substantially more detailed than PIs for other older drugs. Phenobarbital is no longer listed on the FDA website, but an older PI was used to obtain FDA-approved information.[4] In instances where PIs lacked important data, ASM pharmacology texts were used to supplement the information in the PIs.[5,6]
- Serum level ranges are based on the clinical experience of American Epilepsy Society (AES) Treatments Committee members.
- PIs use the former terminology "partial onset seizures"; Table 1 uses the current terminology "focal onset seizures."[7]
- Regulatory language for approval of monotherapy versus adjunctive treatment has changed over the past decades.[8]
- In Table 1, all drugs are approved for monotherapy and adjunctive treatment unless otherwise stated.
- Phenytoin maintenance dosing in Table 1 is from the PI, but modern research and experience indicate that adult dose requirements vary considerably from 200 to 600 mg/day. We advise that the reader consult modern sources for recommended maintenance dosing.[9]
- **Important**: Actual practice of providers may differ substantially from official approved indications, doses, dose frequency, and other parameters.

Precautions for ASMs:

- All ASMs confer an elevated risk of suicidal ideation and behavior and an increased risk of teratogenesis.
- All women becoming pregnant while taking ASMs (also called antiepileptic drugs or AEDs), are encouraged to enroll themselves with the North American Antiepileptic Drug Pregnancy Registry by calling 1-888-233-2334 or visiting www.aedpregnancyregistry.org.[10]
- In the United States, report ASM adverse events to www.fda.gov/medwatch.[11]

Important Notes:

- This document is not intended to constitute treatment recommendations but instead to provide an easy reference listing of products on the market.
- PI information is updated on an ongoing basis, and the FDA database PI sources for each ASM should be consulted for the most current information.

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Drugs, Formulations, and DEA Scheduling	FDA-Approved Seizure/Syndrome Type, Mono- or Adjunctive Therapy, and Patient Age	Proposed Mechanism(s) of Action(s)	Pharmacokinetics (ADME)	Recommended Initial Dose and Patient Age	Minimum and Maximum Maintenance Doses	Serum Level Range	Selected Possible Adverse Reactions	Contraindications, Warnings, and Precautions	Drug-Drug Interactions (DDI) and Other Considerations
adrenocortico-tropic hormone (ACTH) IM injection (80 U/mL)	Epileptic spasms Monotherapy Younger than 2 y	Stimulates adrenal gland to secrete cortisol, corticosterone, aldosterone, and several weakly androgenic steroids	Not adequately characterized $t_{1/2}$ = 0.25 h (IV)	N/A	Multiple regimens Manufacturer: 75 U/m^2 IM bid for 2 wk, then taper over 2 wk to avoid adrenal insufficiency	N/A	New infections or worsening of latent infections, adrenal insufficiency, Cushing syndrome, salt and water retention, hypertension, paralytic ileus, hypokalemic alkalosis, gastric ulcers, GI bleeding, weight gain, bowel perforation, fever, behavior or mood disturbances (e.g., irritability)	Contraindications: IV use, and use with congenital or other infections, recent surgery, uncontrolled hypertension, or sensitivity to porcine proteins Do not administer with live or live-attenuated vaccines Long-term use: worsened diabetes or myasthenia gravis, cataracts, glaucoma, loss of endogenous ACTH, osteoporosis, decreased growth	DDI not studied Consider weekly to twice weekly BP and glucose monitoring, monitoring electrolyte levels intermittently (hypokalemia), and treatment with a histamine 2 (H2) blocker Hypothyroidism and hepatic cirrhosis may result in enhanced effect
brivaracetam (BRV) Tablet, oral solution 10 mg/mL, IV solution 50 mg/5 mL Schedule V	Focal onset in patients 1 month and older.	Inhibits synaptic vesicle protein SV2A	F ~100% Protein binding <20% Metabolism: 1st - hydrolysis, 2nd - CYP2C19 hydroxylation, CYP2C9 hydrolysis then renal excretion $t_{1/2}$ = 9 h	***Children***: <11 kg = 0.75-1.5 mg/kg bid 11-20 kg = 0.5-1.25 mg/kg bid 20-50 kg = 0.5-1 mg/kg bid ≥50 kg = 25-50 mg bid ***Adults***: 50 mg bid	***Children***: <11 kg = 0.75-3 mg/kg bid 11-20 kg = 0.5-2.5 mg/kg bid 20-50 kg = 0.5-2 mg/kg bid Children> 50 kg, use adult dosing ***Adults***: 25-100 mg bid	Not establish-ed	Somnolence, fatigue, N/V, dizziness, irritability, aggression, anger, agitation, tearfulness, depression, mood swings, anxiety, psychotic symptoms, disturbance in gait and coordination, and decreased WBC count	Bronchospasm, Angioedema In all stages of hepatic impairment reduce BRV dosage No adjustments required in renal insufficiency Not recommended in patients requiring hemodialysis	Rifampin decreases BRV by 45%; EIASMs decrease BRV by 19%-26% BRV increases PHT by 20% (via CYP2C19) and CBZ-epoxide **by 198%** (via inhibition of epoxide hydrolase) No added efficacy when combined with LEV

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cannabidiol (CBD) Oral solution 100 mg/mL	Seizures associated with LGS, tuberous sclerosis complex, or Dravet syndrome At least 1 y	Unclear Does not interact at CB1 or CB2 receptors Potential targets include blockade of orphan G protein-coupled receptor 55 (GPR55); agonist at transient receptor potential vanilloid receptor (TRPV1); modulation of adenosine-mediated signaling	Low F, but meals can increase by 4-fold Tmax = 2.5-5 h Extensively metabolized, principally via CYP3A4 and CYP2C19 7-OH-CBD metabolite appears to be active Protein binding >90% High-fat meals increase extent of absorption >4- to 5-fold Elimination $t_{1/2}$ ~60 h; effective $t_{1/2}$ ~17 h	LGS and Dravet syndrome: 5 mg/kg/d divided bid x 1 wk. Then may increase to 10 mg/kg/d divided bid Tuberous sclerosis complex: 5 mg/kg/d divided bid x 1 wk. Increase as tolerated weekly by 5 mg/kg/d divided bid	LGS and Dravet syndrome: 10-20 mg/kg/d divided bid Tuberous sclerosis complex: 25 mg/kg/day divided bid for tuberous sclerosis complex	Not establish-ed	Somnolence/ sedation that may be increased with concomitant CLB, potentially due to increase in *N*-des-methylclobazam Elevated transaminase level (>3x upper limit of normal), particularly at higher CBD doses and with concomitant VPA Decreased appetite, weight loss, diarrhea, vomiting, rash, fever, infections, insomnia, sleep disorder, hematologic abnormalities, increased creatinine Hypersensitivity reactions include pruritis, erythema, and angioedema	Obtain baseline serum ALT, AST and total bilirubin levels in all patients Obtain periodic liver enzyme levels, especially if patient is receiving higher dose CBD or concomitant VPA with or without CLB Artisanal formulations of CBD are not biopharma-ceutically equivalent and should not be substituted Dose should be reduced in patients with moderate to severe hepatic impairment	Drugs that inhibit or induce CYP3A4 or CYP2C19 may alter CBD kinetics - clinical relevance unclear CBD inhibits CYP2C19, so it increases the *N*-desmethyl-CLB level by 3-fold and increases DZP CBD may inhibit CYP2C9 (increasing PHT, and may increase anticoagulant effect of warfarin), CYP2B6, CYP2C8, and CYP1A2, and UGT1A9 and UGT2B7 substrates May increase EVL levels several-fold May use with ketogenic diet May administer via non-polyvinyl chloride feeding tubes

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carbamazepine (CBZ) IR/ER tablet, ER capsule, chewable tablet, suspension 100 mg/5 mL	Focal onset, GTCS, mixed (not absence) seizure types May aggravate absence or myoclonic seizures in generalized epilepsies	Enhance rapid inactivation of Na^+ channels; block L-type Ca^{2+} channel	F = 70% (ER formulations may be less), Protein binding = 76% Metabolism: CYP3A4 to CBZ 10,11 epoxide; hydroxylated and conjugated metabolites found in urine more than feces Time-dependent clearance (autoinduction) $t_{1/2}$ = 25-65 h initially, then $t_{1/2}$ = 12-17 h after autoinduction is completed 3-5 wk later	***Children***: < 6 y = 10-20 mg/kg/d divided doses 2-4x daily ***Adults:*** 2-3 mg/kg/d divided bid or tid	***Children:*** <35 mg/kg/d ***Adults:*** Increase every 2-3 wk up to 2400 mg/d (divided tid or 4x/d for IR; bid for ER)	4-12 mcg/mL	Sedation, diplopia, ataxia, dizziness, blurred vision, incoordination, hyponatremia, N/V, increased intraocular pressure, fever, chills, elevated ammonia, decreased T3, T4, increased LFTs Low WBC counts, pancytopenia Lowers 25-OH vitamin D levels and serum calcium leading to osteo-porosis Avoid in porphyrias	Contraindications: bone marrow suppression; with use of nefazadone, boceprevir, or delavirdine; in hypersensitivity to TCAs; with MAOIs (serotonin syndrome) SJS and TEN (increased with HLA-B*1502, 10x increase with Asian ancestry), aplastic anemia, agranulocytosis, DRESS, rash (SJS, TEN, rash, and DRESS moderately associated with HLA-A*3101) Arrhythmias and other cardiovascular disorders; Use with caution in 2nd and 3rd degree heart block	Induces CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4, affecting OCs, warfarin, and many other drugs CBZ metabolism is inhibited by drugs which inhibit CYP3A4 (e.g. macrolides, azol antifungals) and grapefruit juice VPA and BRV can inhibit epoxide hydrolase and increase CBZ-epoxide. In patients with hepatic impairment, monitor CBZ concentration

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cenobamate (CNB) Tablet Schedule V	Focal onset Adults	Enhance rapid and slow inactivation of Na^+ channels; inhibits non-inactivating persistent Na^+ current; positive allosteric modulator of $GABA_A$ ion channel	F = 88%, Protein binding = 60% Metabolism: glucuronidation by UGT2B7 and oxidation by multiple CYP isozymes Tmax = 1-4 h $t_{1/2}$ = 50-60 h	12.5 mg/d weeks 1 and 2 25 mg/d weeks 3 and 4 50 mg/d weeks 5 and 6 100 mg/d weeks 7 and 8 150 mg/d weeks 9 and 10	200 mg/d; may increase by increments of 50 mg/d every 2 wk up to 400 mg/d maximum	10-35 mcg/mL	Somnolence and fatigue, especially when used with CLB (see DDIs) – consider reducing CLB and other sedating ASMs Dizziness, ataxia, diplopia, blurred vision, vertigo, especially combined with other sodium-channel blocking ASMs – consider reducing those ASMs Cognitive dysfunction, N/V, constipation, decreased appetite, hyperkalemia (K^+ > 5 mEq/L) Shortening of QT interval	Contraindication: Familial short QT syndrome DRESS (multiorgan hypersensitivity) occurred in 3 of 953 patients in initial trials using rapid up titration, but in 0 of 1339 adults using approved slow titration Caution should be exercised when used with drugs which shorten the QT interval (eg, RUF) Mild to moderate renal or hepatic impairment: Use caution and reduced dose Severe renal or hepatic impairment: Use is not recommended	CNB inhibits CYP2C19, so PHT increases 70-84%, PB increases 34-37%, and *N*-desmethyl-CLB, and possibly LCM, increases substantially CNB induces CYP3A4, so CBZ decreases 23% CNB induces glucuronidation, so LTG decreases 21-52% PHT induces CNB metabolism, so CNB level decreases 28% CNB can decrease effectiveness of OCs and may decrease midazolam and bupropion levels CNB increases the omeprazole level 2-fold

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clobazam (CLB) Tablet, oral suspension (2.5 mg/mL), oral film Schedule IV	LGS Adjunctive Tx At least 2 y	$GABA_A$ receptor agonist; binds between α and γ subunits CLB is a 1,5-BDZ (all other BDZs are 1,4)	F = 100% Protein binding = 85% Tmax = 0.5-4 h Metabolized by *N*-demethylated CYP3A4 to *N*-desmethyl-CLB, which is metabolized to inactive metabolite by CYP2C19 $t_{1/2}$ = 36-42 h; 71-82 h for metabolite	≤30 kg = 5 mg/d for at least 1 week >30 kg = 5 mg bid for at least 1 week	≤30 kg = up to 10 mg bid >30 kg = up to 20 mg bid	CLB: 30-300 ng/ml N-desmethyl CLB: 300-3000 ng/ml	Rash, sedation, fever, URI, drooling, constipation, urinary tract infection, insomnia, irritability, depression, dependence, withdrawal effects, vomiting, ataxia, bronchitis, pneumonia With BDZs assess each patient's risk for abuse, misuse, and addiction	DRESS, SJS, and TEN Use with opioids can cause profound sedation, respiratory depression, coma, and death Use lower dose in elderly, known CYP2C19 poor metabolizers, and those with mild or moderate liver failure. Not studied in patients with severe hepatic or renal impairment	Weak CYP3A4 inducer, so may affect OCs CLB inhibits CYP2D6 (e.g., dextromethorphan) CBD, CNB, STP, ethanol and CYP2C19 inhibitors (e.g., fluconazole, fluvoxamine, omeprazole) inhibit CLB metabolism
clonazepam (CZP) Tablet, ODT tablet Schedule IV	LGS, myoclonic and absence seizures No age specified	$GABA_A$ receptor agonist; binds between α and γ subunits	F = 90% Protein binding = 85% Tmax = 1-4 h CYP3A4 reduces 7-nitro group; 4-amino derivative is acetylated, hydroxylated, and glucuronidated; metabolites are renally excreted $t_{1/2}$ = 30-40 h	***Children***: ≤10 y or ≤30 kg = 0.01-0.03 mg/kg/d, not to exceed 0.05 mg/kg/d given in 2-3 divided doses ***Adults***: <1.5 mg tid	***Children***: 0.1-0.2 mg/kg/d ***Adults***: <20 mg/d	0.04-0.07 mcg/mL	Sedation; ataxia, dizziness; hypersalivation; respiratory depression; porphyrogenic; impaired cognition or motor skills; agitation, anxiety, irritability, anger, nightmares, hallucination, psychoses, depression, dependence, tolerance With BDZs assess each patient's risk for abuse, misuse, and addiction	Use with opioids can cause respiratory depression, coma, and death Contraindications: acute narrow angle glaucoma, significant liver disease, sensitivity to BDZs Use caution in patients with renal impairment and underlying respiratory impairment	Worsened or new TCS VPA + CZP may cause absence SE; withdraw all BDZs gradually to help avoid SE CBZ, LTG, PB and PHT decrease CZP levels ~38% Oral antifungal agents (eg, fluconazole) may inhibit CZP metabolism

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eslicarbazepine acetate (ESL) tablet	Focal onset At least 4 y	Enhances Na^+ channel rapid inactivation; blocks hCav3.2 Ca^{2+} channel; enhances K+ conductance	F = 90% Protein binding = 40% ESL acetate hydrolyzed to ESL; renal excretion as ESL and ESL glucuronide $t_{1/2}$ = 13-20 h	***Children***: 11-21 kg = 200 mg/d 22-31 kg = 300 mg/d 32-38 kg = 300 mg/d >38 kg = 400 mg/d ***Adults***: 400 mg/d	Given once daily ***Children***: 11-21 kg = 400-600 mg/d 22-31 kg = 500-800 mg/d 31-38 kg = 600-900 mg/d >38 kg = 800-1600 mg/d ***Adults***: 800-1600 mg/d	Possibly 10-35 mcg/mL (as OXC MHD)	1%-1.5% hyponatremia (<125 mmol/L); dizziness, sedation, cognitive disturbance, blurred vision, diplopia, HA, N/V, disturbance in gait and coordination, tremor; elevated ALT, AST and bilirubin; pancytopenia, leukopenia, agranulocytosis; decreased T3 and T4 levels.	SJS and TEN (increased risk with HLA-B*1502), angioedema, DRESS, anaphylaxis Obtain baseline liver enzyme and bilirubin levels. In moderate to severe renal impairment reduce dose 50%. Has not been studied in severe hepatic impairment	EIASMs induce ESL metabolism ESL induces OCs, statins, and S-warfarin ESL inhibits CYP2C19, so it increases CLB and PHT levels
ethosuximide (ESM) Capsule (gel), oral solution	Absence	Affects low-threshold, slow, T-type Ca^{2+} thalamic currents	F ~ 93% Metabolism: CYP3A4 and CYP2E1 clearance may be nonlinear at higher doses (saturable) $t_{1/2}$ ~ 30 h (children), ~ 60 h (adults)	***Children***: 3-6 y = 250 mg/d ***Children & Adults***: 6+ y = 250 mg bid	***Children***: optimal is 20 mg/kg/d ***Adults***: 1500 mg divided bid or tid	40-100 mcg/mL	N/V, abdominal pain, anorexia, weight loss, diarrhea, sedation, dizziness, ataxia, leukopenia, HA, behavior changes, sleep disturbance, depression, hyperactivity, irritability, psychosis, hallucinations, gingival hypertrophy, tongue swelling	SJS, rash, DRESS, leukopenia, agranulocytosis, pancytopenia, eosinophilia, thrombocytopenia, systemic lupus erythematosus Abnormal liver and renal function tests Use cautiously in patients with renal or hepatic disease	Monitor CBC and CMP tests May increase TCS

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everolimus (EVL) Tablets for suspension	Tuberous sclerosis complex-associated focal Adjunctive Tx At least 2 y	mTOR inhibitor	Protein binding = 74% Intake of fatty foods can reduce systemic exposure 20%-30% CYP3A4 substrate $T_{1/2}$ = 30 h	5 mg/m^2 once daily	New dose = current dose multiplied by (target concentration divided by current concentration)	Target: 5-15 ng/mL	Stomatitis (>30%), non-infectious pneumonitis Bacterial, fungal, viral, and proto-zoal infection, including opportunistic infection; avoid live vaccines Myelosuppression, embryofetal toxicity, pneu-monia, irregular menses, fever, diarrhea, rash, lymphedema, radiation sensitization	Impaired wound healing, hypersensitivity (anaphylaxis, dyspnea, flushing, chest pain, angioedema), renal failure, increased risk of angioedema with ACE inhibitor, hyperglycemia, thrombocytopenia, neutropenia, anemia, hyper-cholesterolemia, hypertriglyceride-emia, increased LFTs, embryofetal toxicity Reduce dose in severe hepatic impairment	EVL increases CBZ, CLB, and OXC levels ~10% Avoid P-pg & strong CYP3A4 inhibitors CBD can increase EVL plasma levels, so monitoring of level is recommen-ded and may require lowering EVL dose.[12,13] Monitor CBC, glucose, and renal function periodically Withold for at least 1 week before elective surgery
felbamate (FBM) Tablet, Suspension (600 mg/5 mL)	***Refractory focal:*** Adults ***LGS:*** Adjunctive Tx At least 2 y	Enhance Na^+ channel rapid inactivation; blocks Ca^{2+} channel, inhibits NMDA receptor; potentiates $GABA_A$ conduc-tance	F = 90%, Protein binding = 23% 40%-50% excreted in urine unchanged; remainder hepatically metabolized to multiple metabolites and conjugates $t_{1/2}$ = 22 h	***Children***: 15 mg/kg/d divided tid or 4 x/d ***Children & Adults***: 14+ y = 1200 mg divided tid or 4 x/d	800-1200 mg tid	60-100 mcg/mL	HA, insomnia, N/V, abdominal pain, anorexia, weight loss, facial edema, anxiety, acne, rash, constipation, diarrhea, increased SGPT, hypophospha-temia, rhinitis, infection, somnolence, ataxia, dizziness, tremor	Aplastic anemia, hepatic failure Contraindications: history of blood dyscrasia or hepatic dysfunction Decreased clearance and increased $t_{1/2}$ in renal impairment Monitor full hematologic and LFTs before, frequently during, and after treatment	Hepatic enzyme inhibitor: Increases CBZ-epoxide, PB, PHT, and VPA levels EIASMs CBZ, PB and PHT decrease FBM level FBM decreases the progestin in OCs but not the estradiol

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fenfluramine (FFA) Oral solution (2.2 mg/mL)	LGS, Dravet syndrome At least 2 y	Both FFA and nor-FFA increase serotonin (5HT) levels, and are agonists at $5HT_{1D}$, $5HT_{2A,}$ $5HT_{2B}$, $5HT_{2C}$, $5HT_4$ receptors thereby increasing GABA signaling FFA may be positive modulator of sigma-1 receptors thereby decreasing glutamate signaling	**F ~ 68-74%** Protein binding = 50% Tmax = 3-5 h No effect of food; may be given via feeding tube Metabolized (75%) via CYP1A2, 2B6 & 2D6 to active metabolite, nor-FEN. CYP2C9, 2C19 & 3A4 may play minor role in metabolism $t_{1/2}$ = 20 h	0.1mg/kg bid	If not taking STP: 0.1-0.35 mg/kg bid (max = 26 mg/d total) If taking STP and CLB: 0.1-0.2 mg/kg bid (max = 17 mg/d total)	Not estab-lished	Decreased appetite, weight loss, diarrhea, somnolence, fatigue, sedation, lethargy, abnormal echocardiogram, serotonin syndrome	hypertension, angle closure glaucoma Mandatory REMS program for: valvular heart disease, pulmonary artery hypertension Echocardiogram is required at baseline, every 6 months on treatment, and 3-6 months after stopping FFA Contraindication: To avoid serotonin syndrome, do not use within 14 days of MAOI and use with caution with other serotonergic drugs Dose adjustment needed in severe renal impairment & mild, moderate & severe hepatic impairment.	STP and CLB can increase FFA levels and decrease levels of nor-FFA Strong CYP1A2 and 2D6 inhibitors increase FFA levels Strong CYP3A4, CYP1A2, CYP2B6 inducers can reduce FFA levels 5HT1A, 1D, 2A & 2C receptor antago-nists (e.g. cypro-heptadine) may reduce FFA efficacy Serotonergic agents (e.g. SSRIs, SNRI, TCA, MAOIs, trazodone, dextromethorphan) increase risk of serotonin syndrome

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gabapentin (GBP) Capsule, tablet, refrigerated oral solution (250 mg/5 mL)	Focal onset Adjunctive Tx At least 3 y	Binds presynaptic α_2-δ subunit of voltage-activated Ca^{2+} channel to modulate Ca^{2+} current	Saturable oral absorption via L-amino acid transferase: F = 60% at 900 mg/d, 34% at 2400 mg/d, and 27% at 4800 mg/d total Protein binding = 3% Renal excretion $t_{1/2}$ = 6 h	***Children***: 3-11 y = 10-15 mg/kg/d divided tid ***Children & Adults***: 12+ y = 300 mg tid	***Children***: 3-4 y = 40 mg/kg/d divided tid 5-11 y = 25-35 mg/kg/d divided tid ***Children & Adults***: 12+ y = 600 mg po tid, but may increase up to 2400-3600 mg/day	4-8.5 mcg/mL	Drowsiness, sedation, fatigue, driving impairment, ataxia, dizziness, nystagmus, diplopia, peripheral edema, weight gain Neuropsychiatric changes (emotional, aggression, cognitive and concentration problems, hyperkinesia) in children aged 3-12	DRESS, anaphylaxis, angioedema Respiratory depression when used with CNS depressants, including opioids, or in the setting of respiratory impairment: consider initiating GBP at lower dose, monitoring patients, and adjusting dose Reduce dose in renal impairment, and in hemodialysis	GBP concentration is increased by morphine GBP decreases hydrocodone exposure Magnesium/ aluminum antacids decrease GBP level 20%
ganaxolone (GNX) oral suspension (50 mg/mL), Schedule V	Cyclin-dependent kinase-like 5 (CDKL5) Deficiency Disorder At least age 2	Positive allosteric modulator (PAM) of $GABA_A$ receptor	F = 99% Protein binding = 50% Tmax = 2-3 h Metabolized by CYP3A4/5, CYP2B6, CYP2C19, and CYP2D6 $T_{1/2}$ = 34 h	Must be taken with food Children: < 28 kg = 6 mg/kg three times daily (18 mg/kg/day) Children & Adults: > 28 kg = 150 mg three times daily (450 mg daily)	Must be taken with food Children: < 28 kg = 21 mg/kg three times daily (63 mg/kg/day) maximum Children & Adults: > 28 kg = 600 mg three times daily (1800 mg daily) maximum	Not estab-lished	Somnolence and sedation (may be potentiated by CNS depressants, including opioids, antidepressants, and alcohol), pyrexia, salivary hypersecretion, and seasonal allergy	Reduce dose in hepatic impairment Ganaxolone exposures when given in renal insufficiency (creatinine clearance <90 mL/min) are not expected to be clinically significant	Avoid concomitant use with strong or moderate CYP3A4 inducers (e.g., CBZ, PHT, PB, and PRM). If these are unavoidable, do not exceed max GNX dose

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lacosamide (LCM) Tablet (IR & ER), oral solution (10 mg/mL), IV solution (200 mg/20 mL) Schedule V	***Focal onset:*** Monotherapy At least 1 mo ***Primary GTCS:*** Adjunctive Tx At least 4 y	Enhances Na^+ channel slow inactivation	F = 100% Demethylated by CYP3A4, CYP2C9, and CYP2C19; 95% renally excreted, 40% as LCM/60% as metabolites $t_{1/2}$ = 15 h	***Children****:* 11-49 kg = 1 mg/kg bid ***Children & Adults***: 50+ kg = 50 mg bid 17+ = 100 mg bid in monotherapy, and 50 mg bid in adjunctive Tx	***Children****:* 11-29 kg = 3-6 mg/kg bid 30-49 kg = 2-4 mg/kg bid ***Children & Adults***: *Adjunctive Tx:* 50+ kg or at least 17 y = 100-200 mg bid *Monotherapy*: 50+ kg or at least 17 y = 150-200 mg bid	4-12 mcg/mL	Dizziness, ataxia, diplopia, HA, nausea, dose-dependent prolongation of PR interval, atrial fibrillation, atrial flutter, and ventricular arrhythmias	Bradycardia, AV block and ventricular tachyarrhythmia, rarely resulting in asystole, cardiac arrest and death. This occurs mostly in proarrhythmic conditions or when taken with medications that affect cardiac conduction (sodium channel blockers, beta-blockers, calcium channel blockers, or potassium channel blockers) or that prolong the PR interval (eg, sodium channel blocker ASMs) For these instances and in 2nd- or 3rd-degree block, obtaining an EKG before treatment and once reaching steady state LCM dose is recommended Syncope (especially with diabetes), DRESS	May "load" with 200 mg oral or IV LCM dose reduction may be needed in patients with renal or hepatic impairment and those who are taking drugs that strongly inhibit CYP3A4 or CYP2C9 or CYP2C19

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lamotrigine (LTG) Tablet (standard, chewable-dispersable, orally disintegrating, and ER)	***Focal onset*:** Adjunctive Tx and conversion to monotherapy At least 16 y ***Focal onset, LGS, primary GTCS*:** Adjunctive Tx At least 2 y	Enhances Na^+ channel rapid inactivation; inhibits Ca^{2+} channels; activates postsynaptic HCN channels	F = 98% Protein binding = 55% Glucuronidated to inactive metabolite $t_{1/2}$ = 25 h, 13 h with EIASMs, and 70 h with VPA	25 mg every 2nd day (with VPA only) 25 mg/d 50 mg/d (with EIASMs only)	***For adults, and children >12 y*:** 50-100 mg bid with VPA alone 75-200 mg bid without VPA or EIASMs 150-250 mg bid with EIASMs ***For children ages 2-12 y*:** See PI for weight-based dosing	4-20 mcg/mL	Dizziness, HA, diplopia, ataxia, tremor, nausea, vomiting, somnolence, insomnia in high doses; aseptic meningitis (rare)	Rash, SJS, TEN, DRESS Hemophagocytic lymphohistocytosis (rare) Blood dyscrasias May widen EKG QRS. Avoid in 2° and 3° heart block. Use caution with ventricular arrhythmias, cardiac disorders and channelopathies (e.g., Brugada syndrome)	EIASMs (CBZ, CNB, PB, PHT, PRM), ethinyl estradiol , rifampin, and ritonavir decrease LTG level 40-50% Pregnancy decreases LTG level ~50%-67% VPA increases LTG level >2-fold Reduce dose in moderate-severe hepatic impairment
levetiracetam (LEV) IR/ER tablet, orally disintegrating tablet, oral solution (100 mg/mL), IV solution (500 mg/5 mL)	***Focal onset:*** At least 1 month ***Myoclonic in JME:*** Adjunctive Tx At least 12 y ***Primary GTCS:*** Adjunctive Tx At least 6 y	Inhibits synaptic vesicle protein SV2A; partially inhibits N-type Ca^{2+} currents	F = 100% PPB <10% Enzymatic hydrolysis (non-CYP) to inactive metabolite ~66% renally eliminated unchanged $t_{1/2}$ = 7 h	***Children*:** 1-5 mo = 7 mg/kg bid 6 mo - <4 y = 10 mg/kg bid 4 - <16 y = 10 mg/kg bid ***Children & Adults*:** 16+ y: 500 mg bid	***Children*:** 1 - <6 mo = 21 mg/kg bid 6 mo - <4 y = 25 mg/kg bid 4 - <16 y = 30 mg/kg bid ***Children & Adults*:** 16+ y: 1500 mg bid (myoclonic JME & primary GTCS) or 500-1500 mg bid (focal onset)	20-50 mcg/mL	Irritability, anger, aggression, depression, suicidal ideation, psychotic symptoms (esp. in children) Somnolence, fatigue, asthenia, dizziness, infection, ataxia, incoordination, anemia, pancyto-penia, leukopenia, neutropenia, agranulocytosis, thrombocytopenia <4 y: increased diastolic BP	SJS and TEN; DRESS (rare), rhabdomyo-lysis, angioedema, anaphylaxis Worsening of seizures, including in patients with *SCN8A* mutations	Plasma LEV level may gradually decrease during pregnancy In patients with renal insufficiency, dose must be reduced propor-tionate to CrCl; hemodialysis eliminates 50% in 4 h

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oxcarbazepine (OXC) Tablet (IR and ER), oral suspension (300 mg/5 mL)	Focal onset ***Monotherapy:*** At least 4 y ***Adjunctive Tx***: At least 2 y	Enhances Na^+ channel rapid inactivation; modulation of high-voltage activated Ca^{2+} channel; enhances K+ conduc-tance	F = 100% Protein binding = 40% OXC is prodrug: reduced 80% to S-licarbazepine and 20% to R-licarbazepine (the MHDs), by hepatic cytosol enzymes MHD is glucuronidated, then renally excreted $t_{1/2}$ = 9 h (MHD) and 2 h (OXC)	***Children***: 2-16 y = 8-10 mg/kg/d divided bid, not to exceed 300 mg bid ***Adults***: 17+ y = 300 mg bid (wk 1), then add no more than 300 mg bid each wk	**Children 2-16 y** <20 kg = 16-60 mg/kg/d 20-29 kg = 900 mg/d 30-39 kg = 1200 mg/d 40+ kg = 1800 mg/d (All doses are divided bid) ***Adults***: 17+ y = 1200-2400 mg divided bid (tid improve tolerability)	10-35 mcg/mL (as MHD)	Dizziness, cognitive problems, somnolence, fatigue nausea, HA, diarrhea, vomiting, URI, constipation, dyspepsia, ataxia, incoordination, nervousness, pancytopenia, agranulocytosis, leukopenia Hyponatremia (<125 mmol/L = 2.5% but increases with age)	SJS and TEN (risk increases with HLA-B*1502, 10x increase with Asian ancestry), DRESS Anaphylaxis, angioedema, cross hypersensitivity with CBZ Mild to moderate hepatic failure: No adjustment Renal failure: Adjust dose; MHD is not dialyzable, but metabolites may be	Induces CYP3A4: At 1200 mg/d, it decreases OC estrogen level Inhibits CYP2C19: At >1200 mg/d, the PHT level increases 40% CBZ, PB, and PHT and rifampin decrease OXC levels 29%-40% Unlike CBZ, no autoinduction or formation of a 10,11 epoxide
perampanel (PER) Tablet, oral solution (0.5 mg/mL) Schedule III	***Focal onset:*** At least 4 y ***Primary GTCS***: Adjunctive Tx At least 12 y	Selective, non-competitive antagonist of AMPA glutamate receptor, inhibiting synaptic-driven influx of Na^+	F = 100%, but food delays by 2 h PPB= 96% Metabolized by CYP3A4 and CYP3A5 to multiple inactive metabolites $T_{1/2}$ = 105 h (~24 h with EIASMs)	***Children and Adults***: 2 mg qhs (4 mg with EIASMs) Suggest giving at HS	***Children and Adults***: Increase no faster than 2 mg/wk (long $t_{1/2}$ suggests slower titration every 3-4 weeks) Minimum = 4-6 mg/day Higher doses may be needed if taking EIASM (8-12 mg/day)	Not estab-lished	Dizziness, vertigo, somnolence, fatigue, irritability, hostility, aggression, anger, HA, ataxia, anxiety, paranoia, euphoric mood, agitation, falls, nausea, vomiting, weight gain, abdominal pain, ataxia, mental status changes	Homicidal ideation (6 in 4368 subjects in preclinical trials), suicidal thoughts, DRESS Use lower dose in mild and moderate hepatic impairment No dose adjustment for mild-moderate renal insufficiency Not recommended in severe hepatic or severe renal impairment	CBZ, OXC, ESL and PHT (not PB) decrease PER plasma level PER at 12 mg/d increases OC metabolism

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phenobarbital (PB) Tablets, elixir (4 mg/mL), IV solution Schedule IV	Focal onset and generalized onset	Nonspecific $GABA_A$ receptor binding: affects both synaptic (phasic) and extra-synaptic (tonic) $GABA_A$ receptors	F ~95% PPB = 45% Hepatically parahydrox-ylated and glucuronidated 25%-50% of unchanged PB and its metabolites are renally excreted $t_{1/2}$ = 79 h (110 h in children and newborns)	***Children***: < 6 y = 3-5 mg/kg/d 6-12 y = 2-3 mg/kg/d ***Children & Adults***: 13+ y = 60 mg/d or 1-4 mg/kg/d	***Children***: Infants = 5-6 mg/kg/d 1-5 y = 8 mg/kg/d 6-12 y = 4-6 mg/kg/d ***Children & Adults***: 13+ y = 1-4 mg/kg/d Adult maximum = 240 mg daily Taper very slowly after chronic use, because barbiturate withdrawal can cause convulsions and delirium and may be fatal	15-45 mcg/mL	Sedation, cognitive slowing, HA, depression, N/V, tolerance, dependence, confusion, decreased REM sleep, hepatic dysfunction, osteoporosis, megaloblastic anemia with chronic use, hypoventilation, bradycardia, and hypotension With pain: Agitation or delirium Children: Irritability, hyperactivity, reduced IQ	SJS, TEN, DRESS, rash, angioedema, respiratory depression, synergistic effects with ETOH or sedatives, psychological and physical dependence Caution should be used with concomitant pain medications and CNS depressants Do not use in hepatic encephalo-pathy, porphyria, marked hepatic impairment, or marked respiratory disease	Elimination is increased by diuretics, alkaline urine and activated charcoal but is decreased by VPA MAOIs prolong the effects of PB PB is a strong CYP3A4 inducer: It increases the metabolism of PHT, LTG, OCs, warfarin, corticosteroids, and many other drugs Monitor CBC and CMP results

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phenytoin (PHT) and fosphenytoin (FOS) ***PHT***: Delayed-release (sodium salt) capsule – has 8% less PHT than prompt (acid) tablet and suspension (25 mg/mL) ***PHT and FOS***: IV (FOS is prodrug of PHT and has higher molecular weight due to PO_4 molecule) (500 mg PE/10 mL)	Focal onset, GTCS Convulsive status epilepticus, prevention and treatment of seizures during neurosurgery, and short-term use when administration of oral PHT is not possible (FOS only)	Enhances rapid inactivation of Na^+ channels	F ~100% (varies by formulation) Protein binding = 90%-95% Metabolized by CYP2C9 and CYP2C19 Excreted in bile as inactive metabolites, reabsorbed in intestines, then renal tubular secretion Nonlinear elimination (zero order) PK (saturable at higher doses) $t_{1/2}$ = Adult: 22 h (7-40 h); longer at higher doses and older age	***Children***: 5 mg/kg/d divided bid or tid ***Adults***: 300 mg/d divided tid ***Children & Adults:*** IV load for status epilepticus: 15-20 mg/kg (PHT) at ≤50 mg/min or 15-20 mg PE/kg (FOS) at ≤2 mg PE/kg/min (children) or ≤150 mg PE/min (adult) IV non-emergent load: 0-16 y = 10-15 mg PE/kg (FOS) at 1-2 mg PE/kg/min or 150 mg PE/min whichever is slower 17+ y = 10-20 mg PE/kg (FOS) at ≤150 mg PE/min	***Children***: 4-8 mg/kg/d divided bid or tid 6-17 y = up to 300 mg/d given once daily or divided bid or tid ***Adults***: 6-17 y = 300-600 mg/d given once daily or divided bid or tid	10-20+ mcg/mL (~10% as free PHT)	Rash, nystagmus, incoordination, dysarthria, ataxia, cognitive slowing, gum hyperplasia, hypertrichosis, lymphadenopathy, pseudolymphoma, lymphoma, Hodgkin disease, low patelets, megalobalastic anemia, leukopenia, pancytopenia, osteoporosis, decreased vitamin D level, porphyrogenic IV PHT: thrombophlebitis, peripheral neuropathy, cerebellar atrophy IV PHT and FOS may produce purple glove syndrome. FOS may produce transient burning, itching and paresthesia due to the phosphate load Decreases T4 level; increases glucose, GGT, and alkaline phosphatase levels	FOS contraindicated in sinus bradycardia, sinoatrial block, 2nd- and 3rd-degree AV block and Stokes-Adams attacks SJS and TEN (especially in patients with Chinese ancestry with HLA-B*1502), DRESS, angioedema, hepatotoxicity PHT must never be given IM or IV in diluents other than normal saline or >50 mg/min (hypotension, bradyarrhythmia, QT prolongation, ventricular tachycardia or fibrillation, asystole and death) FOS may be given IM and IV up to 150 mg PE/min EKG, respiratory and blood pressure monitoring is essential during IV PHT and IV FOS infusion	CNB, ESM, FBM, OXC, MSM, TPM, acute alcohol intake, and many other drugs increase PHT levels CBZ, DZP, VGB, chronic alcohol intake and many other drugs decrease PHT levels PB and VPA have variable effects on PHT and vice versa; PHT induces metabolism of CBZ, FBM, LTG, OXC, TPM, and many other drugs In SE, the full effect of IV PHT and FOS is delayed, so concomitant administration of an IV BDZ is needed Monitor unbound (free) serum level in hepatic or renal impairment or hypoalbuminemia Slow CYP2C9 and CYP2C19 metabo-lism occurs in 1% and 3% of persons, respectively, requiring lower maintenance doses

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pregabalin (PGB) Capsule, oral solution 20 mg/mL (Extended release form not FDA-approved for epilepsy) Schedule V	Focal onset Adjunctive Tx At least age 1 month	Binds pre-synaptic α_2-δ subunit of Ca^{2+} channel to modulate Ca^{2+} current, resulting in decreased glutamate concentration, NE level, and substance P release	F = 90% Protein binding = low Negligible metabolism, renal excretion $t_{1/2}$ = 6 h	***Children***: <30 kg = 3.5 mg/kg/d (1 mo to <4 y = divided tid; 4+ y = divided bid or tid) 30+ kg = 2.5 mg/kg/d divided bid or tid ***Adults:*** 17+ y = ≤150 mg/d divided bid or tid	***Children***: <30 kg = 14 mg/kg/day (1 mo to <4 y = divided tid; 4+ y = divided bid or tid) 30+ kg = 10 mg/kg/d divided bid or tid ***Adults:*** 600 mg divided bid or tid Reduce dose for CrCl ≤60, mL/min	3-10 mcg/mL	Dizziness, somnolence, dry mouth, peripheral edema, diplopia, blurred vision, weight gain, ataxia, attention and concentration problems; increased CK level (uncommon)	Angioedema (face, mouth, throat, larynx), rash, hives, dyspnea, wheezing Respiratory depression with concomitant CNS depressants (including opioids) or with underlying respiratory impairment	No DDI with ASMs Additive cognitive and gross motor effects with opiates, benzodiazepines, and ethanol Weight gain occurs when taken with thiazolidinedione anti-diabetes drugs
primidone (PRM) Tablet Schedule IV	Focal onset and TCS	Nonspecific $GABA_A$ receptor binding: affects both synaptic (phasic) and extra-synaptic (tonic) $GABA_A$ receptors	F = 100% Protein binding <5% PRM and its metabolites (PB and PEMA) are active ASMs $t_{1/2}$ = 12 h (derived PB is 79 h)	***Children***: <8 y = 50 mg qhs ***Children & Adults***: 8+ y = 100-125 mg qhs	***Children***: <8 y = 375-750 mg/d (10-25 mg/kg/d) ***Children & Adults***: 8+ y = 750-2000 mg/d divided tid or 4x/d	6-12 mcg/mL (plus derived PB)	Diplopia, nystagmus, drowsiness, ataxia, vertigo, N/V, fatigue, irritability, emotional disturbance, impotence	Contraindications: Porphyria, PB allergy Rash, RBC hypoplasia and aplasia, agranulocytosis, megaloblastic anemia (folate responsive)	DDIs similar to PB

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rufinamide (RUF) Tablet, oral suspension (40 mg/mL)	LGS Adjunctive Tx At least 1 y	Enhances Na^+ channel rapid inactivation	F ≥ 85% PPB = 34% Absorption is slow (Tmax = 4-6 h) and nonlinear PK due to low solubility at higher doses, but is helped by food Extensively metabolized by hydrolysis, then renal excretion $t_{1/2}$ = 6-10 h	***Children***: 10 mg/kg/d (max 400 mg/d) divided bid ***Adults***: 400-800 mg/d divided bid; lower dose w/ VPA	***Children***: Child maximum = 45 mg/kg/d (up to 3200 mg/d) divided bid ***Adults***: Adult maximum = 3200 mg/d divided bid Take with food	5-48 mcg/mL	Shortening of QT interval, leukopenia HA, N/V, dizziness, fatigue, ataxia, gait disturbances, somnolence, coordination problems	Contraindication: Familial short QT syndrome DRESS, Rash, SE Caution should be exercised when used with drugs which shorten the QT interval Not recommended in patients with severe liver failure	Induces CYP3A4, so decreases estradiol 22% at ≥800 mg bid and mildly decreases CBZ and LTG levels Mildly increases PB and PHT levels VPA increases RUF level 16%-70% CBZ, PHT, PB, and PRM decrease RUF level 19%-46% Hemodialysis: RUF level decreases 30%
stiripentol (STP) Capsule, powder for suspension, sachets	Dravet syndrome Adjunctive Tx with clobazam At least 6 months weighing at least 7 kg	Positive allosteric modulator of $GABA_A$ receptor at γ and δ subunits; indirect effect to raise plasma level of CLB and its metabolite; inhibits LDH activity; inhibits T-type Ca currents	Precise F value unknown but likely high, as majority of drug (parent and metabolite) eliminated in urine PPB = 99% Nonlinear; Metabolized by CYP1A2, CYP2C19, and CYP3A4 $t_{1/2}$ = 4.5-13 h (longer at higher doses)	10-15 mg/kg/d divided bid, then increase every 1-2 wk	50 mg/kg/d divided bid or tid depending on age and weight Maximum 3000 mg/day divided bid or tid	Not establish-ed	Somnolence, decreased weight and appetite, neutropenia, thrombocyto-penia, agitation, hypotonia, N/V, tremor, dysarthria, insomnia	Alcohol and other CNS depressants may increase sedation and somnolence Not recommended for use in patients with moderate or severe renal or hepatic impairment	STP inhibits CYP3A4 and CYP2C19: it increases CLB level 2-fold, increases *N*-desmethyl-CLB level 5-fold If somnolence occurs, consider CLB dose reduction of 25%-50% Powder contains phenylalanine PHT, CBZ, and PB decrease STP levels

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tiagabine (TGB) Tablet	Focal onset Adjunctive Tx At least 12 y	Selective GABA reuptake inhibitor (SGRI): inhibits GABA reuptake from synapse into neurons and glia	F = 90% Protein binding= 96% Metabolized by CYP3A4 and glucuronidation Metabolites are excreted in urine and feces $t_{1/2}$ = 8 h (2-5 h with EIASMs)	***Children & Adults***: 12+ y = 4 mg once daily (use lower initial dose if not taking EIASMs) Do not use loading dose	***Children & Adults***: 12+ y = 32-56 mg/d divided bid (56 mg is with concomitant EIASMs)	5-70 mcg/mL	Dizziness, N/V, somnolence, fatigue, tremor, cognitive slowing, anxiety, diarrhea, abdomen pain, worsened pre-existing spike-and-slow-wave complexes in EEG	Serious rash, moderately severe generalized weakness, may bind ocular melanin Worsened generalized seizures and SE in people with epilepsy Seizure and SE in patients without epilepsy	PHT, CBZ, PB, and PRM decrease TGB levels VPA increases free TGB level 40% due to high protein binding Hepatic failure increases free TGB level Take with food

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topiramate (TPM) Tablet, capsule (IR and ER), sprinkle	***Focal onset and GTCS:*** At least 2 y ***LGS:*** Adjunctive Tx At least 2 y	Inhibits voltage-dependent Na^+ channels, kainate glutamate receptors, and carbonic anhydrase; enhances $GABA_A$ currents	F = 80% Protein binding = 15%-41% and decreases at higher concentrations Not extensively metabolized. Urinary excretion 70% as unchanged drug $t_{1/2}$ = 21 h	***Children***: 2-9 y = 25 mg qpm ***Children & Adults***: 10+ y = 25 mg bid	≤11 kg = 75-125 mg bid 12-22 kg = 100-150 mg bid 23-31 kg = 100-175 mg bid 32-38 kg = 125-175 mg bid >38 kg = 125-200 mg bid	7-30 mcg/mL	Language and cognitive (confusion, memory, word-finding, attention, concentration) disturbances Kidney stones, increased urinary Ca^{2+}, decreased urinary citrate Paresthesia, anorexia, weight loss, fatigue, somnolence, dizziness, anxiety, depression or mood problems, abnormal vision, fever, taste perversion, diarrhea, URI	SJS and TEN. Acute myopia w/ secondary angle closure glaucoma and vision loss, visual field defects Oligohydrosis and hyperthermia (esp. children) Hypochloremic MA; chronic untreated MA in children may lead to decreased growth, increased alkaline phosphatase level, hypophosphatemia, and osteomalacia Hyperammonemia and encephalopathy +/- VPA Hypothermia with VPA Use cautiously with CNS depressants	Decreased OC efficacy (TPM >200 mg/d) Monitor Li^{2+} level with higher-dose TPM Renal impairment: use ½ dose and supplement after hemodialysis PHT and CBZ lower TPM level Use with other carbonic anhydrase inhibitors (AZM, ZNS) increases risk of MA and kidney stones Other DDIs exist Hydration is recommended to reduce kidney stone formation

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valproic acid (VPA) and divalproex sodium Tablet (IR and ER), capsule, sprinkle, IV solution (100 mg/mL)	***Focal onset and absence:*** Monotherapy ***Multiple seizure types that include absence:*** Adjunctive Tx	Inhibits voltage-dependent Na^+ and T-type Ca^{2+} channels, enhances biosynthesis and inhibits degradation of GABA	F = 90% at 40 mcg/mL and 81.5% at 135 mcg/mL, so free VPA level is dose-dependent, (ER's F = 85% of IR) Metabolism: >40% mito-chondrial β-oxidation, 30%-50% glucuron-idation, <15%-20% other oxidation Nonlinear PK: total level increases with dose to a lesser extent due to saturable PPB, free VPA level increases linearly Elimination PK: children 3 mo-10 y have 50% faster clearance, those aged 68+ y have ~40% lower clearance $t_{1/2}$ = 9-16 h	***Children & Adults***: 10+ y = 15 mg/kg/d; increase by 5-10 mg/kg/d at weekly intervals <10 y = dose not established but children aged 3 mo-10 y have 50% higher clearance expressed on weight	***Children & Adults***: 10+ y = 60 mg/kg/d divided bid or tid (IR) or daily (ER)	50-100+ mcg/mL	Hyperammonemia +/- encephalopa-thy (esp. w/ TPM); decreased platelet count and aggregation, coagulopathy; hypothermia, tubulointerstitial nephritis Weight gain or loss, abdominal pain, anorexia, N/V, increased appetite, diarrhea, constipation Irregular menses, polycyctic ovary syndrome, potential fertility problems in males Tremor, alopecia, hair texture change, blurred vision, ataxia, amnesia, asthenia, depression, diplopia, dizziness, peripheral edema, rash, abnormal thinking, tinnitus	***Contraindications***: Women of child-bearing potential and in pregnancy unless other ASMs fail, and they are using effective contra-ception (esp. true for migraine prophylaxis); hepatic disease or significant dysfunction; mitochondrial disorders with *POLG* mutation, urea cycle disorders Hepatotoxicity (esp. in children <2 y receiving multiple ASMs, and in patients with metabolic disorders, intellectual delay, organic brain disease, and mitochondrial disorders) Pancreatitis; Gestational: Substantial risk of major congenital malformations (esp. neural tube defects), intellectual delay, decreased IQ, and autism	Monitor periodically: Platelet count, INR, PTT, CBC, NH_3 levels, and LFTs CBZ, PHT, PB, PRM, methotrexate and rifampin decrease VPA level FBM increases VPA level Monitor VPA levels with aspirin, carbapenem, and estrogen-OCs VPA may inhibit metabolism or affect binding of CZP, DZP, ESM, LTG, PHT, and TGB With RUF, start VPA at a low dose and increase to clinical effect TPM with VPA increases risk of encephalopathy and increased NH_3 level Other DDIs: TCAs, propofol, warfarin, zidovudine CBD with VPA increases risk of elevated LFTs

Table 1. Antiseizure medications (ASMs) for chronic and subacute treatment of seizures. January 2024. (See Abbreviations.)

Drugs, Formulations, and DEA Scheduling	FDA-Approved Seizure/Syndrome Type, Mono- or Adjunctive Therapy, and Patient Age	Proposed Mechanism(s) of Action(s)	Pharmacokinetics (ADME)	Recommended Initial Dose and Patient Age	Minimum and Maximum Maintenance Doses	Serum Level Range	Selected Possible Adverse Reactions	Contraindications, Warnings, and Precautions	Drug-Drug Interactions (DDI) and Other Considerations
vigabatrin (VGB) Tablet, powder for oral solution (500 mg)	***Epileptic spasms (ES):*** Monotherapy 1 mo to 2 y ***Refractory FIAS:*** Adjunctive Tx At least 2 y	Irreversibly inhibits GABA trans-aminase (GABA-T) resulting in increased GABA concentra-tion in the CNS	F = 100% PPB = 40% Extensive binding to RBCs. No significant hepatic metabolism. Renal excretion $t_{1/2}$ = 10 h (10+ y) or 5.7 h (infants)	***ES***: 25 mg/kg bid ***FIAS***: ***Children***: 2-16 y = 175-250 mg bid (weight-based) ***Children & Adults***: >60 kg or 17+ y = 500 mg bid	***ES***: 75 mg/kg bid ***FIAS***: ***Children***: 2-16 y = 525-1000 mg bid (weight-based) ***Children & Adults***: >60 kg or 17+ y = 1500 mg bid	Not establish-ed	Somnolence, nystagmus, dizziness, tremor, blurred vision, uncoordination, impaired memory, weight gain, arthralgia, ataxia, tremor, URI, aggression, diplopia, peripheral neuropathy in adults, edema	Permanent visual field constriction, central retinal damage with decreased visual acuity, abnormal MRI signal changes and intramyelinic edema in infants, decreased ALT and AST levels, anemia, sedation Adjust dose in renal impairment	Induces CYP2C9, so decreases PHT level 18% Increases CZP level 30% Stop if no substantial FIAS decrease in 3 mo Complete REMS follow-up forms
zonisamide (ZNS) Capsule	Focal onset Adjunctive Tx At least 16 y	Enhances rapid inactivation of Na^+ channels; decreased low-threshold T-type Ca^{2+} currents; binds $GABA_A$ BDZ ionophore; mild carbonic anhydrase-inhibiting effects; facilitates dopamine and serotonin transmission	F = 100% Protein binding= 40% to albumin Linear PK up to 800 mg/d but increases disproportion-ally above that dose due to an 8-fold binding to RBCs Partial hepatic metabolism Renal excretion $t_{1/2}$ = 69 h, 27-38 h with EIASM, 46 h with VPA	***Children & Adults***: 16+ y = 100 mg/d, increase by 100 mg every 2 weeks	***Children & Adults***: 16+ y = increase by 100 mg every 2 weeks to 400-600 mg/d given once daily or bid	10-40 mcg/mL	Somnolence, fatigue, anorexia, weight loss, dizziness, ataxia, agitation, irritability, depression, psychosis, speech or language disturbance, psychomotor slowing, kidney stones (risk increased when used with TPM or acetazolamide), rash, hyperammonemia and encephalopathy Acute myopia and secondary angle closure glaucoma	SJS, TEN, DRESS, hepatic necrosis, agranulocytosis, decreased WBC counts, aplastic anemia, oligohydrosis and hyperthermia in children, hyperchloremic MA (especially if used with other carbonic anhydrase inhibitors) Chronic untreated MA may lead to decreased growth rate in children, increased risk of kidney stones, increased alkaline phosphatase level, hypophosphatemia, osteomalacia	Adjust dose in patients with renal impairment ZNS $t_{1/2}$ significantly decreases with CBZ, PB, and PHT, and moderately decreases with VPA Increased severity of MA and risk of kidney stones when used with other carbonic anhydrase inhibitors (AZM, TPM) ZNS is a non-arylamide sulfonamide- use with caution in patients with sulfa allergy

Table 2. Antiseizure Medications (ASMs) for treatment of acute repetitive seizures. January 2024. (See Abbreviations.)

Drugs, Formulations, and DEA Scheduling	FDA Approved Seizure/ Syndrome Type, Mono- or Adjunctive Therapy, and Patient Age	Proposed Mechanism(s) of Action(s)	Pharmacokinetics (ADME)	Recommended Initial Dose and Patient Age	Minimum and Maximum Maintenance Doses	Selected Possible Adverse Reactions	Contraindications, Warnings, and Precautions	Drug-Drug Interactions (DDI) and Other Considerations
diazepam (DZP) Intranasal spray (individual spray units = 5 mg, 10 mg, 15 mg, 20 mg) Schedule IV	Seizure cluster, acute repetitive seizures At least 6 y	$GABA_A$ receptor agonist; binds between α and γ subunits	Data from adults and children >6 y: Tmax = 1.5 h F = 97% compared with IV; 2- to 4-fold-less variability in systemic exposure than rectal gel Elimination PK same as rectal DZP	***Children***: 6-11 y (0.3 mg/kg) 10-18 kg = 5 mg 19-37 kg = 10 mg 38-55 kg = 15 mg 56-74 kg = 20 mg ***Children & Adults***: 12+ y (0.2 mg/kg) 14-27 kg = 5 mg 28-50 kg = 10 mg 51-75 kg = 15 mg 76+ kg = 20 mg	2nd dose may be given 4-12 h later prn Maximum dose: 2 doses to treat a single episode, and no more than 1 episode every 5 days Not indicated for chronic daily therapy	CNS depression, somnolence, HA, nasal discomfort, dysgeusia, epistaxis See next entry (DZP rectal gel) for complete listing	Use with opioids can cause respiratory depression, coma, and death Contraindicated in narrow-angle glaucoma With BDZs assess each patient's risk for abuse, misuse, and addiction	No dose adjustments required based on concomitant medications See next entry (DZP rectal gel) for complete listing
diazepam (DZP) Rectal gel (5 mg/mL) Schedule IV	Acute repetitive seizures At least 2 y	$GABA_A$ receptor agonist; binds between α and γ subunits	F = 90% Tmax = 1.5 h Protein binding = 95+% Metabolism (CYP2C19 and CYP3A4) principally to *N*-desmethylDZP (active) Clearance is highly variable likely due to CYP2C19 slow metabolism in 3%-5% of Caucasians Rapid initial distribution phase (~1 h) is followed by a prolonged terminal elimination phase (30-60 h) Terminal elimination $t_{1/2}$ of active metabolite *N*-desmethylDZP is up to 100 h	***Children:*** 2-5 y = 0.5 mg/kg 6-11 y = 0.3 mg/kg 12+ y = 0.2 mg/kg ***Adults***: 0.2 mg/kg	Weight-based, repeat once prn 4-12 h after first dose Give no more often than every 5 days or 5x/mo Not recommended for chronic, daily use due to tolerance	Sedation, dizziness, depression, fatigue, motor and cognitive impairment, dependence Tonic SE has occurred with IV DZP use for absence SE Withdrawal effects after chronic use	Use with opioids can cause respiratory depression, coma, and death Contraindicated in narrow-angle glaucoma With BDZs assess each patient's risk for abuse, misuse, and addiction	May cause absence SE Clearance is slowed 2- to 5-fold with alcoholic cirrhosis CNS-depressant effects potentiated by VPA, PB, narcotics, phenothiazines, MAOIs, and other antidepressants Inhibitors of CYP2C19 (cimetidine) and CYP3A4 (azoles) may increase DZP levels Inducers of CYP2C19 (rifampin) and CYP3A4 (CBZ, PB, PHT) may increase elimination

Table 2 (continued). Antiseizure Medications (ASMs) for treatment of status epilepticus and acute repetitive seizures. January 2024. (See Abbreviations.)

Drugs, Formulations, and DEA Scheduling	FDA Approved Seizure/ Syndrome Type, Mono- or Adjunctive Therapy, and Patient Age	Proposed Mechanism(s) of Action(s)	Pharmacokinetics (ADME)	Recommended Initial Dose and Patient Age	Minimum and Maximum Maintenance Doses	Selected Possible Adverse Reactions	Contraindications, Warnings, and Precautions	Drug-Drug Interactions (DDI) and Other Considerations
midazolam (MDZ) Intramuscular 50 mg/10 mL multidose vial IM autoinjector (10 mg in 0.7 mL) Schedule IV	Status epilepticus Adult	$GABA_A$ receptor agonist; binds between α and γ subunits	F = 44% Protein binding = 97% Gut and hepatic metabolism via CYP3A4 to active metabolite 1-hydroxymidazolam $t_{1/2}$ of parent and active metabolite = 2-6 h and 2-7 h, respectively	10 mg IM in mid-outer thigh (vastus lateralis muscle) by personnel with adequate training in recognition and treatment of SE and first aid/basic airway management		Upper airway obstruction, agitation, and pyrexia Not recommended in narrow-angle glaucoma	Serious cardiorespiratory adverse reactions have occurred, sometimes resulting in death or permanent neurologic injury Use with other CNS depressants may increase risk of hypoventilation, airway obstruction, desaturation, or apnea, and may contribute to profound or prolonged drug effect	Use with caution in patients receiving CYP3A4 inhibitors With BDZs assess each patient's risk for abuse, misuse, and addiction
midazolam (MDZ) Intranasal spray (individual spray unit = 5 mg) Schedule IV	Seizure clusters, acute repetitive seizures At least 12 y	$GABA_A$ receptor agonist; binds between α and γ subunits	Data from adults: F = 44% Protein binding = 97% Tmax (5-mg dose) = 17 min Cmax = 54.7 ng/mL Less variability in absorption compared with IV MDZ Gut and hepatic metabolism via CYP3A4 to active metabolite 1-hydroxymidazolam $t_{1/2}$ of parent and active metabolite = 2-6 h and 2-7 h, respectively	***First dose:*** 5 mg (1 spray) into 1 nostril ***Second dose (if needed):*** 10 min following the first dose = 5 mg (1 spray) into *opposite* nostril	Maximum dose: No more than 2 intranasal doses to treat 1 episode Should not be used to treat more than 1 episode every 3 days Not for chronic daily therapy	CNS depression, somnolence, impaired cognition, HA, nasal discomfort, runny nose, throat irritation	Use with opioids can cause respiratory depression, coma, and death Contraindicated in narrow-angle glaucoma With BDZs assess each patient's risk for abuse, misuse, and addiction	Use with caution in patients receiving CYP3A4 inhibitors

Table 3. Medications for Initial Treatment of Convulsive Status Epilepticus.[6,1414] January 2024. (See Abbreviations.)

Drug - Generic Name	Route/Dose
lorazepam	IV: 0.1 mg/kg Maximum dose = 4 mg May repeat once
midazolam	IM: 5 mg (patient weight 13-40 kg) 10 mg (patient weight > 40 kg)
diazepam	IV: 0.15-0.2 mg/kg Maximum dose = 10 mg May repeat once

Table 4. Antiseizure Medications (ASMs) Enzymatic Considerations

Enzyme	Substrates	Enzyme Inhibitors	Enzyme Inducers
CYP3A4	cannabidiol, carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, everolimus, felbamate, lacosamide, midazolam, oxcarbazepine, perampanel, stiripentol, tiagabine, zonisamide,		carbamazepine, eslicarbazepine, felbamate, oxcarbazepine, perampanel, phenobarbital phenytoin, primidone, rufinamide, stiripentol, topiramate, cenobamate
CYP2C19	brivaracetam, cannabidiol, clobazam, diazepam, lacosamide, phenobarbital, phenytoin, primidone, stiripentol, valproate, zonisamide	cannabidiol, eslicarbazepine, felbamate, topiramate, valproate, cenobamate	carbamazepine, phenobarbital, phenytoin, primidone, stiripentol
CYP2C9	carbamazepine, lacosamide, phenobarbital, primidone, valproate	perampanel, stiripentol, valproate, cannabidiol	carbamazepine, phenobarbital, primidone
CYP2B6	clobazam, perampanel, valproate		carbamazepine, perampanel
CYP1A2	stiripentol	cannabidiol, stiripentol	
UGT	cannabidiol, diazepam, lamotrigine, oxcarbazepine	valproate	lamotrigine, phenobarbital, primidone
Epoxide hydrolase	carbamazepine 10,11 epoxide	valproate, brivaracetam	

Abbreviations

ACTH = adrenocorticotropic hormone
ADME = absorption, distribution, metabolism, and excretion
AE = adverse event
ALT = alanine aminotransferase
AST = aspartate aminotransferase
BDZ = benzodiazepine
bid = twice a day
BP = blood pressure
BRV = brivaracetam
CBC = complete blood cell count
CBD = cannabidiol
CBZ = carbamazepine
CK = creatine kinase
CLB = clobazam
Cmax = maximum plasma concentration
CMP = comprehensive metabolic panel
CNB = cenobamate
CNS = central nervous system
CrCl = creatinine clearance
CYP = cytochrome P
CZP = clonazepam
d = day
DDI = drug-drug interaction
DEA = Drug Enforcement Administration
DRESS = drug reaction with eosinophilia and systemic symptoms (formerly known as multiorgan hypersensitivity)
DZP = diazepam
EIASM = enzyme-inducing antiseizure medication (e.g., CBZ, PHT, PB, PRM)
EKG = electrocardiogram
ER = extended release
ES = epileptic spasms
ESL = eslicarbazepine acetate
ESM = ethosuximide
EtOH = ethyl alcohol
EVL = everolimus
F = bioavailability
FBM = felbamate
FFA = fenfluramine
FIAS = focal impaired awareness seizure
focal onset = focal-onset seizures with or without progression to bilateral tonic-clonic convulsions (formerly known as partial-onset seizures)
FOS = fosphenytoin
GABA = γ-aminobutyric acid
GBP = gabapentin
GGT = γ-glutamyl transferase
GI = gastrointestinal
GTCS = generalized-onset tonic-clonic seizure
h = hour
HA = headache
HCN = hyperpolarization-activated, cyclic nucleotide-gated
IM = intramuscular
INR = international normalized ratio
IQ = intelligence quotient
IR = immediate release
IV = intravenous
LCM = lacosamide
LEV = levetiracetam
LFT = liver function test
LGS = Lennox-Gastaut syndrome
LTG = lamotrigine
mo = month
MA = metabolic acidosis
MAOI = monoamine oxidase inhibitor
MDZ = midazolam
MHD = monohydroxy derivative of OXC (R- and S-licarbazepine)
mTOR = mammalian target of rapamycin
N/A = not applicable
Na+ = sodium
N-desmethyl-CLB = N-desmethylclobazam
NE = norepinephrine
NMDA = N-methyl-D-aspartate
nor-FEN = norfenfluramine
N/V = nausea and vomiting
OC = oral contraceptive
OXC = oxcarbazepine
PB = phenobarbital
PE = phenytoin sodium equivalent
PEMA = phenylethylmalonamide
PER = perampanel
PGB = pregabalin
PHT = phenytoin
PI = FDA-approved prescribing information
PK = pharmacokinetics
PRM = primidone
prn = as needed
PTT = partial thromboplastin time
q6h = every 6 hours
qhs = every night at bedtime
qpm = every afternoon or evening
RBC = red blood cell
REMS = risk evaluation and mitigation strategies
RUF = rufinamide
SGPT = serum glutamic-pyruvic transaminase
SJS = Stevens-Johnson syndrome
SE = status epilepticus
STP = stiripentol
$t_{1/2}$ = half-life
TCA = tricyclic antidepressant
TEN = toxic epidermal necrolysis
TGB = tiagabine
tid = three times a day
Tmax = time at which Cmax is observed
TPM = topiramate
Tx = therapy
URI = upper respiratory infection
VGB = vigabatrin
VPA = valproic acid
WBC = white blood cell
wk = week
y = year
ZNS = zonisamide

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