



Pediatric Epilepsy Treatment

7

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Introduction

In this chapter, we outline the primary pharmacologic, dietary, and surgical treatments for pediatric epilepsy. Over the past two decades, there has been a significant increase in available treatment options. The medications currently available are diverse in structure and proposed mechanisms of action (Table 7.1) [1–4]. Treatment decisions are often based on the consideration of seizure semiology, epilepsy syndrome, and side effects. Efficacy data is relatively limited in pediatric epilepsy treatment. We aim to highlight available data, as well as review treatment practices from the MassGeneral for Children Pediatric Epilepsy Program. This chapter is intended to be an overview of seizure treatment options. For individual patient care needs, please review the medication dosing recommendations at your institution and collaborate with the pharmacy team to guide specific therapeutic choices and titration schedules.

Antiseizure Medication (ASM) Management

Initiation of Treatment

Following a first-time seizure, treatment is typically deferred. After a single unprovoked event, Stroink et al. found that 46% of children did not have a second event within a two-year follow-up [5, 6]. However, after two unprovoked seizures, Hauser

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Table 7.1 Proposed mechanisms of action for antiseizure medications

| | Ion transport modulation | | | Neurotransmitter modulation | | | | | Other | |
|-------------------------|--------------------------|------|----|-----------------------------|-------------------|------------------|-----------|---------------|-------|------------------------------|
| | Na+ | Ca2+ | K+ | GABA _A receptor | GABA transaminase | GABA transporter | Glutamate | NMDA receptor | | Carbonic anhydrase inhibitor |
| Rufinamide | ■ | | | | | | | | | |
| Lacosamide | ■ | | | | | | | | | |
| Lamotrigine | | | | | | | ■ | | | |
| Cenobamate | | | | ■ | | | | | | |
| Benzodiazepines | | | | ■ | | | | | | |
| Fosphenytoin | | | | | | | | | | |
| Phenytoin | | | | | | | | | | |
| Carbamazepine | | | | | | | | | | |
| Oxcarbazepine | | | | | | | | | | |
| Eslicarbazepine acetate | | | | | | | | | | |
| Valproate | ■ | | | | ■ | | | | | |
| Topiramate | ■ | | | | | | | | | |
| Sulthiame | | | | | | | | | | |
| Zonisamide | | | | | | | | | | |
| Acetazolamide | | | | | | | | | | |
| Perampanel | | | | | | | | | | |
| Pregabalin | | | | | | | | | | |
| Gabapentin | | | | | | | | | | |
| Brivaracetam | ■ | | | | | | | | | |
| Levetiracetam | | | | | | | | | | |
| Ethosuximide | | | | | | | | | | |
| Felbamate | | | | | | | | | | |
| Phenobarbital | | | | | | | | | | |
| Primidone | | | | | | | | | | |
| Stiripentol | | | | | | | | | | |
| Vigabatrin | | | | | | | | | | |
| Tiagabine | | | | | | | | | | |
| Fenfluramine | | | | | | | | | | |
| ACTH | | | | | | | | | | |
| Cannabidiol | ▨ | | | | | | | | | |

CRH: corticotropin-releasing hormone

CRMP-2: collapsin response mediator protein-2

EAC-1: excitatory amino-acid carrier-1

* High concentrations

Reference (1–4)

Binds CRMP-2
 Tetrazole alkyl carbamate derivative
 Increased chloride permeability
 Inhibits calcium-calmodulin protein phosphorylation
 Inhibits calcium-calmodulin protein phosphorylation

Increase dopamine / serotonin, increase EAC-1

Antagonist of the AMPA-type glutamate receptor
 Modulates the release of glutamate, noradrenaline, substance P

Binds SV2A
 Binds SV2A; may indirectly modulate GABA and glycine activity

Possible serotonergic effects
 Stimulates cortisol release, inhibits CRH

et al. found that recurrence rates increased to about 75% in a population, across age groups [6, 7]. Treatment is therefore typically initiated after the second unprovoked seizure [6]. Patients with significant EEG abnormalities, or with a structural or metabolic etiology, are at higher risk for recurrence, and treatment may be initiated following a single event [8].

First ASM

The following parameters should be considered when choosing the first antiseizure medication: seizure type(s), epilepsy syndrome/etiology, age, comorbidities, and medication interactions [6]. To date, there are relatively few randomized control trials to support recommendations for first-line treatment in pediatric epilepsy. The following is a brief review of the data in select seizure types.

In a multicenter study evaluating initial treatment for children less than 3 years of age presenting with new onset non-syndromic epilepsy, levetiracetam was most often used first-line (62%) regardless of semiology [9]. It is important to note that this treatment practice is not based on efficacy data but rather consensus. The International League Against Epilepsy Treatment Guidelines review efficacy data for specific treatments as initial monotherapy for patients with newly diagnosed or untreated epilepsy [10]. Criteria for levels of evidence are presented in Table 7.2 [10].

For focal seizures, there is evidence to support treatment with oxcarbazepine (level A) [10]. For carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin, evidence supports possible efficacy (level C) [10]. Finally, for clobazam, clonazepam, lamotrigine, and zonisamide, evidence supports potential efficacy (level D) for focal seizures [10].

For generalized tonic-clonic seizures, there is level C evidence to support treatment with carbamazepine, phenobarbital, phenytoin, topiramate, and valproate [10]. For absence seizures, there is level A evidence to support treatment with ethosuximide and valproate and level C evidence to support treatment with lamotrigine [10]. For juvenile myoclonic epilepsy, there is level D evidence for treatment with topiramate, levetiracetam, and valproate [10].

There is a growing body of literature to support treatment decisions based on epilepsy syndrome or genotype. A few examples will be briefly reviewed here. For patients with Dravet syndrome ~60% of whom have an *SCN1A* mutation, primary treatment recommendations include valproate, clobazam (and other benzodiazepines), stiripentol, and topiramate [11, 12]. For patients with myoclonic atonic epilepsy, primary pharmacologic treatment choices include valproate, ethosuximide, and topiramate [13–16]. For patients with Landau-Kleffner syndrome and epilepsy with continuous spike-wave during sleep (CSWS), high-dose oral diazepam, ACTH, or corticosteroids should be considered. Alternative treatments include lamotrigine, valproate, and topiramate [8]. See Chap. 4 for additional syndrome-specific treatment recommendations. General guidelines for treatment dosing are outlined in Table 7.3 [1–3, 17–26].

There are some medications that may increase seizure frequency in certain situations. This holds true primarily for treating generalized seizures with medications typically used for focal epilepsy. Glauser et al. review that carbamazepine,

Table 7.2 Relationship between clinical trial ratings and level of evidence and conclusions by the International League Against Epilepsy

| Combinations of clinical trial ratings | Level of evidence | Conclusions for efficacy as monotherapy |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-----------------------------------------|
| ≥ 1 Class I study or meta-analysis meeting class I criteria sources OR ≥ 2 Class II studies | A | Established as effective |
| 1 Class II study or meta-analysis meeting class II criteria | B | Probably effective |
| ≥ 2 Class III double-blind or open-label studies OR 1 Class III double-blind or open-label study OR ≥ 1 Class IV clinical study OR Data from expert committee reports, opinions from experienced clinicians | C | Possibly effective |
| Class I: Prospective randomized control trial (RCT) or meta-analysis of RCTs that meets the following criteria: 1) Efficacy as a primary outcome 2) Treatment ≥ 48 weeks 3) Double blind 4) For superiority trials: superiority demonstrated For non-inferiority trials or failed superiority trials: rigorous criteria to demonstrate efficacy (methods described Ref. 10) 5) Study exit: not forced by a predetermined number of treatment emergent seizures 6) Appropriate statistics Class II: Prospective RCT or meta-analysis of RCTs that meets all the criteria of Class I except: Treatment ≥ 24 weeks but <48 weeks OR For non-inferiority trials or failed superiority trials: rigorous criteria to demonstrate efficacy but wider parameter compared to Class I (methods described Ref. 10) Class III: Prospective RCT or meta-analysis not meeting criteria for Class I or Class II Class IV: Evidence from non-randomized, prospective, controlled or uncontrolled studies, case series or expert reports | D | Potentially effective |

Ref. [10]

Table 7.3 Typical dosing for pediatric antiseizure medications

| | Starting dose (mg/kg/day) | Maintenance dose (mg/kg/day) | Number of daily doses | Target level (mcg/mL) |
|--------------------------------------|----------------------------------------|-------------------------------|-----------------------|-----------------------|
| Acetazolamide | 3–6 | 10–20 | 1–2 | |
| ACTH ^a | 150 IU/m ² /day | 85–250 IU/m ² /day | 2 | |
| Brivaracetam ^b | 1–2.5 | 5 (max) | 2 | |
| Cannabidiol | 5 | 10–25 | 2 | |
| Carbamazepine | 2–10 | 10–30 | 2–4 | 4–12 |
| Cenobamate ^c | 12.5 mg/day | 200–400 mg/day | 1 | |
| Clobazam | 0.1–0.2 | 0.8–2 | 2 | |
| Clonazepam ^d | 0.01–0.02 | 0.1–0.2 | 2–3 | |
| Diazepam | IV 0.15–0.2 mg/kg/dose | | | |
| Intranasal ^e | | | PR | |
| | 10–18 kg: 5 mg | | | 2–5 y: 0.5 mg/kg |
| | 19–37 kg: 10 mg | | | 6–11 y: 0.3 mg/kg |
| | 38–55 kg: 7.5 mg x2 | | | ≥ 12 y: 0.2 mg/kg |
| | ≥ 56 kg: 10 mg x2 | | | |
| Eslicarbazepine acetate ^f | 200 mg/day | 400–600 mg/day | 1 | |
| Ethosuximide | 5–10 | 20–40 | 1–3 | 40–100 |
| Felbamate | 15 | 15–45 | 3–4 | |
| Fenfluramine | 0.2 | 0.7 | 2 | |
| Fosphenytoin | 10–20 mg PE/kg | 4–5 | 1–4 | 10–20 |
| | Loading dose | | | Phenytoin level |
| Gabapentin | 10–15 | 25–50 | 3 | |
| Lacosamide | 2 | 4–12 | 2 | |
| Lamotrigine – monotherapy | 0.4 | 2–8 | 2 | |
| Lamotrigine – with valproate | 0.15 | 1–5 | 2 | |
| Lamotrigine – with enzyme inducers | 0.6 | 5–15 | 2 | |
| Levetiracetam | 20 | 30–100 | 2 | |
| Lorazepam | IV 0.1 mg/kg | | | |
| Midazolam | IV 0.1 mg/kg | | | |
| | IM 0.2 mg/kg | | | |
| | Intranasal | | | |
| | 0.2 mg/kg | | | |
| | ≥ 12 y: 5mg, may repeat x1 after 10min | | | |
| Oxcarbazepine | 8–10 | 30–40 | 2–3 | |
| Perampanel ^g | 2 mg/day | 4–8 mg/day | 1 | |
| Phenobarbital | 1–4 | 5–6 ^h | 1–2 | 10–40 |
| Phenytoin | 5 | 5–10 | 1–2 | 10–20 |
| Pregabalin ⁱ | 3.5–5 | 14 (max) | 2–3 | |
| Primidone | 1–2 | 10–20 | 2–4 | 5–12 |
| Rufinamide | 10 | 45 | 2 | |
| Stiripentol | 10–50 | 50–75 | 2–3 | |
| Sulthiame | 5 | 5–10 | 2 | |
| Tiagabine ^j | 0.1 | 0.5–2.0 | 2–4 | |
| Topiramate | 0.5–3 | 3–9 | 2–3 | 5–20 |
| Valproate | 10–15 | 20–60 | 2–3 | 50–150 |
| Vigabatrin | 50 | 150 (max) | 2 | |
| Zonisamide | 1–2 | 5–12 | 1–2 | |

- a. Treatment course is typically a minimum of 2 weeks followed by a 2-week taper
- b. 11–19 kg; see appendix for other weight-specific dosing
- c. Adolescents and adults
- d. ≤ 12 years
- e. Children 6–11 years, see appendix for dosing ≥ 12 years
- f. 11–21kg; see appendix for dosing > 21kg
- g. ≥ 4 years
- h. Infants, see appendix for dosing across age groups
- i. Infant to < 4 years
- j. > 12 years; see appendix for dosing with enzyme-inducing ASMs

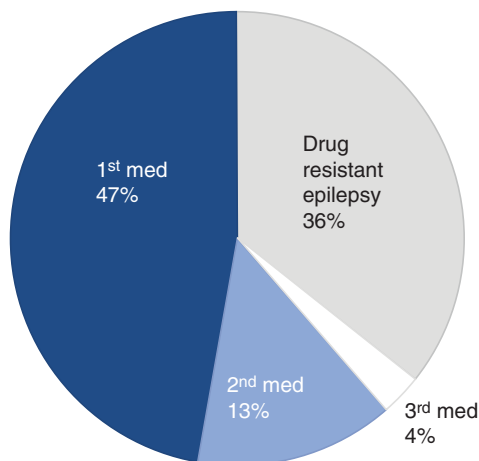
Refs. [1–3,17–26]

oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin are contraindicated in the treatment of absence seizures as they can exacerbate seizures in this context [10]. For juvenile myoclonic epilepsy, a similar set of treatments (with the addition of gabapentin and the exclusion of phenytoin) have been shown to exacerbate seizures [10]. In Dravet syndrome, sodium channel blockers, including carbamazepine, lamotrigine, and phenytoin, may worsen seizures and should be avoided [11, 27].

Second- and Third-Line Therapy

Kwan et al. found that 53% of patients across age groups failed initial monotherapy [28]. By comparison, in a pediatric cohort, Camfield et al. found improved outcomes with only 17% of patients showing failure of first-line therapy [29]. Poor response to first-line treatment portends poor long-term prognosis. With ineffective treatment response to initial monotherapy, only 11% eventually became seizure free [28]. Fig. 7.1 depicts seizure response rates across age groups following sequential medication trials [28]. In their review, Raspall-Chaure et al. describe that for patients who do not show a therapeutic response at an average ASM dose, only an additional 13–15% of patients will respond to an increase to maximal dosing [8]. Despite this fact, a given medication should be trialed near or just under maximal dosing before determining it a treatment failure. When the treatment choice has been determined to be ineffective, the clinician should reduce the dose of the first agent to the average therapeutic range and then add a second agent [8]. Once the second agent is therapeutic, the first-line agent should be slowly tapered

Fig. 7.1 Response to medication in previously untreated epilepsy across age groups [28]



and stopped, if possible, as monotherapy is typically the goal at this stage [8]. In many circumstances, however, a second agent is simply added on when the initial agent has shown incomplete efficacy. Again, poor early treatment response seems to portend poor prognosis. With failure of second-line treatment, less than 10% of individuals typically achieve long-term seizure freedom [8]. After two or three medications have been trialed as monotherapy, polytherapy is considered [8].

Drug-Resistant Epilepsy

In a prospective study of Dutch children, 12% of the cohort had a period of seizure intractability during the 15-year study interval [30]. Drug-resistant epilepsy is defined as failure to respond to two appropriately selected and trialed medications [6, 31]. At this point, dietary, surgical, and neuromodulating therapies should be considered. These non-pharmacologic treatments will be discussed later in the chapter.

There is no evidence to support increased efficacy with polytherapy compared to monotherapy [6]. Rational treatment theories recommend striving to choose two or more therapies that target different mechanisms of action. However, this hypothesis has limited data to support it as a superior treatment strategy. Human and animal data suggest three primary mechanistic combinations that may show improved clinical benefit: (1) combining a sodium channel blocker with a drug enhancing GABAergic inhibition; (2) combining two GABA mimetic agents; (3) combining an AMPA antagonist with an NMDA antagonist [32]. There are also a few specific ASM combinations that may have a synergistic effect in certain disease states. Examples of synergistic combinations include valproate with ethosuximide for absence seizures or myoclonic atonic epilepsy, valproate with lamotrigine for absence or myoclonic seizures, and stiripentol with clobazam for Dravet syndrome [11, 33–36].

With polytherapy, medication interactions are an important consideration. Many ASMs have interactions with each other as well as with many other classes of medications through hepatic enzyme-inducing or enzyme-inhibiting effects. A primary example is when valproate and lamotrigine are co-administered: valproate acts as a hepatic inhibitor of the metabolism of lamotrigine, and, as such, the lamotrigine dose typically needs to be significantly decreased to prevent toxicity (see appendix for detailed recommendations for valproate to lamotrigine cross titration) [1, 37, 38]. Table 7.4 highlights ASM interaction trends [1, 37]. Drug interactions should be evaluated by the treating provider whenever new medications are added and throughout the treatment course.

Treatment Side Effects

Side-effect profile is one of the primary considerations when selecting an ASM. There are two primary types of ASM side effects: neurotoxic and idiosyncratic. Neurotoxic side effects are a risk with nearly all ASMs and include symptoms such as somnolence, cognitive impairment, behavioral changes, vision

changes, and ataxia [8]. These side effects are dose-dependent and are thought to be more common with older medications than the newer generations of ASMs [8]. Idiosyncratic reactions are unpredictable and may include rash, Stevens-Johnson syndrome (SJS), serum sickness, agranulocytosis, aplastic anemia, and hepatotoxicity [8, 39]. One of the most important idiosyncratic reactions is SJS, classically described with lamotrigine treatment but also seen with other ASMs. The risk of serious rash from lamotrigine can be significantly decreased with a slow titration schedule. Primary risk factors for developing a rash (serious or not) with lamotrigine treatment include: a history of another ASM-related rash, young age, and co-treatment with valproate [8, 40]. See Tables 7.5 [1–3, 11, 23, 41] and 7.6 [1–3, 11, 42] for further details regarding medication side effects.

Laboratory Monitoring

Epilepsy treatment may include monitoring goal serum levels (Table 7.3) and/or following routine laboratory screening data, depending on the medication and patient risk factors. For many medications, routine laboratory screening is not indicated, felbamate being the notable exception. Among adults taking felbamate, there have been reports of fatal hepatic failure and aplastic anemia. Given the severity of a possible reaction, routine monitoring for agranulocytosis and hepatotoxicity is recommended [8, 43]. For other medications, laboratory evaluation is recommended in specific clinical circumstances depending on the medication, such as prior to surgery in patients taking valproate. Laboratory studies in this case should be sent to evaluate for hemostatic dysfunction (labs may include platelet count, PT, aPTT, TT, fibrinogen, vWF, factor XIII) [8, 44]. The clinician should have a very low threshold for checking laboratory tests if a patient presents with symptoms that could be explained by ASM toxicity. For example, a patient on valproate who presents with vomiting should have pancreatic and liver enzymes checked [8]. Routine ASM serum levels are not typically monitored for all medications. Some medications require drug level monitoring, including phenytoin, given its nonlinear kinetics, and carbamazepine, given the narrow therapeutic window [11, 45] Camfield et al. suggest that for patients on monotherapy with incomplete seizure control and no evidence of neurotoxicity, dosing may be increased without obtaining a medication level [45]. Similarly, for patients on monotherapy experiencing neurotoxicity, dosing should be decreased, again without obtaining a level. Clinical circumstances in which ASM levels may be helpful typically surround polytherapy [45]. If a patient presents with possible toxicity and/or uncontrolled seizures and it is unclear which medication may be causing the problem, ASM levels may provide guidance [8, 45].

Discontinuation of Treatment

When patients have been seizure free for 2 years, treatment discontinuation is typically considered. This clinical practice is supported by results of a Cochrane Review, which showed a 34% increased risk of seizure recurrence in patients for whom

Table 7.4 Potential impact on serum medication levels with concomitant dosing of antiseizure medications

| | Group A | | | | | | | | | | Group B | | | | | | | | | |
|-------------------------|---------|----|----|----|----|----|----|----|----|----|---------|----|----|----|----|----|----|----|----|----|
| Acetazolamide | | | | | | | | | | | | | | | | | | | | |
| ACTH | | | | | | | | | | | | | | | | | | | | |
| Bivacacetam | | | | | | | | | | | | | | | | | | | | |
| Cannabidiol | | | | | | | | | | | | | | | | | | | | |
| Carbamazepine | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A |
| Cenobamate | | | | | | | | | | | | | | | | | | | | |
| Clobazam | | | | | | | | | | | | | | | | | | | | |
| Clonazepam | | | | | | | | | | | | | | | | | | | | |
| Diazepam | | | | | | | | | | | | | | | | | | | | |
| Eslicarbazepine acetate | | | | | | | | | | | | | | | | | | | | |
| Ethosuximide | | | | | | | | | | | | | | | | | | | | |
| Felbamate | | | | | | | | | | | | | | | | | | | | |
| Fenfluramine | | | | | | | | | | | | | | | | | | | | |
| Fosphenytoin | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A |
| Gabapentin | | | | | | | | | | | | | | | | | | | | |
| Lacosamide | | | | | | | | | | | | | | | | | | | | |
| Lamotrigine | | | | | | | | | | | | | | | | | | | | |
| Levetiracetam | | | | | | | | | | | | | | | | | | | | |
| Lorazepam | | | | | | | | | | | | | | | | | | | | |
| Midazolam | | | | | | | | | | | | | | | | | | | | |
| Oxcarbazepine | | | | | | | | | | | | | | | | | | | | |
| Perampanel | | | | | | | | | | | | | | | | | | | | |
| Phenobarbital | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A |
| Phenytoin | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A |
| Pregabalin | | | | | | | | | | | | | | | | | | | | |
| Primidone | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A | 1A |
| Rufinamide | | | | | | | | | | | | | | | | | | | | |
| Stiripentol | | | | | | | | | | | | | | | | | | | | |
| Sulthiame | | | | | | | | | | | | | | | | | | | | |
| Topiramate | | | | | | | | | | | | | | | | | | | | |
| Valproate | | | | | | | | | | | | | | | | | | | | |
| Vigabatrin | | | | | | | | | | | | | | | | | | | | |
| Zonisamide | | | | | | | | | | | | | | | | | | | | |

x Avoid or careful consideration
 α carbamazepine-10, 11-epoxide
 β 10-hydroxycarbamazepine
 γ N-desmethylclobazam
 δ N-desmethylclonazepam
 ε 10-monohydroxy
 φ Phenobarbital
 θ Leviratracetam may decrease therapeutic efficacy of birivacacetam
 * Chronic benzodiazepine use will increase serum concentration of fosphenytoin / phenytoin; short-term use is less likely to have this effect
 † bold/highlight format indicates a change that is more likely to be clinically significant

Refs. [1,37]

ASM treatment was discontinued prior to the two-year mark [46]. This rate of recurrence was further increased for patients with an abnormal EEG and/or focal seizures, so for this cohort, a minimum of 2 years prior to medication discontinuation was recommended [46]. In this same review, however, the authors noted that there remains insufficient data to guide the timing of medication discontinuation for

Table 7.6 Critical/potentially life-threatening side-effects of antiseizure medications

| | Acetazolamide | ACTH | Bivalirudin | Carbamazepine | Concomitant | Clobazam | Clozapem | Diazepam | Ethosuximide | Etosuximide | Febrile | Ferriuramine ^d | Fosphenytoin ^e | Gabapentin | Lucosamide | Lamotrigine | Levetiracetam | Lorazepam | Midsazolam | Oxcarbazepine | Perampanel | Phenytoin | Pregabalin | Primidone | Rufinamide | Stiripentol | Sufisiam | Topiramate | Valproate | Vigabatrin | Zonisamide | | | | | |
|------------------------------------|---------------------------------------|------|-------------|---------------|-------------|----------|----------|----------|--------------|-------------|---------|---------------------------|---------------------------|------------|------------|-------------|---------------|-----------|------------|---------------|------------|-----------|------------|-----------|------------|-------------|----------|------------|-----------|------------|------------|--|--|--|--|--|
| Neurologic | Encephalopathy | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Status epilepticus | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Serotonin syndrome | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Psychiatric disorder / SI | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Visual field deficit | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Glaucoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Systemic | Peripheral neuropathy | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Acute toxic reaction ^a | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Hypersensitivity reaction / SJS / TEN | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Systemic lupus erythematosus | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Cardiac arrhythmia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Increased PR interval | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Decreased QT interval | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Cardiac valvular disease | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Mycardial dysfunction | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Hypotension | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Respiratory depression ^b | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Angioedema | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Hepatotoxicity | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Pancreatitis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Renal dysfunction | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Metabolic acidosis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Nephrolithiasis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Rhabdomyolysis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Hyponatremia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Hypoglycemia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hematologic dyscrasia ^c | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Lymphoma | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Immunosuppression | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hypogammaglobulinemia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Oligohidrosis / hyperthermia | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

a. Acute toxic reaction: sedation, ataxia / dizziness, nausea / vomiting
 b. Typically seen at high dose and/or in combination with additional CNS depressant
 c. Hematologic dyscrasia: agranulocytosis, neutropenia / leukopenia, aplastic anemia, thrombocytopenia
 d. Theoretical risk for cardiac valvular disease and pulmonary hypertension; not identified in recent studies
 e. With long-term use, side-effect profile follows that of phenytoin; with acute IV infusion, there is risk for myocardial dysfunction and hypotension
 f. Nonconvulsive or absence status epilepticus

SI: suicide ideation
 SJS: Stevens-Johnson syndrome
 TEN: toxic epidermal necrolysis

Reference [1–3,11,42]

expected [48]. In these self-limited syndromes, indications for initiating therapy include: frequent seizures, young age (4 years or less), daytime seizures, generalized tonic-clonic seizures, a history of status epilepticus, or seizures causing significant distress/limiting quality of life for the patient or their family [48]. Treatment is also indicated if seizures are a likely component of an epileptic encephalopathy.

Febrile seizures are typically not treated with ASMs. Provoked seizures, such as those related to intoxication or trauma, are typically not treated [11]. Prophylactic treatment in the setting of concomitant intraparenchymal hemorrhage or subdural hemorrhage in high-risk populations remains controversial, given that the evidence to support this practice is mixed [49, 50].

Dietary Treatment

Dietary therapy is one of the most effective treatments available in the field of pediatric epilepsy. Consensus guidelines recommend offering dietary therapy to patients who have failed to respond to two appropriately selected and dosed anti-convulsants [51]. Dietary therapy is widely used in the treatment of both focal and generalized epilepsies. Therapeutic diets can also be effective in treating epileptic encephalopathies, such as infantile spasms [51–55]. The ketogenic diet is highly effective for patients across age groups and a range of seizure types and etiologies

[56]. In a meta-analysis of three randomized controlled trials of the ketogenic diet, 52% of the participants in the intervention group showed a seizure frequency reduction of $\geq 50\%$ [57].

The classic ketogenic diet is a high-fat, low-carbohydrate diet. With this treatment, patients are followed by a dietician who works with their neurologist. The ketogenic diet simulates a fasting state, and metabolism shifts from glycolysis toward fatty acid oxidation. All meals maintain a macronutrient ratio of 4:1 or 3:1 of fats to combined carbohydrates and protein. Meal preparation requires special attention to the above ratios, micronutrients, and fluid status. Maintaining the appropriate nutrient ratios often requires the use of a gram scale. Formula preparations are also commercially available.

Historically, the ketogenic diet has been difficult to tolerate for some patients. However, in recent years, the availability of compatible foods and recipe books created by patients and families has made this approach more palatable. Although data supporting the classic ketogenic diet is most robust, there are also other less restrictive diets that may be equally as effective. The low glycemic index treatment and the modified Atkins diet have been developed as liberalized versions of the classic ketogenic diet [58, 59]. These less restrictive diets allow more freedom in food choice, and less precision is required with meal preparation compared to the classic diet.

There are some seizure and metabolic disorders in which ketogenic diet is considered a primary therapy. Patients with pyruvate dehydrogenase deficiency may receive significant benefit in general neurologic outcomes and longevity with the ketogenic diet, as this therapy allows for a bypass of the metabolic defect and provides ketones as an alternative form of fuel to glucose [60]. Ketogenic diet is considered first-line therapy in patients with GLUT-1 glucose transporter deficiency, as it provides ketone bodies to the CNS, rather than glucose which cannot enter neurons [61]. The following populations may also be particularly responsive to the ketogenic diet: Angelman syndrome, complex 1 mitochondrial disorders, Dravet syndrome, myoclonic atonic epilepsy, febrile infection-related epilepsy syndrome, Ohtahara syndrome, and tuberous sclerosis complex [51].

Dietary therapy is contraindicated in patients with certain inborn errors of metabolism, including disorders of fatty acid mitochondrial transport, β -oxidation, and other mitochondrial cytopathies [56]. Gastrointestinal side effects are the most common in ketogenic diet therapy and typically occur during the initial first few weeks of treatment [51]. Additional side effects may include decreased linear growth, transient hypertriglyceridemia, metabolic acidosis, and nephrolithiasis [51]. Concomitant treatment with oral citrate salts may help prevent renal stones [62]. There have been rare cases of increased liver transaminases, hepatosteatosis, and cholelithiasis during the first year of treatment with the ketogenic diet [63]. Other rare but reported adverse effects with dietary therapy include cardiomyopathy, prolonged QTc interval, as well as pancreatitis [56].

The duration of epilepsy diet treatment is variable. Reasons to discontinue treatment include: lack of efficacy, poor compliance, and/or intolerable side effects [64].

If the patient has not demonstrated a positive treatment response, treatment is typically discontinued after 3–6 months. If a significant treatment response is seen (>50% decrease in seizure frequency), clinicians may consider discontinuing therapy after 2 years [51]. In one study, 80% of patients who became seizure free on the ketogenic diet remained so after treatment was discontinued [65]. Dietary therapy can be abruptly stopped in an emergency, but often the diet is weaned with gradual reintroduction of carbohydrates over a period of 1–3 months [51].

Epilepsy Surgery

For patients with drug-resistant epilepsy, epilepsy surgery should be considered. In recent years, there have been increased efforts to prevent the delay of surgical evaluation for pediatric patients with drug-resistant epilepsy [66]. Primary pathologies in pediatric epilepsy for which surgical intervention may be targeted include the following: cortical dysplasia, developmental brain tumors such as dysembryoplastic neuroepithelial tumor, ganglioglioma, perinatal injuries including stroke, hippocampal sclerosis, gliosis of any cause, tuberous sclerosis, hypothalamic hamartoma, Rasmussen's encephalitis, and vascular malformations [66].

For lesional surgery, patients undergo an extensive workup to evaluate their candidacy for surgical resection. With this evaluation, teams aim to lateralize and localize an epileptic focus as well as determine the cortical function of the region at and surrounding it [67]. Phase 1 of the presurgical evaluation is largely noninvasive and may include some combination of the following: ictal and interictal EEG monitoring, magnetoencephalography (MEG), MRI/MRS, functional MR imaging, interictal positron emission tomography (PET), ictal/interictal single-photon emission computed tomography (SPECT), neuropsychological assessment, or intracarotid sodium amobarbital testing (Wada test). Phase 2 may include invasive monitoring with intracranial (subdural) or intracerebral electrodes, stereo-electroencephalography, electrocorticography, or cortical stimulation [67].

Lesional surgery is typically categorized as temporal and extra-temporal. Anterior temporal, selective mesial resection (amygdalohippocampectomy), and neocortical (extended) lesionectomy are the primary temporal resection strategies [68]. The most common primary temporal lesions are tumors, cortical dysplasia, and hippocampal sclerosis. Rates of seizure freedom following temporal resection range from 58% to 85% [68]. Surgical resection of extra-temporal lesions is often more challenging, given that the epileptic focus can be more difficult to localize and there is higher risk of damaging areas of eloquent cortex adjacent to the lesion [69]. Surgical planning may therefore involve more extensive invasive monitoring in extratemporal locations [69]. Typically, surgical outcomes are more guarded in extratemporal resection, but can still be quite successful. In a meta-analysis of 37 studies of pediatric extra-temporal epilepsy surgery, 56% of patients were seizure free post-operatively [69, 70].

Functional hemispherectomy is a surgical technique that has evolved from early iterations that involved complete resection of a hemisphere to modern

disconnection approaches [71]. Surgical hemispheric disconnection is considered for patients with catastrophic hemispheric epilepsy most frequently in the setting of Rasmussen syndrome. It may also be employed for patients with hemiconvulsion-hemiplegia-epilepsy syndrome, Sturge-Weber syndrome, hemimegalencephaly, multilobar cortical dysplasia, perinatal infarction, or porencephalic cysts [71].

Corpus callosotomy is a surgical disconnection technique that aims to block the spread of epileptic discharges between the hemispheres [72]. This surgical procedure may be staged, with an initial disconnection of the anterior corpus callosum, preserving the connection at the splenium. If seizures persist, the patient may return to the operating room for complete disconnection. In some cases, it may be undertaken as a single-stage complete callosotomy [72]. This procedure is considered for patients with severe refractory epilepsy for whom lesion resection is not possible, due to bilateral foci or primary generalized seizures. Corpus callosotomy is most frequently used to target a reduction in atonic seizures, which can result in severe injury. Patients with atonic seizures related to Lennox-Gastaut syndrome are often considered for corpus callosotomy [72].

Patients with an epileptic focus in eloquent cortex may not be candidates for lesion resection but might be considered for surgical intervention with multiple subpial transection of the lesion. This surgical technique involves multiple vertical incisions made perpendicular to the surface of the cortex, resulting in the interruption of the short horizontal fiber intracortical connections [73]. The goal is to disrupt the synchronization and spread of epileptogenic discharges while preserving baseline cortical function [73]. Populations who may benefit from this technique include patients with Landau-Kleffner syndrome, cortical dysplasia, epilepsia partialis continua, and Rasmussen's encephalitis [73].

A number of surgical techniques that have recently emerged may be less invasive than open resection. One example is stereotactic MRI-guided laser thermal ablation of the epileptogenic lesion [74, 75]. There are currently two FDA-approved systems, Visualase (Medtronic, Minneapolis, MN, USA), and NeuroBlate (Monteris Medical, Plymouth, NM, USA) [75]. In this technique, a laser probe is introduced through a burr hole in the skull and advanced with imaging guidance to the epileptic focus. Thermal ablation of the lesion is monitored in real time with MR-thermography [76]. One of the benefits is the ability to target deep lesions. There are few reports of the use of this technique in the pediatric epilepsy population, but the adult literature has shown some encouraging results [76]. Possible surgical targets for laser interstitial thermal therapy include hypothalamic hamartomas, cortical dysplasias (including insular lesions), corpora callosa, and periventricular heterotopias [76].

Finally, radiosurgical treatment for pediatric epilepsy is emerging as a viable treatment option. With the Gamma Knife technique, multiple stereotactic ionizing beams of radiation are targeted to the epileptic focus while limiting radiation exposure to the surrounding tissue [77]. This technique may be used for patients with mesial temporal lobe epilepsy with high risk for memory loss or who have previously undergone open surgery and had incomplete seizure control with prior resective surgery [77]. Radiosurgical intervention is also employed to treat hypothalamic hamartomas and cavernous malformations, and to perform callosotomies [77].

Neurostimulation

For patients with drug-resistant epilepsy who are not candidates for surgical resection, neuromodulation may be considered. The primary technology used in pediatric epilepsy is the vagus nerve stimulator (VNS). It is FDA-approved for patients 4 years and older for focal seizures, but it is commonly used for multiple seizure types and drug-resistant epilepsy syndromes [78, 79]. With VNS, a device is surgically placed subcutaneously in the left clavicular or lateral thoracic region similar to a cardiac pacemaker. An electrode is wrapped around the left vagus nerve and directs electrical impulses afferently into the brain. Efferent stimulation along the vagus nerve is blocked to prevent disruption of normal autonomic function. Stimulation is cycled at scheduled frequencies and can be programmed by clinicians using an external device. In the setting of aura or a seizure event, a magnet can be swiped over the device by the patient or caregiver to trigger a longer pulse stimulus to potentially abort or truncate the seizure [79]. Newer models (since July 2015) have an auto-detect feature that triggers a pulse of stimulation if there is an abrupt increase in heart rate, considered a proxy for seizure activity [78]. A meta-analysis of 74 clinical studies across age groups demonstrated 50% of patients had a greater than 50% reduction in seizures [79, 80]. Early side effects include hoarseness and cough, but these frequently improve with time [78]. There are low rates of surgical adverse events, but there is a risk of possible vocal cord paralysis related to the implantation procedure [78].

A second type of neuromodulation for refractory epilepsy is responsive neurostimulation. Though not currently approved for patients under 18 years, responsive neurostimulation is a technique that involves surgical implantation of a stimulator in the skull that is connected to up to two subdural or depth electrodes placed at the seizure focus [78]. The device collects continuous EEG data and provides cortical stimulation when abnormal electrical activity is detected prior to a seizure. NeuroPace, Inc. (Mountain View, CA, USA) was the first system to become FDA-approved [75, 79]. In a randomized control trial of adult patients, 59% of subjects responded to treatment at the 6-year mark, with a median reduction in seizures of 66% [79, 81]. Current use in pediatrics is off-label in specialized epilepsy centers [79].

Deep brain stimulation (DBS) is an additional neuromodulatory technique that shows some promising results but is not currently approved for use in pediatric patients [79]. Similar to the use of this technique in movement disorders, a generator is placed subcutaneously superficial to the pectoral muscles, and depth electrodes are placed in the brain. Options for electrode placement include the anterior or centromedian nucleus of the thalamus, hippocampus, globus pallidus, cerebellum, or the site of suspected seizure onset [78, 79, 82]. The exact mechanism by which DBS exerts its antiseizure effect is unknown. It has been proposed that DBS may disrupt the neural networks involved in seizure propagation [79, 83]. Pediatric efficacy data are limited, but one series of 13 pediatric subjects with electrodes in the centromedian nucleus of the thalamus demonstrated greater than 50% reduction in seizures in 92% of patients at 18 months [84]. In a systematic review of DBS

treatment in 40 patients with drug-resistant epilepsy, 13% became seizure free and 85% showed reduction in seizure frequency [23, 85].

Status Epilepticus

Convulsive status epilepticus is the most common pediatric neurologic emergency [86]. Though the duration of seizure activity qualifying as status epilepticus has fluctuated over the years, the current consensus from the 2012 Neurocritical Care Society's Guideline on the Evaluation and Management of Status Epilepticus and the 2016 American Epilepsy Society's Guideline for Status Epilepticus Management defines status epilepticus as 5 minutes of continuous clinical or electrographic seizure activity [87–89]. Refractory status epilepticus is defined as persistent seizure activity following an initial abortive treatment (benzodiazepine) and an appropriate second antiseizure medication [88].

Treatment algorithms aim to stop both clinical and electrographic seizures within 60 minutes of presentation [88]. However, treatment should be initiated after 5 minutes of seizure activity, whether in the community or in the emergency department. Timing is critical. Chin et al. found for every minute that passed between the onset of status epilepticus and initiation of therapy, there was a 5% cumulative increase in the risk of developing refractory status epilepticus [86, 90]. Lewena et al. found that the first one or two medications administered were effective for 86% of cases when given within 20 minutes of seizure onset but were effective for only 15% of cases when seizure duration exceeded 30 minutes [86, 91]. The time from status onset to first, second, and third ASM dosing is positively correlated with the duration of refractory status epilepticus [92, 93]. One proposed mechanism for this phenomenon is that with prolonged status epilepticus, inhibitory GABA receptors on the neuronal cell membrane are internalized, making benzodiazepines less effective [86, 94, 95].

Etiology of Pediatric Status Epilepticus

Etiology is critical when approaching the question of treatment. Status epilepticus is classified into 5 categories: prolonged febrile convulsion, acute symptomatic (CNS infection, head injury, acute vascular accident), remote symptomatic (previous neurological abnormality), idiopathic epilepsy-related (known idiopathic epilepsy, or when the presentation allows a diagnosis of idiopathic epilepsy to be made), progressive encephalopathy (epilepsy secondary to a neurodegenerative process), and unclassified [96]. In a multicenter study of infants in the United Kingdom presenting in refractory convulsive status epilepticus, acute symptomatic causes were the most common (28.5%); in patients 1–5 years of age, prolonged febrile convulsions were the most common (33.8%); in patients over 5 years of age, remote symptomatic status was the most common (36–40%) [96]. A multicenter study in Australia and New Zealand reported that 67% of patients presenting in status had a

history of prior seizure, and 35% carried a diagnosis of epilepsy. In this same study, 3% were found to have meningitis/encephalitis, and 1% had an electrolyte disturbance or hypoglycemia [97].

Status Epilepticus Treatment Pathway

Stabilization of the airway, breathing, and circulation, emergent diagnostic, and emergent treatment for status epilepticus should occur in tandem [89]. Patients should be assessed for airway protection and adequacy of oxygenation, ventilation, and perfusion. Peripheral intravenous access should be established. Finger-stick glucose should be checked, and the following STAT labs should be sent: complete metabolic panel, complete blood count with differential, PT/PTT, blood gas, toxicology screen, and anticonvulsant levels [88, 89]. Fig. 7.2 outlines a status epilepticus treatment reference [86–89, 98–101].

The American Academy of Neurology reported the following clinical data for pediatric patients in status epilepticus: low antiseizure medication levels (32%), neuroimaging abnormalities (8%), electrolyte disturbances (6%), inborn errors of metabolism (4%), ingestion (4%), central nervous system infections (13%), and positive blood cultures (3%) [89, 98].

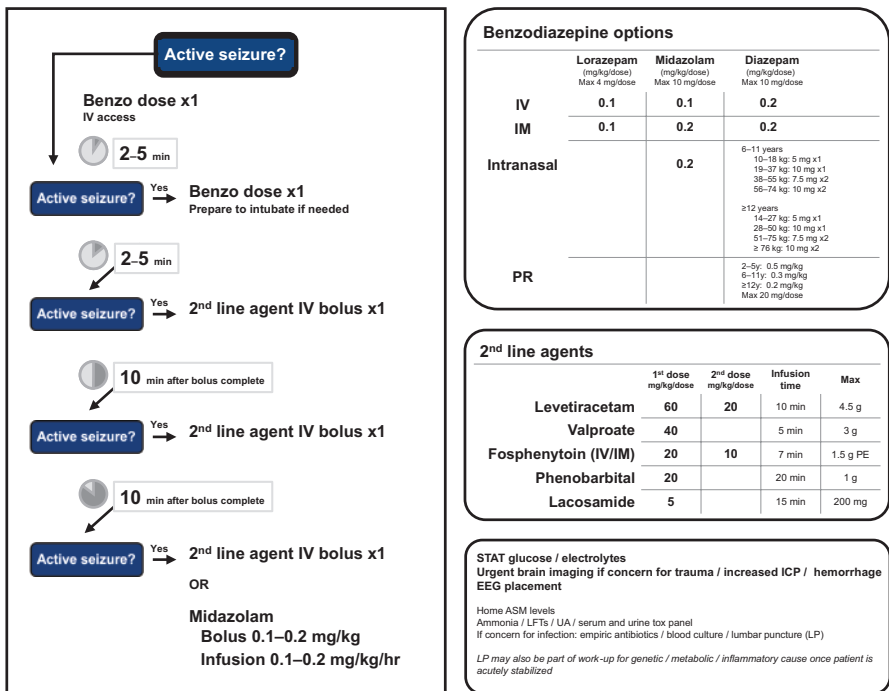


Fig. 7.2. Status epilepticus treatment reference. Refs. [86–89,98–101]

First-Line Treatment

Status epilepticus treatment is classified as (1) emergent, (2) urgent, and (3) refractory [86]. **Emergent** antiseizure treatment should start with a benzodiazepine.

If the patient has IV/IO access

Lorazepam IV 0.1 mg/kg/dose (max 4 mg) **or**
Diazepam IV 0.15–0.2 mg/kg/dose (max 10 mg)

If the patient does not have IV access

Midazolam IM 0.2 mg/kg/dose (MAX 10 mg) **or**
Midazolam intranasal 0.2 mg/kg/dose **or**
Midazolam buccal 0.5 mg/kg/dose
or
Diazepam PR
2–5 years: 0.5 mg/kg
6–11 years: 0.3 mg/kg
≥ 12 years: 0.2 mg/kg (max 20 mg)

If the seizure persists for 5 minutes following the first treatment, a second benzodiazepine dose should be administered [89]. Lorazepam, diazepam, and midazolam have equivalent efficacy and risk of respiratory depression [87, 89]. Metabolic derangements, including hypoglycemia, hypocalcemia, hyponatremia, and hypomagnesemia should be treated expeditiously [89].

Second-Line Treatment

In a series of over 500 pediatric cases, 70% required additional treatment beyond benzodiazepines to control convulsive status epilepticus [89, 97]. If the seizure persists, **urgent** treatment with an intravenous loading dose of one of the following four agents is indicated: fosphenytoin, levetiracetam, phenobarbital, or valproate. Efficacy data are limited to guide rank order of these options. The Established Status Epilepticus Treatment Trial (ESETT), a randomized, blinded, adaptive trial, showed non-superiority between fosphenytoin, valproate, and levetiracetam for convulsive status epilepticus [102]. In this trial, these medications did not differ significantly with regard to safety [102]. Further analysis of the data showed no difference in the efficacy of the three options by age group, including a pediatric population (<18y) [103]. The American Epilepsy Society's guidelines, when comparing valproate and phenobarbital, describe that valproate has equivalent efficacy but better tolerability [87, 88]. A meta-analysis of the four medications found phenytoin had lower efficacy (50%) when compared to levetiracetam (69%), phenobarbital (74%), and valproate (76%) [89, 104]. Lacosamide is an alternative agent that may be used for acute status management, although data in children are limited. For patients with

epilepsy on standing ASM treatment, giving an IV loading dose of one of the patient's medications may be prudent. Beyond this, clinicians should consider the medication side-effect profiles in the context of the patient's current clinical circumstances and hemodynamics to help guide second-line agent selection. Valproate should be avoided in the setting of hepatic dysfunction, metabolic or mitochondrial disease, pancreatitis, or thrombocytopenia, or in patients less than 2 years of age with status epilepticus of unknown etiology [88, 89]. Given the risk for cardiac dysfunction, fosphenytoin should be avoided if a patient is in a low cardiac output state or at increased risk for arrhythmias. Similarly, particularly with rapid infusion, phenobarbital may precipitate hypotension, respiratory depression, or apnea and has the potential for prolonged sedative effect.

Urgent Workup

For patients with a history of trauma or malignancy, or in cases when the etiology of status is unknown, neuroimaging should be performed urgently [89]. Glucose and electrolytes should be evaluated immediately. Further laboratory workup to evaluate the cause of status may include lumbar puncture, urine toxicology screen, and a screen for inborn errors of metabolism. If infectious source is on the differential, CSF should be sent for cell counts, gram stain, culture, protein, glucose, and herpes simplex virus PCR, followed by the initiation of empiric coverage with antibiotics and acyclovir [89].

EEG Monitoring

EEG monitoring should be initiated within 15–60 minutes in cases where there is concern for ongoing seizure activity or the patient is not returning to baseline, raising concern for nonconvulsive status epilepticus [88, 89]. Long-term EEG monitoring may be indicated for 24–48 hours following presentation in status epilepticus depending on the clinical course.

Refractory Status Epilepticus Treatment

Refractory status epilepticus occurs in 10–40% of children with status epilepticus [89]. In the ESETT trial, approximately half of patients showed seizure cessation following initial loading dose of a second-line agent [102]. For persistent seizure activity, the Neurocritical Care Guidelines indicate that clinicians may consider giving a repeat loading dose of the selected second-line treatment or may move on to load with an alternative agent (phenobarbital, fosphenytoin, valproic acid, levetiracetam) [88, 89].

For persistent seizure activity following repeat loading doses, treatment transitions to the initiation of continuous infusion of anesthetic agents. At this point, patients should have a secured airway and be in a critical care unit with EEG in

place. In a multicenter study of pediatric refractory status, midazolam (78%) was the first anesthetic agent used with an initial loading dose of 0.1–0.2 mg/kg and a continuous infusion rate of 0.1–0.2 mg/kg/hr [101]. EEG should be actively followed with possible repeat bolus doses of 0.1 mg/kg and titration of the midazolam infusion every 5–30 minutes by 0.05–0.1 mg/kg/hr, to a goal of seizure suppression. In the event that midazolam fails to achieve seizure control at a dose of 1 mg/kg/hour, a transition to pentobarbital should be considered. Pentobarbital treatment can be initiated with a loading dose of 2–5 mg/kg followed by a continuous infusion at a rate of 0.5–1 mg/kg/hour. The initial bolus may be repeated in the absence of seizure suppression. Titrate to seizure suppression on EEG, re-bolusing with 1–2 mg/kg and increasing the continuous infusion by 0.5 mg/kg/hr to a max rate of 5 mg/kg/hr. Alternative agents to consider include propofol and ketamine. Currently, there is no consensus standard of care for the rate of anesthetic titration and/or max dosing for pediatric refractory status epilepticus care. The above recommendations represent expert opinion.

The Neurocritical Care Society guidelines recommend 24–48 hours of electrographic seizure control prior to initiation of a wean of continuous infusion treatments for refractory status [88, 89]. Broader workup for refractory status epilepticus may include the following: antibodies or PCR for viral encephalitides, autoantibody testing, or testing for inborn errors of metabolism [89, 105]. EEG monitoring is indicated throughout anesthetic treatment and for at least 24 hours after treatment is weaned [89, 106]

Conclusions

Pediatric epilepsy treatment requires evaluation and consideration of multiple variables and longitudinal care. Our collective goal for each child should be seizure freedom. Becoming comfortable with treatment options and effectively optimizing the regimen in an ever-changing research and clinical landscape is a true life's work. Unfortunately, head-to-head efficacy trials are limited, but there is a developing literature of syndrome-specific treatment and genotype-phenotype correlations to further guide treatment choice.

Dietary treatments have been shown to be as effective as any known pharmaceutical option and should be readily included among pediatric epilepsy treatment options. Our understanding of the therapeutic mechanisms and physiologic impact of dietary therapy continues to expand and will inform broader access and application. Evaluation for epilepsy surgery should be pursued in cases of refractory epilepsy without delay. Surgical techniques, specifically options for minimal and noninvasive intervention, continue to evolve offering the promise of improved seizure control and preserved function of surrounding eloquent cortex. The further development of treatment pathways for status epilepticus, focusing on the emergent nature of the disease and the necessity for rapid event capture, aims to improve outcomes and prevent lasting harm.

This work focusing on eliminating seizures for children, at the bench and at the bedside, holds immeasurable promise for the future for patients and families, in the

way of improved neurodevelopmental outcomes, systemic health and wellness, mitigating the risk of SUDEP, and improved quality of life.

Appendix: Antiseizure Medications

Acetazolamide

Section References: [1, 3, 107]

Acetazolamide is a broad-spectrum agent typically used for absence and focal seizures. It is also used in the treatment of GTCs, tonic/atonic, and myoclonic seizures. It may be used for catamenial epilepsy, Lennox-Gastaut syndrome (LGS), Landau-Kleffner/CSWS, and juvenile myoclonic epilepsy (JME).

Mechanism of Action

Inhibitor of brain carbonic anhydrase. This leads to increase in intracellular CO₂ and decrease in intracellular pH, which results in depression of neuronal activity.

Dosing

< 12 years:

Start treatment with 3–6 mg/kg/day given in 1–2 doses

Increase by 3–6 mg/kg/day every 3–7 days

Goal of 10–20 mg/kg/day

≥ 12 years:

Start 250 mg/day given in 1–2 doses

Increase by 250 mg/day every 3–7 days

Goal of 250–1000 mg/day

Side Effects

Neurologic: somnolence/lethargy, blurred vision, paresthesia

Systemic: GI symptoms, metabolic acidosis, anorexia

Critical/Potentially Life-Threatening Side Effects

Systemic: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hepatotoxicity, renal failure, metabolic acidosis, nephrolithiasis, agranulocytosis, aplastic anemia

Lab Monitoring

May evaluate baseline and periodic sodium bicarbonate, but this is not routine practice.

Adrenocorticotrophic Hormone (ACTH)

Section References: [1, 3, 8, 108, 109]

ACTH is typically used to treat infantile spasms (IS). It may also be used for severe epileptic encephalopathies including Landau-Kleffner syndrome, CSWS, LGS, Doose syndrome, Dravet syndrome, and Ohtahara syndrome. This medication must be administered intramuscularly.

Mechanism of Action

Stimulates cortisol release and inhibits cortisol-releasing hormone which has been reported as a proconvulsive neuropeptide.

Dosing

< 2 years:

Start 150 units/m²/day IM divided in 2 doses

Treatment course is typically a minimum of 2 weeks followed by a 2-week taper

Side Effects

Neurologic: irritability, insomnia

Systemic: hypertension, weight gain, hyperglycemia

Critical/Potentially Life-Threatening Side Effects

Systemic: myocardial dysfunction, immunosuppression, *Pneumocystis pneumonia*

Clinical/Lab Monitoring

Prior to treatment

Vital signs/blood pressure

UA, stool guaiac, CBC, Chem10 (electrolytes, BUN/Cr, Ca, Mg, phosphate)

Consider baseline echocardiogram

Throughout treatment

Blood pressure daily x1 week, then 3x weekly, urine glucose and stool guaiac

2x weekly

After 2–4 weeks: CBC with differential, Chem10

Consider follow-up echocardiogram

Avoid vaccines for 10 days prior to/during treatment. Treatment should include concomitant H2 antagonist for gut protection.

Brivaracetam

Section References: [1–3, 24, 110]

Brivaracetam is a broad-spectrum agent. The majority of data has been gathered in the treatment of focal seizures, but it has also shown promising results in the treatment of generalized seizures in adults [110].

Mechanism of Action

The mechanism is incompletely understood. It binds synaptic vesicle protein SV2A, involved in synaptic vesicle exocytosis. It is also a partial antagonist of sodium channels.

Dosing

<11 kg:

Start 1.5–3 mg/kg/day divided in 2 doses

Max 6 mg/kg/day

11–19 kg:

Start 1–2.5 mg/kg/day divided in 2 doses

Max 5 mg/kg/day

20–49 kg:

Start 1–2 mg/kg/day divided in 2 doses

Max 4 mg/kg/day

≥ 50 kg or ≥ 16 years:

Start 50–100 mg/day divided in 2 doses

Max 200 mg/day

Adding to levetiracetam does not likely provide additional benefit and may cause decreased efficacy.

Side Effects

Neurologic: somnolence/fatigue, irritability, ataxia/dizziness

General: GI symptoms

Critical/Potentially Life-Threatening Side Effects

Systemic: Hypersensitivity reaction

Lab Monitoring

Not required

Cannabidiol

Section References: [2–4, 20, 23, 111–113]

Cannabidiol is a broad-spectrum agent with suggested efficacy against both focal and generalized events. Treatment may be considered for LGS, Dravet syndrome, and tuberous sclerosis complex.

Mechanism of Action

The mechanism of action is incompletely understood. The antiseizure effect is likely not mediated by cannabinoid receptors [2, 111]. A potential mechanism has been proposed in which cannabidiol results in decreased intracellular calcium (via targets GPR55 and TRPV1), thereby reducing neuroexcitability. There may also be a therapeutic effect through modulation of adenosine-mediated signaling [4].

Dosing

Start 5 mg/kg/day divided in 2 doses
Increase by 5 mg/kg/day every 7 days
Goal 10–25 mg/kg/day

Side Effects

Neurologic: somnolence, irritability, insomnia
Systemic: GI symptoms, transaminitis, anorexia/weight loss

Critical/Potentially Life-Threatening Side Effects

Systemic: Hypersensitivity reaction

Lab Monitoring

Consider sending liver function tests (LFTs) at baseline, 1, 3, 6 months and then periodically; repeat labs within 1 month of dose change.

Carbamazepine

Section References: [1–3, 8, 11, 20, 114]

Carbamazepine is used to treat both focal seizures and primary GTCs. In some cases, it may cause seizure worsening for patients with idiopathic generalized epilepsies and/or epileptic encephalopathies. Carbamazepine should not be used to treat myoclonic, atonic, or absence seizures, as it may cause seizure exacerbation.

Mechanism of Action

Inhibits voltage-gated sodium channels, L-type calcium channels, and glutamate release.

Dosing

< 6 years:

Start 2–10 mg/kg/day divided in 2–3 (tab) or 4 (suspension) doses

Increase by 5–10 mg/kg/day every 7 days

Goal of 10–30 mg/kg/day

6–12 years:

Start 100 mg/day divided in 2 doses (tab) or 4 doses (suspension)

Increase by 100 mg/day every 7 days

Goal 600–1000 mg/day

> 12 years:

Start 200 mg/day divided in 2 doses (tab) or 4 doses (suspension)

Increase by 200 mg/day every 7 days

Goal of 800–1200 mg/day

Side Effects

Neurologic: somnolence, diplopia/blurred vision, ataxia/dizziness, headache

Systemic: GI symptoms, hyponatremia, leukopenia, rash, pruritis

Critical/Potentially Life-Threatening Side Effects

Neurologic: psychosis/mania

Systemic: SJS/TEN/hypersensitivity reaction, cardiac conduction disturbance, hyponatremia, bone marrow suppression, hypogammaglobulinemia

Lab Monitoring

Consider baseline CBC, Na, LFTs. Consider screening for HLA-B*1502 allele for patients with Asian ancestry due to potential increased risk for SJS/TEN. Repeat Na once treatment is therapeutic. Repeat Na and/or Chem10 periodically; LFTs and thyroid function tests as needed. Repeat CBC at 1–3 months after the start of treatment and every 6 months thereafter. Monitor for vitamin D deficiency with 25-hydroxyvitamin D levels.

Cenobamate

Section References: [2, 115]

Cenobamate is typically used for the treatment of focal seizures.

Mechanism of Action

A tetrazole alkyl carbamate derivative, it acts as an inhibitor of voltage-gated sodium channels and potentially also enhances GABA inhibition.

Dosing

Adults:

- Start 12.5 mg/daily
- Week 3–4: 25 mg/daily
- Week 5–6: 50 mg/daily
- Week 7–8: 100 mg/daily
- Week 9–10: 150 mg/daily
- Week 11-ongoing: 200 mg/day

Side Effects

Neurologic: somnolence/fatigue, dizziness, headache, diplopia

Critical/Potentially Life-Threatening Side Effects

Systemic: decreased QT interval, hypersensitivity reaction

Lab Monitoring

Defer routine monitoring. Consider monitoring LFTs and potassium as clinically indicated.

Clobazam

Section References: [1–3, 11, 20, 41, 116]

Clobazam is a broad-spectrum agent. It has a therapeutic role as monotherapy as well as adjuvant therapy. It is notably effective in the treatment of Dravet syndrome and LGS. For Dravet, clobazam can be paired with stiripentol for synergistic effect. Tolerance, dependence, and/or excessive sedation are not typically clinical limitations.

Mechanism of Action

Clobazam is a 1–5 benzodiazepine, with a nitrogen at the 1 and 5 positions on the diazepine ring. This differs from other benzodiazepines used in epilepsy treatment which host nitrogen at the 1 and 4 positions. Clobazam is a GABA_A agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

Dosing

< 12 years:

- Start 0.1–0.2 mg/kg/day daily at night

Increase by 0.1–0.25 mg/kg/day every 7 days
Goal of 0.8–2 mg/kg/day divided in 2 doses

≥12 years:

Start 5–10 mg/day at night
Increase by 5 mg/day every 7 days
Goal 40 mg/day given in 1–2 doses (max 80 mg/day)

Side Effects

Neurologic: somnolence, irritability/aggressiveness, ataxia, insomnia
Systemic: GI symptoms

Critical/Potentially Life-Threatening Side Effects

Systemic: SJS/TEN, respiratory depression

Lab Monitoring

Defer routine monitoring. May consider periodic monitoring of CBC and LFTs. Levels should be monitored when used with cannabidiol.

Clonazepam

Section References: [1–3, 11, 20, 117]

Clonazepam is a broad-spectrum agent used to treat both focal and generalized seizures. Efficacy against myoclonic and atonic seizures is most notable. It has a wide range of uses, particularly for epileptic encephalopathies, and is often employed as adjunctive therapy. It may also be used as an acute abortive treatment for seizure clusters.

Mechanism of Action

Clobazam is a type of benzodiazepine, a GABA_A agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

Dosing

≤ 12 years:

Start 0.01–0.02 mg/kg/day divided in 2–3 doses (max start 0.5 mg)
Increase by 0.05 mg/kg/day or ≤ 0.25 mg/day every 3–7 days
Goal of 0.1–0.2 mg/kg/day

> 12 years:

Start 0.25 mg at night
Increase by 0.25 mg/day every 7 days.
With titration, divide in 2–3 doses/day
Goal of 4–10 mg/day or 0.05–0.2 mg/kg/day

Side Effects

Neurologic: somnolence/fatigue, confusion, hyperexcitability, behavior changes, ataxia/impaired coordination

Critical/Potentially Life-Threatening Side Effects

Systemic: respiratory depression

Lab Monitoring

Defer routine monitoring. May consider periodic monitoring of CBC and LFTs.

Diazepam

Section References: [1, 3, 20, 118]

Diazepam is typically used as an acute abortive therapy for status epilepticus or seizure clusters.

Mechanism of Action

Diazepam is a type of benzodiazepine. GABA_A agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

Dosing

Abortive treatment options

PR dosing:

2–5 years: 0.5 mg/kg

6–11 years: 0.3 mg/kg

≥ 12 years: 0.2 mg/kg (max 20 mg)

Intranasal dosing:

6–11 years

10–18 kg: 5 mg in 1 nostril

19–37 kg: 10 mg in 1 nostril

38–55 kg: 7.5 mg x2, 1 spray in each nostril

56–74 kg: 10 mg x2, 1 spray in each nostril

≥ 12 years

14–27 kg: 5 mg, 1 nostril

28–50 kg: 10 mg, 1 nostril

51–75 kg: 7.5 mg x2, 1 spray in each nostril

≥ 76 kg: 10 mg x2, 1 spray in each nostril

IV dosing:

> 1 month

0.15–0.2 mg/kg/dose (max 10 mg/dose)

Side Effects

Neurologic: somnolence/fatigue, confusion, ataxia/dizziness

Critical/Potentially Life-Threatening Side Effects

Systemic: hypotension, respiratory depression

Lab Monitoring

Defer routine monitoring. May consider periodic monitoring of CBC and LFTs.

Eslicarbazepine Acetate

Section References: [1–3, 20, 119–121]

Eslicarbazepine acetate is used to treat focal seizures with or without secondary generalization. Like carbamazepine, eslicarbazepine acetate is contraindicated for primary generalized seizures due to the potential for exacerbation.

Eslicarbazepine acetate shares a chemical structure with carbamazepine and oxcarbazepine, a dibenzazepine nucleus with a 5-carboxamide substitute, but has an acetate group at the 10,11 position. Eslicarbazepine acetate and oxcarbazepine are pro-drugs, both metabolizing to the active licarbazepine. This metabolism results in both S and R chiral forms [120]. Both compounds are metabolically active, but the S form may cross the blood–brain barrier more effectively and potentially be less toxic. Oxcarbazepine metabolizes to chiral ratio S:R of 4:1, whereas eslicarbazepine acetate metabolizes to a ratio of 20:1 [120]. There is evidence for improved side-effect profile and stable seizure control when transitioning from oxcarbazepine to eslicarbazepine acetate [121].

Mechanism of Action

Inhibits voltage-gated sodium channels. May also impact glutamate release.

Dosing

11–21 kg:

Start 200 mg/day

Increase by 200 mg/day every 7 days

Goal 400–600 mg/day dosed daily

22–31 kg:

Start 300 mg/day

Increase by 300 mg/day every 7 days

Goal 500–800 mg/day

32–38 kg:

Start 300 mg/day

Increase by 300 mg/day every 7 days

Goal 600–900 mg/day

> 38 kg:

Start 400 mg/day

Increase by 400 mg/day every 7 days

Goal 800–1200 mg/day

≥ 12 years:

Start 400 mg daily

Increase by 400 mg/day every 2 weeks

Max dose 1200 mg/day

Side Effects

Neurologic: somnolence, impaired attention, diplopia/blurred vision, tremor, ataxia/dizziness, headache

Systemic: GI symptoms, abnormal liver function, hyponatremia

Critical/Potentially Life-Threatening Side Effects

Systemic: SJS/TEN, cardiac conduction disturbance (AV block, prolonged PR interval), hyponatremia

Lab Monitoring

Consider baseline CBC, sodium, LFTs. Consider screening for HLA-B*1502 allele for patients with Asian ancestry due to potential increased risk for SJS/TEN. Repeat sodium once treatment is therapeutic. Repeat Chem10 and LFTs to monitor for renal and hepatic function every 12 months. Consider monitoring 25-hydroxyvitamin D levels.

Ethosuximide

Section References: [1–3, 122]

Ethosuximide is principally used to treat absence seizures. In rare cases, it may also be used to treat atonic or myoclonic seizures. Ethosuximide is ineffective and contraindicated in the treatment of focal seizures and generalized tonic-clonic-seizures.

Mechanism of Action

Reduces the number or the conductance of low-threshold (T-type) calcium channels in thalamic neurons.

Dosing

2–12 years:

Start 5–10 mg/kg/day

Increase by 5–10 mg/kg/day every 7 days

Goal 20–40 mg/kg/day in 1–3 doses (max 60 mg/kg/day or 2000 mg/day)

> 12 years:

Start 250 mg/day

Increase by 250 mg/day every 7 days

Goal 750–1500 mg/day divided in 2–3 doses

Side Effects

Neurologic: somnolence, headache

Systemic: hiccups, GI symptoms, anorexia/weight loss

Critical/Potentially Life-Threatening Side Effects

Systemic: SJS/TEN, systemic lupus erythematosus, agranulocytosis/aplastic anemia

Lab Monitoring

Baseline CBC with repeat at 2 months and then as needed thereafter.

Felbamate

Section References: [1–3, 11, 20, 123]

Felbamate is a broad-spectrum agent used to treat both focal and generalized epilepsy. It is effective in the treatment of tonic/atonic, myoclonic, and absence seizures as well as infantile spasms. It is reserved for patients with LGS and/or severe refractory seizures. It is not currently first-line therapy for any indication. This is due to the side-effect profile which includes a black box warning for aplastic anemia and hepatotoxicity. Dosing can be challenging due to narrow therapeutic range and significant medication interactions. Given this, close laboratory monitoring follow-up with the prescribing team is essential for treatment.

Mechanism of Action

Inhibits N-methyl-D-aspartate (NMDA)-induced intracellular calcium currents and excitatory activity. It also potentiates GABA activity.

Dosing

2–14 years:

Start 15 mg/kg/day divided in 3–4 doses

Increase by 15 mg/kg/day at every 7 days

Goal 15–45 mg/kg/day

> 14 years:

- Start 1200 mg/day divided in 3–4 doses
- Increase by 600–1200 mg/day every 7 days
- Goal 3600 mg/day

May consider 20% reduction in concomitant ASMs (phenytoin/valproate/pheno-barbital/carbamazepine) with the start of felbamate to avoid toxicity. Provide slower medication titration if the patient is not taking an enzyme-inducing ASM prior to the start of felbamate.

Side Effects

Neurologic: irritability, ataxia/dizziness, headache, insomnia
Systemic: GI symptoms, anorexia/weight loss

Critical/Potentially Life-Threatening Side Effects

Systemic: hepatotoxicity, aplastic anemia

Lab Monitoring

Recommend baseline CBC and LFTs with repeat CBC every 2 weeks and repeat LFTs every 4 weeks.

Fenfluramine

Section References: [23, 25, 41, 124]

Fenfluramine is an amphetamine derivative that has been shown to be effective for patients with LGS and Dravet syndrome. It was initially FDA approved for weight loss but was removed from the market in 1997 with safety concerns for the development of pulmonary hypertension and valvular heart disease. Over the past two decades there have been reports of potential efficacy against seizures with a novel serotonergic mechanism [23]. Fenfluramine was reapproved by the FDA in 2020 for treatment for patients with Dravet syndrome. In the 2019 trial, there were no reported cases of pulmonary hypertension or valvular disease in children or young adults [41, 124]. In the United States, there is a REMS program to facilitate prescriber education, routine cardiac monitoring, and reporting of these potential adverse events.

Mechanism of Action

The mechanism is unknown. Modulation of NMDA receptor-mediated excitation and/or serotonergic effects are two mechanisms that have been proposed.

Dosing

≥ 2 years:

- Start 0.2 mg/kg/day divided in 2 doses
- Increase by 0.2 mg/kg/day every 4–7 days
- Goal of 0.7 mg/kg/day (max 13 mg)

Side Effects

Neurologic: somnolence/fatigue

Systemic: GI symptoms, anorexia/weight loss

Critical/Potentially Life-Threatening Side Effects

Neurologic: serotonin syndrome

Systemic: cardiac valvular disease, pulmonary hypertension

Clinical Monitoring

Through the REMS program, cardiac echo is recommended at baseline prior to the start of treatment, every 6 months during treatment, and then once 3–6 months after the completion of treatment.

Fosphenytoin

Section References: [1–3, 125]

Fosphenytoin is a water-soluble prodrug of phenytoin. It is an IV formulation primarily used as an abortive therapy for status epilepticus. It may also be used as a substitute for phenytoin when enteral access is limited; this is typically short term.

Both phenytoin and fosphenytoin are used for focal seizures with or without secondary generalization. They may also be effective against some generalized seizures including primary GTC or for patients with mixed semiology, including tonic seizures. Fosphenytoin has the potential to worsen a subset of generalized seizures, typically myoclonic and absence. Fosphenytoin should be avoided for patients with LGS and progressive myoclonic epilepsies.

Mechanism of Action

Blocks voltage-gated sodium channels and modulates sustained repetitive firing. It also inhibits calcium channels and calcium sequestration and inhibits calcium-calmodulin protein phosphorylation.

Dosing

Status epilepticus:

Loading dose: 20 mg PE/kg IV

Seizure prophylaxis:

Loading dose: 10–15 mg PE/kg IV

Maintenance dosing: 4–5 mg/kg/day divided in 1–4 doses

With acute IV infusion, there is risk for myocardial dysfunction and hypotension. With long-term use, the side-effect profile follows that of phenytoin (see below).

Gabapentin

Section References: [1–3, 11, 20, 126]

Gabapentin is primarily used to treat focal seizures with or without secondary generalization. In some cases, it may worsen generalized seizures.

Gabapentin is a GABA analog and structurally similar to pregabalin. Its effect as an antiseizure treatment, however, does not seem to be mediated by modulation of GABA.

Mechanism of Action

Binds to voltage-gated presynaptic calcium channels which inhibit inward calcium currents and decrease neurotransmitter release.

Dosing

3–5 years:

Start 10–15 mg/kg/day divided in 3 doses
Increase by 8–10 mg/kg/day daily for 3 days
Goal 40–50 mg/kg/day

6–12 years:

Start 10–15 mg/kg/day divided in 3 doses
Increase by 10 mg/kg/day daily for 3 days
Goal 25–35 mg/kg/day

> 12 years:

Start 300 mg/day daily
Increase by 300 mg/day daily divided in 3 doses
Goal 900–1800 mg/day (max 3600 mg/day)

Side Effects

Neurologic: somnolence/fatigue, diplopia/blurred vision, nystagmus, tremor, ataxia/dizziness

Systemic: GI symptoms, increased appetite/weight gain

Critical/Potentially Life-Threatening Side Effects

Systemic: pancreatitis, leukopenia

Lab Monitoring

Consider baseline LFTs and Chem10 to evaluate liver and renal function. Baseline CBC with repeat after 3 and 6 months of treatment.

Lacosamide

Section References: [1–3, 20, 127–129]

Lacosamide is primarily used to treat focal seizures. In some cases, it may be trialed for the treatment of refractory generalized seizures, but efficacy data are limited in

pediatrics [128, 129]. With parenteral administration, it may be used for status epilepticus or if enteral access is limited.

Mechanism of Action

Enhanced slow inactivation of sodium channels, leading to stabilization of hyperexcitable neuronal membranes and inhibition of repetitive firing. A second proposed mechanism suggests that lacosamide may bind collapsin response mediator protein-2 (CRMP-2), a possible contributor to epileptogenesis.

Dosing

11–29 kg:

Start 2 mg/kg/day divided in 2 doses
Increase by 2 mg/kg/day every 7 days
Goal 6–12 mg/kg/day

30–49 kg:

Start 2 mg/kg/day divided in 2 doses
Increase by 2 mg/kg/day every 7 days
Goal 4–8 mg/kg/day

≥ 16 years or ≥ 50 kg:

Start 100 mg/day divided in 2 doses
Increase by 100 mg/day every 7 days
Goal 200–400 mg/day

Side Effects

Neurologic: diplopia/blurred vision, ataxia/dizziness/impaired coordination, headache

Systemic: GI symptoms

Critical/Potentially Life-Threatening Side Effects

Systemic: prolonged PR interval

Lab Monitoring

May consider baseline LFTs and Chem10 to evaluate liver and renal function with repeat labs every 12 months. May alternatively defer routine lab monitoring. Recommend baseline ECG to evaluate PR interval and identify potential preexisting arrhythmias.

Lamotrigine

Section References: [1–3, 20, 38, 130–132]

Lamotrigine is a broad-spectrum agent used to treat both focal and generalized seizures, including primary GTCs, tonic/atonic, and absence seizures. For generalized epilepsy syndromes with myoclonic seizures, specifically JME, lamotrigine can have mixed results with a subset showing worsening myoclonic seizures [3, 130, 132]. For patients with Dravet syndrome or progressive myoclonic epilepsy, lamotrigine is typically avoided [1].

Mechanism of Action

Inhibition of voltage-gated sodium channels limiting repetitive firing and stabilizing the neuronal membrane. The mechanism is incompletely understood, but there is a decrease in the release of excitatory neurotransmitters including glutamate and aspartate.

Dosing

2–12 years:

Week 1–2: 0.4 mg/kg/day

Week 3–4: 0.8 mg/kg/day

Increase by 0.4–0.8 mg/kg/day every 7–14 days thereafter

Goal 2–8 mg/kg/day divided in 2 doses

Concomitant treatment with valproate

Week 1–2: 0.15 mg/kg/day

Week 3–4: 0.3 mg/kg/day

Increase by 0.15–0.3 mg/kg/day every 7–14 days thereafter

Goal 1–5 mg/kg/day divided in 2 doses

Concomitant treatment with enzyme inducing ASMs (carbamazepine, phenytoin, phenobarbital, primidone)

Week 1–2: 0.6 mg/kg/day

Week 2–4: 1.2 mg/kg/day

Increase by 0.6–1.2 mg/kg/day every 7–14 days thereafter

Goal 5–15 mg/kg/day divided in 2 doses

> 12 years:

Week 1–2: 25 mg/day

Week 3–4: 50 mg/day

Increase by 50–100 mg/day every 7–14 days thereafter

Goal 100–400 mg/day divided in 2 doses

Concomitant treatment with valproate

Week 1–2: 25 mg every other day

Week 3–4: 25 mg/day

Increase by 25–50 mg/day every 7–14 days thereafter

Goal 100–200 mg/day divided in 2 doses

Concomitant treatment with enzyme-inducing ASMs

Week 1–2: 50 mg/day

Week 3–4: 100 mg/day

Increase by 50–100 mg/day every 7–14 days thereafter

Goal 200–500 mg/day divided in 2 doses

Steps for cross titration of valproate to lamotrigine [38]

1. Hold valproate dose constant and titrate lamotrigine up to 200 mg/day as above (*concomitant treatment with VPA*).
2. Maintain lamotrigine dose constant, and taper valproate by decrements of 500 mg/day every 7 days until a dose of 500 mg/day is reached.
3. Increase lamotrigine to 300 mg and simultaneously decrease valproate to 250 mg for one week.
4. Stop the valproate and increase lamotrigine by 100 mg/day each week until goal dose is reached.

Side Effects

Neurologic: somnolence, anxiety, irritability, ataxia/dizziness, headache, insomnia
Systemic: GI symptoms, rash

Critical/Potentially Life-Threatening Side Effects

Systemic: SJS/TEN, cardiac conduction abnormalities, hepatotoxicity, hematological abnormalities, hypogammaglobulinemia

Lab Monitoring

May consider baseline CBC with repeat at 3 and 6 months, and every 12 months thereafter; LFTs at baseline with repeat every 12 months.

Levetiracetam

Section References: [1–3, 20, 133]

Levetiracetam is a broad-spectrum agent used to treat both focal and generalized seizure types. The IV formulation may also be used as abortive therapy in status epilepticus.

Mechanism of Action

The mechanism is incompletely understood. It binds synaptic vesicle protein SV2A, involved in synaptic vesicle exocytosis. It inhibits high-threshold (N-type) calcium channels and may indirectly modulate GABA and glycine activity.

Dosing

Status epilepticus

60 mg/kg IV loading dose

Seizure treatment

< 12 years:

Start 20 mg/kg/day divided in 2 doses

Increase by 10–20 mg/kg/day every 7–14 days

Goal 30–100 mg/kg/day

≥ 12 years:

Start 500–1000 mg/day divided in 2 doses

Increase by 500 mg/day every 7–14 days

Goal 2000–3000 mg/day

Side Effects

Neurologic: somnolence, anxiety, irritability/emotional lability, asthenia, dizziness/ataxia

Critical/Potentially Life-Threatening Side Effects

Neurologic: suicide ideation/psychosis

Systemic: SJS/TEN, hepatotoxicity, pancytopenia, hypogammaglobulinemia

Lab Monitoring

Not required

Lorazepam

Section References: [1–3, 134]

Lorazepam is a broad-spectrum agent typically used as an acute abortive therapy for status epilepticus or intermittent use for seizure clusters.

Mechanism of Action

Lorazepam is a type of benzodiazepine, a GABA_A agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

Dosing

Status epilepticus

0.1 mg/kg IV

Side Effects

Neurologic: somnolence, cognitive dysfunction, dysarthria, ataxia/dizziness

Critical/Potentially Life-Threatening Side Effects

Systemic: respiratory depression, hypotension

Midazolam

Section References: [1–3, 26]

Midazolam is a broad-spectrum agent typically used as an acute abortive therapy for status epilepticus or intermittent use of seizure clusters.

Mechanism of Action

Midazolam is a type of benzodiazepine. GABA_A agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

Dosing

Acute abortive treatment/status epilepticus

Intranasal dosing:

0.2 mg/kg once (max 10 mg/dose)

≥ 12 years:

5 mg to one nostril, after 10 min, may repeat dose to the other nostril if needed

IM dosing:

0.2 mg/kg/dose (max 10 mg/dose)

IV dosing:

0.1–0.2 mg/kg/dose

Side Effects

Neurologic: somnolence, cognitive dysfunction, dysarthria, ataxia/dizziness

Critical/Potentially Life-Threatening Side Effects

Systemic: hypotension, respiratory depression

Oxcarbazepine

Section References: [1–3, 20, 135]

Oxcarbazepine is used to treat focal seizures with or without secondary generalization. Like carbamazepine, oxcarbazepine is contraindicated for primary generalized seizures due to the potential for exacerbation.

Oxcarbazepine shares a chemical structure with carbamazepine and eslicarbazepine acetate, a dibenzazepine nucleus with a 5-carboxamide substitute, but differs with a keto group at the 10 position. Oxcarbazepine is a pro-drug, metabolizing to a 10-monohydroxy derivative.

Mechanism of Action

The 10-monohydroxy metabolite acts to block voltage-gated sodium channels. This stabilizes the membrane and prevents repetitive neuronal firing. It also increases potassium conductance, modulates high-threshold calcium channels, and reduces the release of glutamate.

Dosing

2–16 years:

Start 8–10 mg/kg/day divided in 2 (< 5y) or 3 (≥ 5y) doses

Increase by 5–10 mg/kg/day every 7 days

Goal 30–40 mg/kg/day (max 60 mg/kg/day)

or

< 20 kg: 600–900 mg/day

20–29 kg: 900–1200 mg/day

30–39 kg: 900–1500 mg/day

40–59 kg: 1500–1800 mg/day

> 16 years:

Start 300 mg/day divided in 2 doses

Increased by 150 mg/day every 2 days

Goal 1200–2400 mg/day

Side Effects

Neurologic: somnolence/lethargy, diplopia, ataxia/dizziness, headache

Systemic: GI symptoms, hyponatremia, rash

Critical/Potentially Life-Threatening Side Effects

Systemic: SJS/TEN/hypersensitivity reaction, cardiac arrhythmia, hyponatremia, agranulocytosis, aplastic anemia, pancytopenia, thrombocytopenia

Lab Monitoring

Consider baseline CBC, Na, LFTs. Consider screening for HLA-B*1502 allele for patients with Asian ancestry due to potential increased risk for SJS/TEN. Repeat Na at 1–2 months or once at treatment is therapeutic, and periodically thereafter. Repeat CBC at 3 and 6 months after the start of treatment. Consider monitoring 25-hydroxyvitamin D levels.

Perampanel

Section References: [1, 2, 17]

Perampanel is a broad-spectrum agent used to treat both focal and generalized seizures.

Mechanism of Action

Antagonist of the AMPA-type glutamate receptor, reducing intracellular calcium, resulting in reduced neuronal excitability.

Dosing

≥ 4 years:

Start 2 mg daily; or 4 mg daily if taking enzyme-inducing ASMs*

Increase by 2 mg/day every 7–14 days

Goal 4–8 mg/day

* *carbamazepine, phenytoin, phenobarbital, primidone*

Side Effects

Neurologic: somnolence/fatigue, irritability, ataxia/dizziness/gait disturbance, headache

Systemic: GI symptoms, weight gain

Critical/Potentially Life-Threatening Side Effects

Neurologic: psychosis, suicide ideation

Systemic: hypersensitivity reaction/DRESS

Lab Monitoring

Defer routine monitoring.

Phenobarbital

Section References: [1–3, 20, 42]

Phenobarbital is effective in the treatment of focal and primary generalized seizures. It is contraindicated for absence seizures. It is often used to treat neonatal seizures (see Chap. 5) and as an abortive therapy for status epilepticus across age groups.

Mechanism of Action

Binds the GABA_A receptor leading to increased chloride ion permeability. This results in neuronal hyperpolarization and enhancing inhibition. May also result in a reduction in calcium-dependent action potentials.

Dosing

Status epilepticus:

15–20 mg/kg IV

Seizure treatment:

Infants:

5–6 mg/kg/day given in 1–2 doses

1–5 years:

3–8 mg/kg/day given in 1–2 doses

> 5 years to adolescents:

2–3 mg/kg/day given in 1–2 doses

> 12 years/adults:

1.5–4 mg/kg/day given in 1–2 doses

or

50–200 mg/day given in 1–2 doses

Side Effects

Neurologic: somnolence/lethargy, impaired attention/cognition, depression/mood changes, behavioral changes/hyperactivity, nystagmus, dysarthria, ataxia

Systemic: GI symptoms, decreased bone density, rash

Rare cases of connective tissue contractures/Dupuytren contracture

Critical/Potentially Life-Threatening Side Effects

Systemic: SJS/TEN/hypersensitivity reaction, respiratory depression/apnea (rapid IV infusion), hepatotoxicity, agranulocytosis/thrombocytopenia

Lab Monitoring

Drug levels, CBC, and LFTs should be monitored. Consider monitoring 25-hydroxyvitamin D levels.

Phenytoin

Section References: [1–3, 20, 136]

Phenytoin is used for focal seizures with or without secondary generalization. They may also be effective against some generalized seizures including primary GTC or for patients with mixed semiology. Phenytoin has the potential to worsen a subset of generalized seizures, typically myoclonic and absence. Phenytoin should be avoided

for patients with LGS and progressive myoclonic epilepsies. For status epilepticus, fosphenytoin is preferred.

Mechanism of Action

Blocks voltage-gated sodium channels and modulates sustained repetitive firing. It also inhibits calcium channels and calcium sequestration and inhibits calcium-calmodulin protein phosphorylation.

Dosing

With the start of treatment, may consider enteral loading dose depending on the clinical circumstances.

Children:

Enteral loading dose:

15 mg/kg/day divided in 3 doses

24 hrs after loading dose: start 5 mg/kg/day given in 1–2 doses

or

Start 5 mg/kg/day given in 1–2 doses

Increase by 5 mg/kg/day every 3–4 weeks

Goal 5–10 mg/kg/day

Adults:

Enteral loading dose:

1 g divided in 3 doses

24 hrs after loading dose: start 300–400 mg/day given in 1–2 doses

or

Start 150–300 mg/day in 1–2 doses

Increase by 50 mg/day every 3–4 weeks

Goal 200–400 mg/day

Side Effects

Neurologic: somnolence, confusion, nystagmus, dysarthria, ataxia/dizziness

Systemic: GI symptoms, decreased bone density, hirsutism, rash, gingival hypertrophy

Critical/Potentially Life-Threatening Side Effects

Neurologic: suicide ideation, peripheral neuropathy

Systemic: SJS/TEN, systemic lupus erythematosus, hepatotoxicity, agranulocytosis/aplastic anemia, lymphadenopathy/lymphoma

Lab Monitoring

Recommend baseline LFTs and Chem10 to evaluate liver and kidney function; repeat screening labs every 12 months. Alternatively, may defer routine monitoring. Consider monitoring folate and 25-hydroxyvitamin D levels.

Pregabalin

Section References: [1–3, 18]

Pregabalin is used for focal seizures with or without secondary generalization. It has the potential to exacerbate primary generalized seizures, specifically myoclonus. Pregabalin is a broad-spectrum GABA analog and structurally similar to gabapentin. Its effect as an antiseizure treatment, however, does not seem to be mediated by modulation of GABA.

Mechanism of Action

Binds to voltage-gated presynaptic calcium channels, inhibiting inward calcium currents. This results in decreased release of neurotransmitters including glutamate, noradrenaline, and substance P.

Dosing

Infant to < 4 years:

Start 3.5–5 mg/kg/day divided in 2–3 doses

Increase by 3–5 mg/kg/day every 7 days

Max 14 mg/kg/day

4–16 years:

< 30 kg

Start 3.5 mg/kg/day divided in 2–3 doses

Increase by 3 mg/kg/day every 7 days

Max 14 mg/kg/day

≥ 30 kg

Start 2.5 mg/kg/day divided in 2–3 doses

Increase 3 mg/kg/day every 7 days

Max 10 mg/kg/day

≥ 17 years

Start 50–150 mg/day divided in 2–3 doses

Increase by 50–150 mg/day every 7 days

Goal 150–600 mg/day (max 600 mg/day)

Side Effects

Neurologic: somnolence, impaired attention, irritability/aggressiveness, tremor, ataxia/dizziness

Systemic: peripheral edema, GI symptoms, weight gain, xerostomia

Critical/Potentially Life-Threatening Side Effects

Systemic: hypersensitivity reaction, AV block, myocardial dysfunction, angioedema, rhabdomyolysis, hypoglycemia, neutropenia

Lab Monitoring

Consider baseline Chem10 to evaluate renal function in the setting of preexisting comorbidities and/or increased risk.

Primidone

Section References: [1–3, 20, 137]

Primidone is effective in the treatment of focal and primary generalized seizures. It is contraindicated for absence seizures.

Mechanism of Action

Primidone has two active metabolites, phenobarbital and phenylethylmalonamide. Primidone has been shown to provide an antiseizure effect independent from phenobarbital, but the mechanism of this effect is not understood.

Phenobarbital is described above; it binds the GABA_A receptor leading to increased chloride ion permeability. This results in neuronal hyperpolarization and enhancing inhibition. It may also result in a reduction in calcium-dependent action potentials.

Dosing

Infants–8 years:

Start 1–2 mg/kg/day given once

Increase every 3 days

Goal 10–25 mg/kg/day (infants); 10–20 mg/kg/day (children) divided in 2–4 doses

or

Day 1–3: 50 mg/day at bedtime

Day 4–6: 100 mg/day divided in 2 doses

Day 7–9: 200 mg/day divided in 2 doses

Day 10: 375–750 mg/day divided in 3 doses

> 8 years – adults:

Day 1–3: 125 mg/day given once

Day 4–6: 200–250 mg/day divided in 2 doses

Day 7–9: 300–375 mg/day divided by 3 doses

Day 10: 750 mg/day divided by 3 doses

Goal 750–1500 mg/day or 10–20 mg/kg/day divided in 3–4 doses

Side Effects

Neurologic: somnolence/lethargy, impaired attention/cognition, depression/mood changes, behavioral changes/hyperactivity, nystagmus, dysarthria, ataxia

Systemic: GI symptoms, decreased bone density, rash

Rare cases of connective tissue contractures

Critical/Potentially Life-Threatening Side Effects

Neurologic: Acute toxic reaction (severe sedation, ataxia/dizziness, nausea/vomiting)

Systemic: SJS/TEN/hypersensitivity reaction, hepatotoxicity, agranulocytosis

Lab Monitoring

Defer routine monitoring. Consider monitoring 25-hydroxyvitamin D levels.

Rufinamide

Section References: [1–3, 20, 138]

Rufinamide is a broad-spectrum agent used to treat both focal and primary generalized seizures with a role in treatment of LGS and epileptic spasms. As a triazole derivative, the chemical structural is unique among current ASMs.

Mechanism of Action

Blocks voltage-gated sodium channels after inactivation, prolonging recovery and preventing return to an active state. This persistent depolarization reduces bursts of high-frequency action potentials.

Dosing

≥ 4 years and < 30 kg:

Start 10 mg/day or 200 mg/kg/day divided in 2 doses

Increase by 10 mg/day or 200 mg/kg/day every 2–7 days

Goal 45 mg/day or 1000 mg/kg/day

Goal 400–600 mg/day *

* *Concomitant treatment with valproate*

Children ≥ 30 kg and adults:

Start 400 mg/day divided in 2 doses

Increase by 400 mg/day every 2 days

Goal

30–50 kg: 1800 mg/day

51–70 kg: 2400 mg/day

> 70 kg: 3200 mg/day

Side Effects

Neurologic: somnolence/fatigue, dizziness/ataxia, headache

Systemic: GI symptoms

Critical/Potentially Life-Threatening Side Effects

Neurologic: status epilepticus

Systemic: hypersensitivity reaction, decreased QTc interval

Lab Monitoring

Consider baseline LFTs and Chem10 for hepatic and renal function; repeat every 12 months. Alternatively, may defer routine monitoring. Recommend baseline ECG to evaluate QTc interval and identify potential preexisting arrhythmias.

Stiripentol

Section References: [1–3, 19, 23]

Stiripentol is used as an adjuvant therapy for synergistic effect with clobazam or valproate, typically for patients with Dravet syndrome and refractory GTCs. Co-treatment with carbamazepine, phenytoin, or phenobarbital is typically avoided due to risk of toxicity.

Mechanism of Action

Activates GABA_A receptor with barbiturate-like mechanisms of increasing chloride ion permeability, neuronal hyperpolarization, and enhanced inhibition. It may also increase GABA levels by inhibiting synaptic uptake and/or inhibiting GABA transaminase. Stiripentol has additional indirect effects; as a CYP inhibitor, it may act to increase serum levels of concomitant ASMs such as clobazam.

Dosing

A broad range of dosing has been reported:

Start 25–50 mg/kg/day divided in 2–3 doses

Increase by 10 mg/kg/day every 7–14 days

Goal 75 mg/kg/day

May consider lower dosing to start:

Start 10–20 mg/kg/day divided in 2–3 doses

Increase over 2–4 weeks

Goal 50 mg/kg/day

Side Effects

Neurologic: somnolence, agitation/irritability, dysarthria, hypotonia, dystonia, tremor, ataxia, insomnia

Systemic: GI symptoms, anorexia/weight-loss

Critical/Potentially Life-Threatening Side Effects

Neurologic: suicide ideation

Systemic: aplastic anemia, leukopenia/neutropenia, thrombocytopenia

Lab Monitoring

Consider baseline LFTs and Chem10 for hepatic and renal function; repeat every 12 months.

Sulthiame

Section References: [1–3]

Sulthiame is used for focal seizures with or without secondary generalization and self-limited epilepsy with centrotemporal spikes. It is also used for epileptic encephalopathies, with specific efficacy for patients with CSWS and myoclonic epilepsies. It is not currently approved for use in the United States but is widely used in Europe.

Mechanism of Action

Inhibits voltage-gated sodium channels and glutamate release. Inhibits carbonic anhydrase which results in decreased inward calcium flow of NMDA receptors, thereby reducing neuronal excitability.

Dosing

Children:

Start 5 mg/kg/day divided in 2 doses
Increase by 5 mg/kg/day after 7 days
Goal 5–10 mg/kg/day

Adults:

Start 100–250 mg/day divided in 2 doses
Increase by 100 mg/day every 7 days
Goal 200–600 mg/day

Side Effects

Neurologic: paresthesia, ataxia/dizziness, headache

Systemic: hyperventilation, metabolic acidosis, anorexia/weight loss, rash

Critical/Potentially Life-Threatening Side Effects

SJS/TEN, renal dysfunction, metabolic acidosis, nephrolithiasis

Lab Monitoring

Consider baseline CBC and Chem10 to evaluate renal function.

Tiagabine

Section References: [1–3, 20, 139]

Tiagabine is used for focal seizures with or without secondary generalization. It may also be considered for epileptic spasms.

Mechanism of Action

Enhanced endogenous GABA effect by blocking GABA reuptake by inhibiting GABA transporter-1.

Dosing

Children > 12 years:

Start 0.1 mg/kg/day

Increase by 0.1 mg/kg/day every 7–14 days

Goal 0.5–2 mg/kg/day divided in 2–4 doses

Concomitant treatment with enzyme-inducing ASMs

> 12 years:

Start 0.25 mg/kg/day

Increase by 0.5–1 mg/kg/day every 7 days

Max 4–8 mg/kg/day divided in 3–4 doses

12–18 years:

Start 4 mg/day

Increase by 4 mg/day every 7 days

Max 32 mg/day divided in 2–4 doses

Side Effects

Neurologic: somnolence/fatigue, cognitive and attention impairment, anxiety, asthenia, tremor, dizziness, headache

Systemic: GI symptoms, ecchymosis

Critical/Potentially Life-Threatening Side Effects

Neurologic: nonconvulsive status or absence status epilepticus, suicide ideation

Concern for possible risk of visual field deficits but data is limited

Systemic: SJS/TEN

Lab Monitoring

Consider baseline CBC as well as LFTs and Chem10 for hepatic and renal function; repeat every 6–12 months. Alternatively, may defer routine monitoring.

Topiramate

Section References: [1–3, 20, 21]

Topiramate is a broad-spectrum agent used to treat both focal and primary generalized events, including primary GTCs, myoclonic and absence seizures. It is used for myoclonic syndromes including Dravet, progressive myoclonic epilepsies, myoclonic atonic epilepsy, and JME. It is also used for LGS and IS.

Mechanism of Action

Multiple described mechanisms of action including inhibition of voltage-gated sodium channels, L-type voltage-gated calcium channels, AMPA glutamate

receptors, and carbonic anhydrase. It binds GABA_A receptors mediating neuronal inhibition. Finally, topiramate may increase potassium channel conduction.

Dosing

Infants and children <12 years:

Start 0.5–1 mg/kg/day divided in 2–3 doses

Increase by 0.5–1 mg/kg/day every 7–14 days

Goal 3–9 mg/kg/day

2–16 years:

Start 1–3 mg/kg/day divided in 2–3 doses

Increase by 1–3 mg/kg/day every 7–14 days

Goal 5–9 mg/kg/day

≥ 17 years:

Start 25–50 mg/day divided in 2 doses

Increase by 25–50 mg/day every 7–14 days

Goal 100–400 mg/day

Side Effects

Neurologic: somnolence/fatigue, cognitive and attention impairment, anxiety, depression/mood changes, paresthesia, ataxia/dizziness
Systemic: metabolic acidosis, anorexia/weight loss, hypohidrosis

Critical/Potentially Life-Threatening Side Effects

Neurologic: acute myopia with secondary angle-closure glaucoma
Systemic: metabolic acidosis, nephrolithiasis, oligohydramnios/hyperthermia

Lab Monitoring

Consider CBC, LFTs, and Chem10 once maximum treatment dose is reached or at 3–6 months following the start of treatment. Alternatively, may defer routine monitoring.

Valproate

Section References: [1–3, 20, 140]

Valproate is a broad-spectrum agent used to treat both focal and primary generalized events including GTCs, tonic/atonic, myoclonic seizures, and absence seizures. It is used for JME and LGS. It may also be used in status epilepticus.

Mechanism of Action

Multiple described mechanisms of action including inhibition of voltage-gated sodium channels and T-type calcium channels, as well as increased potassium

channel conduction. There is an increase in GABA concentrations by multiple proposed modalities including increased glutamic acid decarboxylase activity, inhibition of GABA transaminase or succinic semialdehyde dehydrogenase. Decreased expression of glutamate transporter-1 has also been described.

Dosing

Status epilepticus:

20–40 mg/kg IV

Seizure treatment:

≤ 12 years

Start 10–15 mg/kg/day divided in 2–3 doses

Increase by 5–15 mg/kg/day every 5–7 days

Goal 20–60 mg/kg/day

> 12 years

Start 200–500 mg/day divided in 2 doses

Increase by 200–500 mg/day every 3–7 days

Goal 1000–1500 mg/day

Side Effects

Neurologic: somnolence/lethargy, asthenia, tremor, ataxia/dizziness, headache

Systemic: GI symptoms, hyperammonemia, elevated liver enzymes, hypocarnitinemia, weight gain, decreased bone density, alopecia, ecchymosis

Critical/Potentially Life-Threatening Side Effects

Neurologic: hyperammonemic encephalopathy

Systemic: SJS/TEN, hepatotoxicity, pancreatitis, agranulocytosis, aplastic anemia, thrombocytopenia, hypogammaglobulinemia

Lab Monitoring

Consider baseline CBC and LFTs; repeat at 2 months after the start of treatment and every 6 months thereafter. Consider monitoring 25-hydroxyvitamin D levels.

Vigabatrin

Section References: [1–3, 11, 22, 141]

Vigabatrin is typically used to treat IS. For patients with tuberous sclerosis complex and IS, it is first line. It may also be used to treat refractory focal seizures with or without secondary generalization. It is contraindicated for primary generalized seizures including absence seizures.

Mechanism of Action

Increases synaptic GABA by irreversibly inhibiting GABA transaminase.

Dosing

Infants:

Start 50 mg/kg/day given in 2 doses
Increase by 25–50 mg/kg/day every 3 days
Max 150–200 mg/kg/day

2–16 years and ≤ 60 kg:

10–15 kg
Start 350 mg/day divided in 2 doses
Increase every 7 days
Goal 1050 mg/day

16–20 kg:

Start 450 mg/day divided in 2 doses
Increase every 7 days
Goal 1300 mg/day

21–25 kg:

Start 500 mg/day divided in 2 doses
Increase every 7 days
Goal 1500 mg/day

26–60 kg:

Start 500 mg/day divided in 2 doses
Increase every 7 days
Goal 2000 mg/day

≥ 17 years and/or > 60 kg:

Start 500–1000 mg/day given in 2 doses
Increase by 500 mg/day every 7 days
Goal 1000–3000 mg/day

Side Effects

Neurologic: Somnolence/fatigue, cognitive impairment, agitation/irritability, tremor, paresthesia, ataxia/dizziness, headache
MRI changes: restricted diffusion on T2 imaging of the basal ganglia, thalamus, brainstem, dentate

Systemic: GI symptoms, weight gain

A visual field deficit develops with vigabatrin treatment in about one third of cases [3, 141]. In the United States, there is a REMS program to support prescriber education and serial ophthalmologic monitoring.

Critical/Potentially Life-Threatening Side Effects

Neurologic: status epilepticus, psychosis

Systemic: hypersensitivity reaction, angioedema

Lab Monitoring

Consider baseline CBC as well as LFTs and Chem10 to evaluate hepatic and renal function; repeat labs every 6–12 months thereafter.

Zonisamide

Section References: [1–3, 20, 108, 142]

Zonisamide is a broad-spectrum agent used to treat both focal and generalized events including primary GTCs, tonic/atonic, myoclonic, and absence seizures. It may be used for epileptic encephalopathies including IS, Ohtahara syndrome, progressive myoclonic epilepsies, and Dravet syndrome.

Mechanism of Action

Blocks voltage-gated sodium channels, T-type calcium channels, and carbonic anhydrase. Decreases GABA transporter-1 expression and glutamate release. Increases extracellular levels of dopamine and serotonin. Increased expression of excitatory amino-acid carrier-1 (EAAC-1).

Dosing

> 6 years:

Start 1–2 mg/kg/day given in 1–2 doses

Increase by 1–2 mg/kg/day every 7–14 days

Goal 5–12 mg/kg/day

Adults:

Start 100 mg/day given in 1–2 doses

Increase by 100 mg/day every 7–14 days

Goal 100–600 mg/day

Side Effects

Neurologic: somnolence/fatigue, cognitive and attention impairment, anxiety, depression, agitation/irritability, paresthesia, ataxia/dizziness

Systemic: GI symptoms, anorexia/weight loss, metabolic acidosis, rash, hypohidrosis

Critical/Potentially Life-Threatening Side Effects

Neurologic: status epilepticus, psychosis, acute myopia with secondary angle-closure glaucoma

Systemic: SJS/TEN, hepatotoxicity, metabolic acidosis, nephrolithiasis, agranulocytosis, aplastic anemia, anhidrosis, hyperthermia

Lab Monitoring

Consider baseline chemistry panel with repeat 3–6 months after the start of treatment. For patients with cognitive impairment, for whom it may be difficult to recognize early signs or symptoms of metabolic acidosis, plan for ongoing periodic lab monitoring of bicarbonate levels.

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