A Summary of Antiseizure Medications Available in the United States: 2020 Update

Revised September 10, 2020

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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 summary. Information on rarely prescribed ASMs may be found elsewhere. 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 July and August 2020 from the most recent FDA-approved prescribing information (PI) for each ASM available in the FDA’s searchable database, Drugs@FDA: FDA-Approved Drugs. 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. In instances where PIs lacked important data, ASM pharmacology texts were used to supplement the information in the PIs.
- 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.”
- Regulatory language for approval of monotherapy versus adjunctive treatment has changed over the past decades.
- 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.
- 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.
- In the United States, report ASM adverse events to www.fda.gov/medwatch.

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.
Table 1. Antiseizure medications (ASMs) for chronic and subacute treatment of seizures. September 10, 2020. (See Abbreviations.)

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<tr>
<th>Drugs, Formulations, and DEA Scheduling</th>
<th>FDA-Approved Seizure/Syndrome Type, Mono- or Adjunctive Therapy, and Patient Age</th>
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<tr>
<td>adrenocorticotropic hormone (ACTH)</td>
<td>Epileptic spasms Monotherapy Younger than 2 y</td>
<td>Stimulates adrenal gland to secrete cortisol, corticosterone, aldosterone, and several weakly androgenic steroids</td>
<td>Not adequately characterized $t_{1/2} = 0.25$ (IV)</td>
<td>N/A</td>
<td>Multiple regimens Manufacturer: 75 IU/m² IM bid for 2 wk, then taper over 2 wk</td>
<td>N/A</td>
<td>New infections or worsening of latent ones, adrenal insufficiency, Cushing syndrome, decreased growth with prolonged therapy, salt and water retention, hypertension, paralytic ileus, hypokalemic alkalosis, gastric ulcers, bleeding, weight gain, bowel perforation, behavior or mood disturbances Long-term use: worsened diabetes or myasthenia gravis, cataracts, glaucoma, loss of endogenous ACTH, osteoporosis</td>
<td>Contraindicated to give IV with congenital or other infections, recent surgery, uncontrolled hypertension, or sensitivity to porcine proteins Do not administer with live or live-attenuated vaccines</td>
<td>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</td>
</tr>
<tr>
<td>brivaracetam (BRV)</td>
<td>Focal onset At least 4 y (IV formulation not approved for those younger than 16 y)</td>
<td>Inhibits synaptic vesicle protein SV2A</td>
<td>$F \approx 100%$ PPB &lt;20% Metabolism: 1st - hydrolysis, 2nd - CYP2C19 hydroxylation, CYP2C9 hydrolysis then renal excretion $t_{1/2} = 9$ h</td>
<td>Children: 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: 25-100 mg bid</td>
<td>Children: 11-20 kg = 0.5-2.5 mg/kg bid 20-50 kg = 0.5-2 mg/kg bid Adults: 25-100 mg bid</td>
<td>Not established Sedation, N/V, dizziness, anger, depression, anxiety, psychosis, and disturbance in gait and coordination</td>
<td>Bronchospasm, Angioedema In all stages of hepatic impairment reduce BRV dosage</td>
<td>Rifampin decreases BRV by 45%; EIASMs decrease BRV by 19%-26% BRV increases PHT by 20% and CBZ-epoxide by 100%</td>
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<tr>
<td>cannabidiol (CBD)</td>
<td>Seizures associated with LGS, tuberous sclerosis complex, or Dravet syndrome</td>
<td>Unclear</td>
<td>Low F</td>
<td>5 mg/kg divided bid x 1 wk</td>
<td>10-20 mg/kg/d divided bid for LGS and Dravet syndrome</td>
<td>25 mg/kg/day divided bid for tuberous sclerosis complex</td>
<td>Not established</td>
<td>Somnolence/sedation that may be increased with concomitant CLB, potentially due to increase in N-desmethylclobazam; elevated transaminase level (&gt;3x upper limit of normal), particularly at higher CBD doses and with concomitant VPA; decreased appetite, weight loss, diarrhea, rash, pruritis, angioedema</td>
<td>Obtain baseline serum ALT, AST and total bilirubin levels in all patients</td>
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<tr>
<td>Oral solution 100 mg/mL</td>
<td>At least 1 y</td>
<td>Does not interact at CB1 or CB2 receptors</td>
<td>Extensively metabolized, principally via CYP3A4 and CYP2C19</td>
<td>Tmax = 2.5-5 h</td>
<td>7-OH-CBD metabolite appears to be active</td>
<td>PPB &gt;90%</td>
<td>&quot;Elevated&quot; transaminase level (&gt;3x upper limit of normal), particularly at higher CBD doses and with concomitant VPA; decreased appetite, weight loss, diarrhea, rash, pruritis, angioedema</td>
<td>Obtain periodic liver enzyme levels, especially if patient is receiving concomitant VPA with or without CLB</td>
<td>CBD inhibits CYP2C19, so it increases the N-desmethyl-CLB level by 3-fold and increases DZP</td>
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<td>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</td>
<td>7-OH-CBD metabolite appears to be active</td>
<td>Tmax = 2.5-5 h</td>
<td>High-fat meals increase extent of absorption &gt;4- to 5-fold</td>
<td>Elimination t1/2 ~60 h; effective t1/2 ~17 h</td>
<td>Elimination t1/2 ~60 h; effective t1/2 ~17 h</td>
<td>Artisanal formulations of CBD are not biopharmaceutically equivalent and should not be substituted</td>
<td>Anticoagulant effect of warfarin, CYP2B6, CYP2C8, and CYP1A2, and UGT1A9 and UGT2B7 substrates</td>
<td>May increase EVL levels several fold</td>
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<td>May use with ketogenic diet</td>
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<td>May administer via non-polyvinyl chloride feeding tubes</td>
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<td>carbamazepine (CBZ)</td>
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<td>Contraindicated in bone marrow suppression; with use of nefazodone, boceprevir, or delavirdine; in hypersensitivity to TCAs, and with MAOIs (serotonin syndrome)</td>
<td>Induces CYP1A2, CYP2B6, CYP2C9/CYP2C19, and CYP3A4, affecting OCs, warfarin, and many other drugs</td>
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| IR/ER tablet, ER capsule, chewable tablet, suspension 100 mg/5 mL | Focal onset, GTCS, Mixed types | Enhance rapid inactivation of Na⁺ channels; block L-type Ca²⁺ channel | F = 70% (ER formulations may be less), PPB = 76% | *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, hyponatremia, N/V; low WBC counts; decreased T3, T4; increased liver enzymes; worsens GTCS in patients with absence seizures |                                                                                      | CBZ metabolism is inhibited by macrolides, propoxyphene, many other drugs which inhibit CYP3A4, and grapefruit juice |
|                                                                                   |                                                                                   |                                 |                        |                                        |                                        |                | Use with caution in 2nd and 3rd degree heart block | Avoid in porphyria                                                                 |

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<td>cenobamate (CNB)</td>
<td>Tablet&lt;br&gt;Schedule V&lt;br&gt;Focal onset&lt;br&gt;Adults</td>
<td>Enhance rapid and slow inactivation of Na⁺ channels; inhibits non-inactivating persistent Na⁺ current; positive allosteric modulator of GABA&lt;sub&gt;A&lt;/sub&gt; ion channel</td>
<td>F = 88%, PPB = 60%&lt;br&gt;Metabolism: glucuronidation by UGT2B7 and oxidation by multiple CYP isozymes&lt;br&gt;T&lt;sub&gt;max&lt;/sub&gt; = 1-4 h&lt;br&gt;t&lt;sub&gt;1/2&lt;/sub&gt; = 50-60 h</td>
<td>12.5 mg/d weeks 1 and 2&lt;br&gt;25 mg/d weeks 3 and 4&lt;br&gt;50 mg/d weeks 5 and 6&lt;br&gt;100 mg/d weeks 7 and 8&lt;br&gt;150 mg/d weeks 9 and 10</td>
<td>200 mg/d; may increase by increments of 50 mg/d every 2 wk up to 400 mg/d maximum</td>
<td>Not established</td>
<td>Shortening of QT interval, somnolence, fatigue, dizziness, ataxia, diplopia, nystagmus, vertigo, cognitive dysfunction, hyperkalemia (K⁺ &gt; 5 mEq/L)</td>
<td>Contraindication: Familial short QT syndrome&lt;br&gt;DRESS (multiorgan hypersensitivity) occurred in 3 of 953 patients in initial trials using a more rapid titration, but in 0 of 1339 adults using the recommended slow up-titration schedule&lt;br&gt;Caution should be exercised when used with drugs which shorten the QT interval (eg, RUF)&lt;br&gt;Mild to moderate renal or hepatic impairment: Use caution and reduced dose&lt;br&gt;Severe renal or hepatic impairment: Use is not recommended</td>
<td>CNB inhibits CYP2C19, so the Cmax of PHT increases 70-84%, PB increases 34-37%, and N-desmethyl-CLB increases substantially&lt;br&gt;CNB induces CYP3A4, so the Cmax of CBZ decreases 23%&lt;br&gt;CNB induces glucuronidation, so the Cmax of LTG decreases 21-52%&lt;br&gt;CNB can decrease the effectiveness of OCs and may decrease midazolam and bupropion levels&lt;br&gt;CNB increases the omeprazole level 2-fold&lt;br&gt;PHT induces CNB metabolism, so the CNB level decreases 28%</td>
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<td>clobazam (CLB)</td>
<td>LGS Adjuvicate Tx At least 2 y</td>
<td>GABA&lt;sub&gt;α&lt;/sub&gt; receptor agonist; binds between α and γ subunits</td>
<td>F = 100% PPB = 85% Tmax = 0.5-4 h Lipophilic; Metabolism: N-demethylated by CYP3A4 &gt; CYP2C19 and CYP2B6, to N-desmethyl-clobazam, which is metabolized by CYP2C19 t₁/₂ = 36-42 h; 71-82 h for metabolite</td>
<td>≤30 kg = 5 mg/d for at least 1 week &gt;30 kg = 5 mg bid for at least 1 week</td>
<td>≤30 kg = up to 10 mg bid &gt;30 kg = up to 20 mg bid</td>
<td>0.25-0.75 mcg/mL</td>
<td>Sedation, fever, URI, drooling, constipation, urinary tract infection, insomnia, irritability, depression, dependence, withdrawal effects, vomiting, ataxia, bronchitis, pneumonia</td>
<td>Rash Rarely SJS, and TEN Use with opioids can cause profound sedation, respiratory depression, coma, and death Use lower dose in older adults, those with known CYP2C19 poor metabolizers, and those with mild or moderate liver failure. Not studied in patients with severe hepatic or renal impairment</td>
<td>Weak CYP3A4 inducer, so may affect OCs CLB inhibits CYP2D6 (dextromethorphan) CBD, CNB, STP, ethanol and CYP2C19 inhibitors (fluconazole, fluvoxamine, omeprazole) inhibit CLB metabolism CLB is a 1,5-BDZ (all other BDZs are 1,4)</td>
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<td>clonazepam (CZP)</td>
<td>LGS, myoclonic and absence seizures No age specified</td>
<td>GABA&lt;sub&gt;α&lt;/sub&gt; receptor agonist; binds between α and γ subunits</td>
<td>F = 90% PPB = 85% Tmax = 1-4 h CYP3A4 reduces the 7-nitro group; 4-amino derivative is acetylated, hydroxylated, and glucuronidated; metabolites are renally excreted t₁/₂ = 30-40 h</td>
<td>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: &lt;1.5 mg tid</td>
<td>Children: 0.1-0.2 mg/kg/d Adults: &lt;20 mg/d</td>
<td>0.04-0.07 mcg/mL</td>
<td>Sedation; dizziness; ataxia, hypersalivation; respiratory depression; porphyrogenic; impaired judgment, cognition, or motor skills Paradoxical agitation, irritability, anger, anxiety, nightmares, hallucination, psychoses, depression, dependence, tolerance</td>
<td>Use with opioids can cause respiratory depression, coma, and death Use with opioids can cause profound sedation, 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</td>
<td>Worsened or new TCS VPA + CZP may cause absence SE; withdraw all BDZs gradually to help avoid SE Periodic CBC and liver tests recommended CBZ, LTG, PB and PHT decrease CZP levels ~38% Oral antifungal agents (eg, fluconazole) may inhibit CZP metabolism</td>
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| eslicarbazepine acetate (ESL) tablet     | Focal onset At least 4 y                                                      | Enhances Na⁺ channel rapid inactivation; blocks hCav3.2 Ca²⁺ channel; enhances K⁺ conductance | F = 90% PPB = 40% ESL acetate hydrolyzed to ESL; renal excretion as ESL and ESL glucuronide t₁/₂ = 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. | SJ 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 Ca²⁺ thalamic currents | F ~ 93%  
Metabolism: CYP3A4 and CYP2E1 clearance may be nonlinear at higher doses (saturable) t₁/₂ ~ 30 h (children), ~ 60 h (adults) | **Children:** 3-6 y = 250 mg/d  
**Children & Adults:** 6+ y = 250 mg bid  
**Adults:** 1500 mg divided bid or tid | **Children:** optimal is 20 mg/kg/d  
**Children:** 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, 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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<td>everolimus (EVL) Tablets for suspension</td>
<td>Tuberos sclerosis complex-associated focal Adjunctive Tx At least 2 y</td>
<td>mTOR inhibitor</td>
<td>PPB = 74% Intake of fatty foods can reduce systemic exposure 20%-30% CYP3A4 substrate T1/2 = 30 h</td>
<td>5 mg/m² once daily New dose = current dose multiplied by (target concentration divided by current concentration) Target: 5-15 ng/mL</td>
<td>Stomatitis (&gt;30%), non-infectious pneumonitis Bacterial, fungal, viral, and protozoal infection, including opportunistic infection Myelosuppression, embryofetal toxicity, pneumonia, irregular menses, fever, diarrhea, rash</td>
<td>Impaired wound healing, hypersensitivity (anaphylaxis, dyspnea, flushing, chest pain, angioedema), renal failure, increased risk of angioedema with ACE inhibitor, hyperglycemia, thrombocytopenia, neutropenia, anemia, increased cholesterol level, increased triglyceride level, increased liver enzymes, embryofetal toxicity Reduce dose in severe hepatic impairment</td>
<td>EVL increases CBZ, CLB, and OXC levels ~10% Avoid strong CYP3A4 and P-glycoprotein inhibitors Case reports suggest that CBD may increase EVL plasma levels. Monitoring may be warranted.12,13</td>
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<tr>
<td>felbamate (FBM) Tablet, Suspension (600 mg/5 mL)</td>
<td>Refractory focal: Adults LGS: Adjunctive Tx At least 2 y</td>
<td>Enhance Na⁺ channel rapid inactivation; blocks Ca²⁺ channel, inhibits NMDA receptor; potentiates GABA&lt;sub&gt;A&lt;/sub&gt; conductance</td>
<td>F = 90%, PPB = 23% 40%-50% excreted in urine unchanged; remainder hepatically metabolized to multiple metabolites and conjugates t1/2 = 22 h</td>
<td>15 mg/kg/d divided tid or 4 x/d Children: 15 mg/kg/d divided tid or 4 x/d Children &amp; Adults: 14+ y = 1200 mg divided tid or 4 x/d</td>
<td>800-1200 mg tid 60-100 mcg/mL</td>
<td>HA, insomnia, N/V, abdominal pain, anorexia, weight loss, facial edema, anxiety, acne, rash, constipation, diarrhea, increased SGPT, hypophosphatemia, rhinitis, infection, somnolence, ataxia, dizziness, tremor Aplastic anemia, hepatic failure Contraindications: history of blood dyscrasia or hepatic dysfunction Decreased clearance and increased t1/2 in renal impairment Monitor full hematologic and LFTs before, frequently during, and after treatment</td>
<td>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</td>
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<tr>
<td>fenfluramine (FEN)</td>
<td>Dravet syndrome</td>
<td>Both FEN and nor-FEN increase serotonin (SHT) levels and are agonists at SHT-2 receptors. FEN may be positive modulator of sigma-1 receptors</td>
<td>F ~ 70% PPB = 50% Tmax = 4-5 h No effect of food; may be given via feeding tube Metabolized (75%) via CYP1A2, 2B6 &amp; 2D6 to active metabolite, nor-FEN. CYP2C9, 2C19 &amp; 3A4 may play minor role in metabolism t1/2 = 20 h</td>
<td>0.1mg/kg bid If not taking STP: 0.1-0.35 mg/kg bid (max total = 26 mg/d) If taking STP and CLB: 0.1-0.2 mg/kg bid (max total = 17 mg/d)</td>
<td>unknown</td>
<td>Decreased appetite, weight loss, diarrhea, somnolence, sedation, lethargy, increased blood pressure, angle closure glaucoma</td>
<td>Valvular heart disease, pulmonary arterial hypertension (REMS program is mandatory) Echocardiogram is required at baseline, every 6 months on treatment, and 3-6 months after stopping treatment To avoid serotonin syndrome, do not use within 14 days of MAO inhibitor and use with caution with other serotonergic drugs</td>
<td>STP and CLB can increase plasma levels of FEN and decrease levels of nor-FEN (dose modification required) CYP inducers can reduce FEN plasma levels 5HT1A, 1D, 2A &amp; 2C receptor antagonists (e.g. cyproheptadine) may reduce FEN efficacy Serotonergic agents (e.g. SSRI, SNRI, TCA, MAO inhibitors, trazodone, St. John’s Wort, dextromethorphan) increase risk of serotonin syndrome</td>
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<td>Oral solution (2.2 mg/mL)</td>
<td>At least 2 y</td>
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<td>Schedule IV</td>
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<td>gabapentin (GBP)</td>
<td>Focal onset</td>
<td>Binds presynaptic α2-δ subunit of voltage-activated Ca²⁺ channel to modulate Ca²⁺ current, resulting in decreased glutamate concentration, NE level, and substance P release</td>
<td>Nonlinear F: absorption from gut via L-amino acid transferase is saturable, so F = 60% at 900 mg/d, 34% at 2400 mg/d, and 27% at 4800 mg/d total PPB = 3% Renal excretion t₁/₂ = 6 h</td>
<td><strong>Children:</strong> 3-11 y = 10-15 mg/kg/d divided tid  <strong>Children &amp; Adults:</strong> 12+ y = 300 mg tid</td>
<td><strong>Children:</strong> 3-4 y = 40 mg/kg/d divided tid 5-11 y = 25-35 mg/kg/d divided tid  <strong>Children &amp; Adults:</strong> 12+ y = 300-600 tid</td>
<td>4-8.5 mcg/mL</td>
<td>Drowsiness, sedation, fatigue, ataxia, dizziness, nystagmus, diplopia, peripheral edema, fever, viral infection, nausea, vomiting, tremor</td>
<td>DRESS, anaphylaxis, angioedema Respiratory depression when used with CNS depressants, including opioids, or in the setting of underlying respiratory impairment. When adding GBP in these instances, consider initiating GBP at lower dose, monitoring patients, and adjusting dose as appropriate Cognitive impairment Neuropsychiatric changes (emotional, aggression, cognitive and concentration problems, hyperkinesia) in children aged 3-12 y Renal insufficiency requires lower dose</td>
<td>GBP concentration is increased by morphine GBP decreases hydrocodone exposure Magnesium/aluminum antacids decrease GBP level 20%</td>
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| lacosamide (LCM)                       | Focal onset                                                                   | Enhances Na+ channel slow inactivation | F = 100% Demethylated by CYP3A4, CYP2C9, and CYP2C19; 95% renally excreted, 40% as LCM/60% as metabolites t₁/₂ = 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  
**Monotherapy:** 50+ kg or at least 17 y = 150-200 mg bid | **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) | 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 |
Table 1 (continued). Antiseizure medications (ASMs) for chronic and subacute treatment of seizures. September 10, 2020. (See Abbreviations.)

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<td><strong>lamotrigine (LTG)</strong></td>
<td><strong>Focal onset:</strong> Withdrawal to monotherapy At least 16 y</td>
<td>Enhances Na+ channel rapid inactivation; inhibits Ca²⁺ channels; activates postsynaptic HCN channels</td>
<td>F = 98% PPB = 55% Vd = 0.9-1.3 L/kg; mostly glucuronidated then renally excreted t₁/₂ = 25 h, 13 h with EIASMs, and 70 h with VPA</td>
<td>25 mg every 2nd day (with VPA only) 25 mg/d 50 mg/d (with EIASMs only)</td>
<td>50-100 mg bid with VPA alone 75-200 mg bid without VPA or EIASMs 150-250 mg bid with EIASMs</td>
<td>4-20 mcg/mL</td>
<td>Dizziness, HA, diplopia, ataxia, nausea, vomiting, somnolence, insomnia in high doses, aseptic meningitis Rash, SJS, TEN, DRESS Hemophagocytic lymphohistocytosis (rare) Blood dyscrasias</td>
<td>EIASMs (CBZ, CNB, PB, PHT, PRM), rifampin, and OCs decrease LTG level 40+% Pregnancy decreases LTG level ~50%-67% VPA increases LTG level &gt;2-fold LTG inhibits dihydrofolate reductase</td>
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<td><strong>levetiracetam (LEV)</strong></td>
<td><strong>Focal onset:</strong> At least 1 month Myoclonic in JME: Adjunctive Tx At least 12 y Primary TCS: Adjunctive Tx At least 6 y</td>
<td>Inhibits synaptic vesicle protein SV2A; partially inhibits N-type Ca²⁺ currents</td>
<td>F = 100% PPB &lt;10% Enzymatic hydrolysis (non-CYP) to inactive metabolite ~66% renally eliminated unchanged</td>
<td>Children: 1-5 mo = 7 mg/kg bid 6 mo - &lt;4 y = 10 mg/kg bid 4 - &lt;16 y = 10 mg/kg bid Children &amp; Adults: 16+ y: 500 mg bid</td>
<td>Children: 1 - &lt;6 mo = 21 mg/kg bid 6 mo - &lt;4 y = 25 mg/kg bid 4 - &lt;16 y = 30 mg/kg bid Children &amp; Adults: 16+ y: 1500 mg bid (myoclonic JME &amp; primary GTCS) or 500-1500 mg bid (focal onset)</td>
<td>20-50 mcg/mL</td>
<td>Somnolence, fatigue, asthenia, dizziness, infection, ataxia, incoordination, anemia, pancytopenia, leukopenia, neutropenia, agranulocytosis, thrombocytopenia &lt;4 y: increased diastolic BP SJS and TEN, rhabdomyolysis, angioedema, anaphylaxis Irritability, aggression, depression, suicidal ideation, psychotic symptoms (especially in children) In patients with renal insufficiency, dose must be reduced proportionate to CrCl; hemodialysis eliminates 50% in 4 h</td>
<td>Plasma LEV level may gradually decrease during pregnancy</td>
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<td>oxcarbazepine (OXC) Tablet (IR and ER), oral suspension (300 mg/5 mL)</td>
<td>Focal onset</td>
<td>Enhances Na+ channel rapid inactivation; modulation of high-voltage activated Ca2+ channel; enhances K+ conductance</td>
<td>OXC is a prodrug: reduced 80% to S-licarbazepine and 20% to R-licarbazepine (the MHDs), by hepatic cytosolic enzymes; MHD is glucuronidated, then renally excreted</td>
<td>Unlike CBZ, there is no autoinduction or formation of a 10,11 epoxide</td>
<td>Children: $2-16,\text{y}$ = 8-10 mg/kg/d divided bid, not to exceed 300 mg bid</td>
<td>2-16 y: $&lt;20,\text{kg}$ = 16-60 mg/kg/d $20-29,\text{kg}$ = 900 mg/d $30-39,\text{kg}$ = 1200 mg/d $40+,\text{kg}$ = 1800 mg/d</td>
<td>10-35 mcg/mL (as MHD)</td>
<td>Dizziness, cognitive problems, somnolence, fatigue, nausea, HA, diarrhea, vomiting, URI, constipation, dyspepsia, ataxia, coordination problems, nervousness, pancytopenia, agranulocytosis, leukopenia, hyponatremia (&lt;125 mmol/L = 2.5%, but the % increases with age)</td>
<td>SJS and TEN (risk increases with HLA-B*1502, 10x increase with Asian ancestry), DRESS</td>
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</table>
| | Monotherapy: At least 4 y | Adults: $17+\,\text{y}$ = 300 mg bid (wk 1), then add no more than 300 mg bid each wk | All above doses are divided bid | Adults: $17+\,\text{y}$ = 1200-2400 mg divided bid (tid may improve tolerability) | | | | | Inhibits CYP2C19: At >1200 mg/d, the PHT level increases 40%
| | Adjunctive Tx: At least 2 y | Adults: $17+\,\text{y}$ = 1200-2400 mg divided bid (tid may improve tolerability) |
| | | $t_{1/2}$ = 9 h (MHD), 2 h (OXC) | | | | | | | CBZ, PB, and PHT and rifampin decrease OXC levels 29%-40% |
**Table 1 (continued). Antiseizure medications (ASMs) for chronic and subacute treatment of seizures.** September 10, 2020. (See [Abbreviations](#).)

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<td><strong>perampanel (PER)</strong></td>
<td><strong>Focal onset:</strong> At least 4 y <strong>Primary GTCS:</strong> Adjunctive Tx At least 12 y</td>
<td>Selective, non-competitive antagonist of AMPA glutamate receptor, inhibiting synaptic-driven influx of Na⁺</td>
<td>F = 100%, but food delays by 2 h PPB= 96% Metabolized by CYP3A4 and CYP3A5 to multiple inactive metabolites T₁/₂ = 105 h (~24 h with EIASMs)</td>
<td><strong>Children &amp; Adults:</strong> 2 mg qhs (4 mg with EIASMs)</td>
<td><strong>Children &amp; Adults:</strong> Increase by no more than 2 mg weekly (long t₁/₂ suggests slower) Minimum = 4 mg Maximum = 8-12 mg qhs (may need lower dose if not taking EIASMs)</td>
<td>Not established</td>
<td>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</td>
<td>Homicidal ideation (6 in 4368 subjects in preclinical trials), suicidal thoughts, DRESS</td>
<td>CBZ, OXC, and PHT (not PB) increase PER metabolism 2-3x causing lower PER level</td>
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<td><strong>Tablet, oral solution (0.5 mg/mL)</strong></td>
<td><strong>Schedule III</strong></td>
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<td>Use lower dose in mild and moderate hepatic impairment</td>
<td>PER at 12 mg/d increases OC metabolism</td>
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<td>phenobarbital (PB)</td>
<td>Focal onset and generalized onset</td>
<td>Nonspecific GABA&lt;sub&gt;α&lt;/sub&gt; receptor binding: affects both synaptic (phasic) and extra-synaptic (tonic) GABA&lt;sub&gt;α&lt;/sub&gt; receptors</td>
<td>F ~95% PPB = 45% Hepatically parahydroxylated and glucuronidated 25%-50% of unchanged PB and its metabolites are renally excreted ( t_{1/2} = 79 \text{ h} ) (110 h in children and newborns)</td>
<td><strong>Children:</strong> Infants = 3-5 mg/kg/d 6-12 y = 2-3 mg/kg/d 13+ y = 60 mg/d or 1-4 mg/kg/d <strong>Adults:</strong> Infants = 8 mg/kg/d 6-12 y = 4-6 mg/kg/d 13+ y = 1-4 mg/kg/d</td>
<td>15-45 mcg/mL</td>
<td>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</td>
<td>SJS, TEN, DRESS, rash, angioedema, respiratory depression, synergistic effects with ETOH or sedatives, psychological and physical dependence Caution should be exercised when used with pain medications and CNS depressants Do not use in hepatic encephalopathy, porphyria, marked hepatic impairment, or marked respiratory disease Taper very slowly after chronic use, because barbiturate withdrawal can cause convulsions and delirium and may be fatal</td>
<td>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</td>
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<td>phenytoin (PHT) and fosphenytoin (FOS)</td>
<td>Focal onset, GTCS Generalized tonic-clonic status epilepticus, prevention and treatment of seizures during neurosurgery, and short-term use when administration of oral PHT is not possible (FOS only)</td>
<td>Enhances rapid inactivation of Na+ channels</td>
<td>F ~100% (varies by formulation) PPB = 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) t1/2 = Adult: 22 h (7-40 h); longer at higher doses and older age</td>
<td>Children: 5 mg/kg/d divided bid or tid Adults: 300 mg/d divided tid Children &amp; 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</td>
<td>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</td>
<td>10-20+ mcg/mL (~10% as free PHT)</td>
<td>Nystagmus, ataxia, coordination impairment, dysarthria, cognitive slowing, gingival hyperplasia, rash, hypertrichosis, lymphadenopathy, pseudolymphoma, lymphoma, Hodgkin disease, thrombocytopenia, leukopenia, pancytopenia, osteoporosis, decreased vitamin D level activates parathyrophenia 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 PHT decreases T4 level and increases glucose, GGT, and alkaline phosphatase levels</td>
<td>FOS is 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 &gt;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</td>
<td>CNI, 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 The full effect of IV PHT and FOS is not immediate, so concomitant administration of an IV BDZ is usually necessary to control SE Monitor unbound (free) serum level in hepatic or renal impairment or hypoalbuminemia A small percentage of persons are slow metabolizers requiring lower maintenance doses</td>
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<td><strong>pregabalin (PGB)</strong></td>
<td>Focal onset and TCS Monotherapy</td>
<td>Non-specific GABA&lt;sub&gt;4&lt;/sub&gt; receptor binding: affects both synaptic (phasic) and extra-synaptic (tonic) GABA&lt;sub&gt;4&lt;/sub&gt; receptors</td>
<td>F = 100% PPB &lt;5% PRM and its metabolites (PB and PEMA) are active ASMs t&lt;sub&gt;1/2&lt;/sub&gt; = 12 h (derived PB is 79 h)</td>
<td><strong>Children:</strong> &lt;8 y = 50 mg qhs <strong>Children &amp; Adults: 8+ y = 100-125 mg qhs</strong></td>
<td><strong>Children: 8-12 mcg/mL (plus derived PB)</strong></td>
<td>6-12 mcg/mL</td>
<td>Diplopia, nystagmus, drowsiness, ataxia, vertigo, N/V, fatigue, irritability, emotional disturbance, impotence</td>
<td>Contraindications: Porphyria, PB allergy Rash, RBC hypoplasia and aplasia, agranulocytosis, megaloblastic anemia (folate responsive)</td>
<td>DDIs similar to PB</td>
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<tr>
<td><strong>primidone (PRM)</strong></td>
<td>Focal onset and TCS Monotherapy</td>
<td>Nonspecific GABA&lt;sub&gt;4&lt;/sub&gt; receptor binding: affects both synaptic (phasic) and extra-synaptic (tonic) GABA&lt;sub&gt;4&lt;/sub&gt; receptors</td>
<td>F = 100% PPB &lt;5% PRM and its metabolites (PB and PEMA) are active ASMs t&lt;sub&gt;1/2&lt;/sub&gt; = 12 h (derived PB is 79 h)</td>
<td><strong>Children: 8-12 mcg/mL (plus derived PB)</strong></td>
<td><strong>Children: 8-12 mcg/mL (plus derived PB)</strong></td>
<td>6-12 mcg/mL</td>
<td>Diplopia, nystagmus, drowsiness, ataxia, vertigo, N/V, fatigue, irritability, emotional disturbance, impotence</td>
<td>Contraindications: Porphyria, PB allergy Rash, RBC hypoplasia and aplasia, agranulocytosis, megaloblastic anemia (folate responsive)</td>
<td>DDIs similar to PB</td>
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**Table 1 (continued).** Antiseizure medications (ASMs) for chronic and subacute treatment of seizures. September 10, 2020. (See Abbreviations.)
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</tr>
</thead>
<tbody>
<tr>
<td><strong>rufinamide (RUF)</strong></td>
<td>LGS, Adjunctive Tx At least 1 y</td>
<td>Enhances Na⁺ channel rapid inactivation</td>
<td>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 t₁/₂ = 6-10 h</td>
<td><strong>Children:</strong> 10 mg/kg/d (max 400 mg/d) divided bid</td>
<td><strong>Children:</strong> Child maximum = 45 mg/kg/d (up to 3200 mg/d) divided bid <strong>Adults:</strong> 400-800 mg/d divided bid; lower dose w/ VPA</td>
<td>5-48 mcg/mL</td>
<td>Shortening of QT interval, leukopenia HA, N/V, dizziness, ataxia, gait disturbances, somnolence, coordination problems</td>
<td>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</td>
<td>Induces CYP3A4, so decreases estradiol 22% at ≥800 mg bid and mildly decreases CBZ and LTG levels RUF mildly increases PB and PHT levels VPA increases RUF level 16%-70% CBZ, PHT, PB, and PRM decrease RUF level 19%-46% Hemodialysis decreases RUF level ~30% Take with food</td>
</tr>
<tr>
<td><strong>stiripentol (STP)</strong></td>
<td>Dravet syndrome with clobazam At least 2 y</td>
<td>Direct effect on GABA&lt;sub&gt;A&lt;/sub&gt; receptor; indirect effect to raise plasma level of CLB and its metabolite 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 t₁/₂ = 4.5-13 h (longer at higher doses)</td>
<td>10-15 mg/kg/d divided bid, then increase every 1-2 wk 50 mg/kg/d divided bid or tid</td>
<td>Not established</td>
<td>Somnolence, decreased weight and appetite, neutropenia, thrombocytopenia, agitation, ataxia, hypotonia, nausea, 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</td>
<td>STP inhibits CYP3A4 and CYP2C19, so it increases CLB level 2-fold and 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</td>
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</table>
Table 1 (continued). Antiseizure medications (ASMs) for chronic and subacute treatment of seizures. September 10, 2020. (See Abbreviations.)

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<tr>
<th>Drugs, Formulations, and DEA Scheduling</th>
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<tr>
<td>tiagabine (TGB) Tablette</td>
<td>Focal onset</td>
<td>Selective GABA reuptake inhibitor (SGRI): inhibits GABA reuptake from synapse into neurons and glia</td>
<td>F = 90% PPB = 96% Metabolized by CYP3A4 and glucuronidation, then metabolites are excreted in urine and feces t₁/₂ = 8 h (2-5 h with EIASMs)</td>
<td><strong>Children &amp; Adults:</strong> 12+ y = 4 mg once daily (use lower initial dose if not taking EIASMs) Do not use loading dose</td>
<td><strong>Children &amp; Adults:</strong> 12+ y = 32-56 mg/d divided bid (56 mg is with concomitant EIASMs)</td>
<td>5-70 mcg/mL</td>
<td>Dizziness, N/V, somnolence, fatigue, tremor, cognitive slowing, anxiety, diarrhea, abdomen pain, worsened pre-existing spike-and-slow-wave complexes in EEG</td>
<td>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</td>
<td>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</td>
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<td>topiramate (TPM)</td>
<td>Focal onset and GTCS: At least 2 y LGS: Adjunctive Tx At least 2 y</td>
<td>Inhibits voltage-dependent Na+ channels, kainate glutamate receptors, and carbonic anhydrase; enhances GABAA currents</td>
<td>F = 80% PPB = 15%-41% and decreases at higher concentrations Not extensively metabolized. Urinary excretion 70% as unchanged drug t1/2 = 21 h</td>
<td><strong>Children:</strong> 2-9 y = 25 mg qpm</td>
<td>≤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 &gt;38 kg = 125-200 mg bid</td>
<td>7-30 mcg/mL</td>
<td>Language and cognitive (confusion, memory, word-finding, attention, concentration) disturbances Kidney stones Paresthesia, anorexia, weight loss, fatigue, somnolence, dizziness, anxiety, depression or mood problems, abnormal vision, fever, taste perversion, diarrhea, hypesthesia, nausea, abdominal pain, URI</td>
<td>SJS and TEN. Acute myopia w/ secondary angle closure glaucoma and vision loss, visual field defects Oligohydrosis and hyperthermia (especially in children) Decreased Cl- MA Hyperammonemia and encephalopathy +/- VPA Hypothermia with VPA Chronic untreated MA may lead to decreased growth in children, increased alkaline phosphatase level, hypophosphatemia, and osteomalacia Decreased OC efficacy (TPM &gt;200 mg/d) Monitor Li2+ level with higher-dose TPM In patients with renal impairment, use ½ dose and supplement after hemodialysis PHT and CBZ lower TPM concentration 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 Use cautiously with CNS depressants</td>
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</tbody>
</table>
### Table 1 (continued). Antiseizure medications (ASMs) for chronic and subacute treatment of seizures. September 10, 2020. (See Abbreviations.)

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<tr>
<td>valproic acid (VPA) and divalproex sodium</td>
<td>Tablet (IR and ER), capsule, sprinkle, IV solution (100 mg/mL)</td>
<td><strong>Focal onset and absence:</strong> Monotherapy</td>
<td>Inhibits voltage-dependent Na⁺ and T-type Ca²⁺ channels, enhances biosynthesis and inhibits degradation of GABA</td>
<td>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)</td>
<td><strong>Children &amp; Adults:</strong> 10+ y = 15 mg/kg/d; increase by 5-10 mg/kg/d at weekly intervals</td>
<td>&lt;10 y = dose not established but children aged 3 mo-10 y have 50% higher clearance expressed on weight</td>
<td>50-100+ mcg/mL</td>
<td>Hyperammonemia +/- encephalopathy (especially with concomitant TPM), thrombocytopenia (especially with trough level &gt;110 mcg/mL), coagulopathy, hypothermia</td>
<td><strong>Contraindications:</strong> Women of childbearing potential and pregnancy, unless other ASMs fail and she is using effective contraception (especially true for migraine prophylaxis); hepatic disease or significant dysfunction; mitochondrial disorders with POLG mutation, urea cycle disorders; Hepatotoxicity (especially in patients aged &lt;2 y receiving multiple ASMs, and in patients with: metabolic disorders, intellectual delay, organic brain disease, and mitochondrial disorders)</td>
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<td>Abdominal pain, alopecia, blurred vision, anorexia, ataxia, amnesia, asthenia, back pain, constipation, depression, diarrhea, diplopia, dizziness, dyspepsia, dyspnea, emotional lability, fever, infection, HA, increased appetite, insomnia, N/V, nervousness, nystagmus, peripheral edema, pharyngitis, rash, rhinitis, somnolence in older adults, abnormal thinking, tinnitus, tremor, weight gain or loss</td>
<td>Elimination PK: children aged 3 mo-10 y have 50% faster clearance, and those aged 68+ y have ~40% lower clearance</td>
<td>t₁/₂ = 9-16 h</td>
<td><strong>Contraindications:</strong></td>
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<td><strong>Multiple seizure types that include absence:</strong> Adjunctive Tx</td>
<td>Metabolism: &gt;40% mitochondrial β-oxidation, 30%-50% glucuronidation, &lt;15%-20% other oxidation</td>
<td>Nonlinear PK: total level increases with dose to a lesser extent due to saturable PBP, free VPA level increases linearly</td>
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<td><strong>With gestational exposure:</strong> Substantial risk of major congenital malformations (especially neural tube defects), intellectual delay, decreased IQ, and autism</td>
<td>Other DDIs: TCAs, propofol, warfarin, zidovudine</td>
</tr>
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Table 1 (continued). Antiseizure medications (ASMs) for chronic and subacute treatment of seizures. September 10, 2020. (See Abbreviations.)

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<tr>
<td>vigabatrin (VGB)</td>
<td>Tablet, powder for oral solution (500 mg)</td>
<td>Epileptic spasms (ES): Monotherapy 1 mo to 2 y</td>
<td>Irreversibly inhibits GABA transaminase (GABA-T) resulting in increased GABA concentrations in the CNS</td>
<td>F = 100% PPB = 40% Extensive binding to RBCs. No significant hepatic metabolism. Renal excretion t₁/₂ = 10 h (10+ y) or 5.7 h (infants)</td>
<td>ES: 25 mg/kg bid FIAS: Children: 2-16 y = 175-250 mg bid (weight-based) Children &amp; Adults: &gt;60 kg or 17+ y = 500 mg bid</td>
<td>Not established</td>
<td>Somnolence, nystagmus, dizziness, tremor, blurred vision, coordination abnormal, memory impairment, weight gain, arthralgia, ataxia, tremor, URI, aggression, diplopia, withdrawal seizure with rapid discontinuation, peripheral neuropathy in adults, edema</td>
<td>Permanent visual field constriction, central retinal damage with decreased visual acuity, abnormal MRI signal changes in infants, intramyelinic edema in infants, decreased ALT and AST levels, anemia, somnolence, and fatigue</td>
<td>Induces CYP2C9, so decreases PHT level 18% Increases CZP level 30% Stop if no substantial decrease in FIAS in 3 mo Complete REMS follow-up forms</td>
</tr>
</tbody>
</table>
Table 1 (continued). Antiseizure medications (ASMs) for chronic and subacute treatment of seizures. September 10, 2020. (See Abbreviations.)

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<tr>
<td>zonisamide (ZNS)</td>
<td>Focal onset</td>
<td>Enhances rapid inactivation of Na⁺ channels; decreased low-threshold T-type Ca²⁺ currents; binds GABA₆ BDZ ionophore; mild carbonic anhydrase-inhibiting effects; facilitates dopamine and serotonin transmission</td>
<td>F = 100% PPB = 40% to albumin Linear PK up to 800 mg/d but increases disproportionally above that dose due to an 8-fold binding to RBCs Partial hepatic metabolism Renal excretion t₁/₂ = 69 h, 27-38 h with EAISM, 46 h with VPA</td>
<td>Children &amp; Adults: 16+ y = 100 mg/d, increase by 100 mg every 2 weeks to 400-600 mg/d given once daily or bid</td>
<td>10-40 mcg/mL</td>
<td>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</td>
<td>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</td>
<td>Adjust dose in patients with renal impairment ZNS t₁/₂ 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 (arylamide sulfonamides may produce severe reactions)</td>
<td></td>
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</tbody>
</table>
Table 2. Antiseizure Medications (ASMs) for treatment of acute repetitive seizures. September 10, 2020. (See Abbreviations.)

<table>
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<tr>
<th><strong>Drug</strong></th>
<th><strong>Formulations, and DEA Scheduling</strong></th>
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<th><strong>Recommended Initial Dose and Patient Age</strong></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>diazepam</strong> (DZP)</td>
<td>Intransanal spray (individual spray units = 5 mg, 10 mg, 15 mg, 20 mg) Schedule IV</td>
<td>Seizure cluster, acute repetitive seizures At least 6 y</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; receptor agonist; binds between α and γ subunits</td>
<td>Data from adults and children &gt;6 y: T&lt;sub&gt;max&lt;/sub&gt; = 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</td>
<td><strong>Children:</strong> 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 <strong>Children &amp; Adults:</strong> 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</td>
<td>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</td>
<td>CNS depression, somnolence, HA, nasal discomfort See next entry (DZP rectal gel) for complete listing</td>
<td>Use with opioids can cause respiratory depression, coma, and death Contraindicated in narrow-angle glaucoma</td>
<td>No dose adjustments required based on concomitant medications See next entry (DZP rectal gel) for complete listing</td>
</tr>
<tr>
<td><strong>diazepam</strong> (DZP)</td>
<td>Rectal gel (5 mg/mL) Schedule IV</td>
<td>Acute repetitive seizures At least 2 y</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; receptor agonist; binds between α and γ subunits</td>
<td>F = 90% T&lt;sub&gt;max&lt;/sub&gt; = 1.5 h PPB = 95+% Metabolism (CYP2C19 and CYP3A4) principally to N-desmethyldiazepam (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&lt;sub&gt;1/2&lt;/sub&gt; of the active metabolite N-desmethyldiazepam is up to 100 h</td>
<td><strong>Children:</strong> 2-5 y = 0.5 mg/kg 6-11 y = 0.3 mg/kg 12+ y = 0.2 mg/kg <strong>Adults:</strong> 0.2 mg/kg</td>
<td>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</td>
<td>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</td>
<td>Use with opioids can cause respiratory depression, coma, and death Contraindicated in narrow-angle glaucoma</td>
<td>May cause absence SE Clearance is slowed 2- to 5-fold in patients with alcoholic cirrhosis CNS-depressant effects potentiated by VPA, PB, narcotics, phenothiazines, MAOIs, and other antidepressants Inhibitors of CYP2C19 (cimetidine) and CYP3A4 (azoles) may decrease DZP clearance Inducers of CYP2C19 (rifampin) and CYP3A4 (CBZ, PB, PHT, dexamethasone) may increase elimination</td>
</tr>
<tr>
<td>Drugs, Formulations, and DEA Scheduling</td>
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<tr>
<td>midazolam (MDZ)</td>
<td>Seizure clusters, acute repetitive seizures</td>
<td>GABA&lt;sub&gt;A&lt;/sub&gt; receptor agonist; binds between α and γ subunits</td>
<td>Data from adults:  F = 44% PPB = 97% T&lt;sub&gt;max&lt;/sub&gt; (5-mg dose) = 17 min C&lt;sub&gt;max&lt;/sub&gt; = 54.7 ng/mL Less variability in absorption compared with IV MDZ Gut and hepatic metabolism via CYP3A4 to active metabolite 1-hydroxymidazolam t&lt;sub&gt;1/2&lt;/sub&gt; of parent and active metabolite = 2-6 h and 2-7 h, respectively</td>
<td><strong>First dose:</strong> 5 mg (1 spray) into 1 nostril <strong>Second dose (if needed):</strong> 10 min following the first dose = 5 mg (1 spray) into opposite nostril</td>
<td>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</td>
<td>CNS depression, somnolence, impaired cognition, HA, nasal discomfort, runny nose, throat irritation</td>
<td>Use with opioids can cause respiratory depression, coma, and death Contraindicated in narrow-angle glaucoma</td>
<td>Use with caution in patients receiving CYP3A4 inhibitors</td>
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<tr>
<td>Schedule IV</td>
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Table 2 (continued). Antiseizure Medications (ASMs) for treatment of acute repetitive seizures. September 8, 2020. (See Abbreviations.)
Table 3. Medications for Initial Treatment of Convulsive Status Epilepticus.\textsuperscript{6,14} September 10, 2020. (See Abbreviations.)

<table>
<thead>
<tr>
<th>Drug - Generic Name</th>
<th>Route/Dose</th>
</tr>
</thead>
</table>
| 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 |
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
Cmax = maximum plasma concentration
CMP = comprehensive metabolic panel
CNG = 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
FEN = 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
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-carbamazepine)
mTOR = mammalian target of rapamycin
M/H = 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
PPB = plasma protein binding
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
t1/2 = half-life
TCA = tricyclic antidepressant
TCS = tonic-clonic seizure
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
Vd = volume of distribution
VGB = vigabatrin
VPA = valproic acid
WBC = white blood cell
wk = week
y = year
ZNS = zonisamide
References


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American Epilepsy Society Treatments Committee, 2020

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