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Review

Epilepsy in Cerebral Palsy: A Brief Narrative Review

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Abstract

Cerebral palsy is defined as "A group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems [1]." Between 30-40% of people with cerebral palsy also have epilepsy [2-4]. Some of the risk factors for developing epilepsy include low birth weight, low APGAR scores, seizures in the neonatal period and first year of life, positive imaging findings, severity of cerebral palsy, intellectual disability and spasticity. Children with epilepsy and cerebral palsy often experience their first seizure before 2 years of age, and may have a higher risk for refractory epilepsy and status epilepticus. Anti-seizure medications are the mainstay of treatment, and are typically chosen based upon the epilepsy syndrome, seizure type, side effect profile and EEG findings. If two or more anti-seizure medications fail to control seizures, early evaluation for surgical options, which could potentially be curative, should be pursued. This review

article examines the pathophysiology of cerebral palsy and epilepsy, summarizes recent literature about risk factors for developing epilepsy, clinical and EEG features, treatment outcomes in children with epilepsy and CP, and discusses management strategies.

Keywords
Cerebral palsy; epilepsy; pediatrics

1. Introduction

Cerebral palsy (CP) is a life-long condition characterized by an early insult to the developing brain [1]. The subtypes of cerebral palsy are categorized based on clinical manifestations and include spastic, dyskinetic, ataxic, and mixed types. Spastic CP is further subdivided based on body region involved, with spastic quadriplegia/quadriparesis referring to equal spasticity in all four limbs, spastic diplegia impacting bilateral lower extremities, and spastic hemiplegia/hemiparesis affecting a single side. Dyskinetic CP manifests primarily as movement disorders such as chorea, athetosis, and dystonia, whereas ataxic CP affects coordination and balance most, and finally a mixed CP subtype has features of more than a single category. With a declining prevalence of about 1.9 cases per 1000 live births [5, 6]. CP is commonly encountered by pediatricians and neurologists. Comorbid conditions include epilepsy, abnormalities in muscle tone and movement, hearing and vision impairments, intellectual disability, mood and neuropsychiatric disorders, including behavior disorders, attention deficit/hyperactivity disorder (ADHD) and autism [7]. Clinical care requires a multi-disciplinary team with input from pediatricians, neurologists, neuropsychologists, psychologists, orthopedists, physiatrists, social workers, speech, physical, and occupational therapists, who work together to maximize developmental potential. The incidence of epilepsy in cerebral palsy has been variably estimated, but in population based cohorts range between 30-40% [2-4]. Epilepsy in children with CP has been associated with memory and cognitive deficits, likely reflecting a more severe underlying injury in addition to the direct impact of epilepsy, especially in cases of refractory epilepsy. The presence of seizures may also generally be associated with a more severe CP phenotype [3, 8, 9]. In some cases, the ongoing seizures may be more disabling than the motor deficits. In this article, we discuss the definition of epilepsy, seizure types, common evaluations and management strategies in the patients with CP and epilepsy.

2. Defining Epilepsy

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The conceptual definition of epilepsy, as formulated by a task force of the International League Against Epilepsy (ILAE) in 2005, is “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the cognitive, psychological, and social consequences of this condition [10].” In 2014 the definition of epilepsy for practical purposes was further refined as (1) At least two unprovoked seizures occurring more than 24 hours apart; or (2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two

unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome [11, 12].

3. Etiology and Pathology of Epilepsy in CP

Any insult to a developing brain can potentially cause CP. Pre- and perinatal injuries and malformations in combination with a genetic vulnerability account for the majority of cases, whereas only about 10% of the cases occur secondary to a postnatal event such as trauma, ischemia, central nervous system infections (meningitis and encephalitis), or a genetic abnormality [12-15]. In some cases, the etiology of CP might remain unknown or idiopathic. The underlying pathways of cell injury are typically induced by an initial infectious, ischemic or hemorrhagic event, which results in inflammation with a release of pro-inflammatory cytokines, oxidative stress, alterations in the extracellular matrix, and an increase in glutamate release, which ultimately results in excitotoxicity [16]. Further details are beyond the scope of this article.

Brain development occurs mainly in the first 20 weeks of pregnancy. Insults including stroke, infection, or genetic abnormalities during this stage lead to abnormalities in proliferation, migration, and organization of developing brain leading to anatomical abnormalities, such as schizencephaly, for example. Injuries are more common from 24-32 weeks of gestation mainly due to the vulnerability of blood supply during this stage of development. The usual causes during this stage are hemorrhage and stroke. Later in pregnancy and early childhood, CP can be caused due to asphyxia, stroke, ischemic (HIE). About 10% of the cases of CP are due to birth asphyxia.

Clinical manifestations of CP reflect the region of the brain that is injured, which may in part be influenced by the timing of the insult. Diffuse brain injuries are more likely to result in spastic quadriplegia and epilepsy, injuries to the middle cerebral artery territory predispose to hemiparesis, basal ganglia injuries result in dyskinetic CP, which primarily presents with disorders of movement. The developing brain may be more susceptible to specific injuries at different periods in development. Brain injury or congenital brain malformations occurring early in pregnancy, for example, may involve a more diffuse brain volume, and thus may result in severe manifestations such as spastic quadriplegia, intellectual disability and epilepsy. Preterm infants tend to incur periventricular white matter injury which is associated with spastic diplegia due to the proximity of lower limb motor neuron fibers to the periventricular area. Injuries occurring later in pregnancy and in term infants may more specifically affect the gray matter or brainstem nuclei, which then produces a pattern of spastic motor deficits. Also near term, the more metabolically active regions of the brain, such as the basal ganglia, are more susceptible to injury from hypoxia. Damage to the basal ganglia manifests as movement disorder associated with dyskinetic CP. The severity of the symptoms depends on the extent and duration of the insult [2, 14].

4. Considerations of Epilepsy in CP

Epilepsy has been reported to affect about 30% to 40% of patients with cerebral palsy [4]. Recent population data analysis from Norway notes a declining prevalence both of CP and epilepsy, which was speculated to be the result of advancements in obstetric and neonatal care [6]. Early suspicion, diagnosis, and management of epilepsy are essential to ensure the best possible prognosis and reduce risks of injury and death related to seizures. Risk factors for developing epilepsy include a spastic CP subtype, low APGAR scores, seizures in the neonatal period

and during the first year of life, family history of epilepsy, positive imaging findings, the severity of cerebral palsy (including the severity of impairment in gross motor and fine motor disorders) and moderate to severe intellectual disability or psychosocial developmental delay [17-19]. Epilepsy is more common in children with more severe motor impairment (Gross Motor Function Classification System (GMFCS) levels IV and V), in children with triplegic/quadriplegic CP compared with other CP subtypes, and in children with intellectual disability [3, 20]. Some large population-based studies also reported that dyskinetic CP is associated with a high risk for epilepsy. Authors postulated this risk may be contributed to by the presence of additional neonatal risk factors for epilepsy in children with dyskinetic CP [20, 21]. Both generalized epilepsy syndromes and focal epilepsy have been described, but focal epilepsy is more prevalent [21]. Seizure semiology can vary just like the motor manifestations of CP. Seizures manifesting as a tonic or atonic seizures or generalized epilepsy such as absence epilepsy can be overlooked due to limitations in baseline cognitive function. Dystonia and involuntary movements may be clinically confused for seizures, and need to be carefully evaluated to exclude epileptic seizures or spasms [20]. Video recordings, and long-term video EEG may be required to capture and characterize episodes of concern. Seizures can manifest at any age, from day 1 of life to later in childhood. The time of presentation may vary based upon the type of CP [22].

Singhi et al. investigated 452 patients with cerebral palsy amongst which 160 patients had both cerebral palsy and epilepsy, the mean age of seizure onset was 19 months. About 60% of patients had seizure onset before the age of 12 months [23]. Children who presented with infantile spasms and/or myoclonic seizures presented notably early in life when compared to other types of seizures. Generalized seizures were the most common type and were mainly seen in spastic quadriplegia and spastic diplegia. This was followed by focal seizures mainly seen in hemiplegic CP [9]. In about 60% of the patients, epilepsy was well controlled, while the remaining patients required polytherapy. Seizure control was better in hemiplegic CP when compared to other types namely quadriplegic and diplegic CP. The risk of epilepsy in patients with ataxic CP, and spastic diplegia, appears to be less.

Infantile spasms are a unique seizure type that commonly present around 6 months of age as an epileptic encephalopathy, which is associated with a high risk for poor developmental outcomes, cerebral palsy, and long-term refractory epilepsy. The seizures commonly occur in clusters, and the semiology is characterized by brief episodes of sudden flexion, extension, or mixed flexion-extension contractions of proximal and trunk muscles followed by a 1-2 second tonic phase. The constellation of epileptic spasms, developmental regression or stagnation and hypsarrhythmia pattern on EEG is referred to as West syndrome. Recently, however, the International League Against Epilepsy has recognized that hypsarrhythmia and developmental regression or stagnation are not always consistent presenting features, thus has proposed the term, Infantile Spasms syndrome for children with infantile spasms, who may not fulfill all criteria for West syndrome [24]. Risk factors for development of infantile spasms include hypoxic ischemic encephalopathy (HIE), intraventricular hemorrhage, cerebral malformations, meningitis, genetic syndromes and perinatal strokes. Certain symptomatic etiologies, such as perinatal strokes, may be associated with a worse outcome compared to other etiologies of IS. In a case series of 10 children with infantile spasms after perinatal stroke, all of the children had cerebral palsy, 9/10 (90%) had ongoing epilepsy, and 8/10 (80%) had cognitive impairment [25]. Some risk factors for the development of infantile spasms may be

modifiable. Recent data from an observational study suggests that in the cases of HIE, for example, therapeutic hypothermia may reduce the risk for infantile spasms, but due to patient sample size, this effect was not statistically significant [26]. Early recognition of infantile spasms is important as first-line treatment options for infantile spasms are unique and include ACTH, oral corticosteroids and vigabatrin, and treatment within the first month of onset of spasms is believed to improve outcomes.

Drug-resistant epilepsy (DRE) or refractory epilepsy is seen in up to 30-50% of patients with epilepsy and CP. A patient is categorized to have DRE when he or she fails to become (and remain) seizure-free with adequate trials of two medications. These seizure medications must be appropriate for the seizure type, tolerated by the person, and tried alone or together with other seizure medications [19, 23, 27].

A 2020 study by Tokatly Latzer et al retrospectively analyzed 281 children with cerebral palsy; 118 had an additional diagnosis of epilepsy. DRE was seen in 44% of patients with epilepsy. The risk of developing refractory epilepsy was highest in children with a history of low Apgar score at 5 minutes, neonatal seizures, focal-onset epilepsy, and focal slowing on the electroencephalogram (EEG). These factors also had additive effects [18]. Another retrospective study by Hanci et al analyzed 229 patients with CP of which 120 had epilepsy. DRE was found in 30% of the patients. The study states that the rate of DRE development was very low in patients with normal EEG findings or with only background rhythm abnormalities on first EEGs during the neonatal period. These factors can be used to predict the development of DRE [17].

In addition to the increased risk for refractory epilepsy, patients with cerebral palsy and epilepsy may have a higher risk of status epilepticus. Carlsson M, et al. reported that almost half of the patients with CP and epilepsy in their study had experienced at least one episode of status epilepticus, compared with 16% or less of children with epilepsy of other etiologies [21]. Status epilepticus is a medical emergency that can lead to acquired brain injury and death. This finding has important treatment implications, as it emphasizes the need for effective preventative and abortive strategies, further detailed in the treatment section.

Despite the increased risk for refractory epilepsy and status epilepticus in some patients with CP, many children with cerebral palsy do experience seizure remission, defined as remaining seizure-free for at least 2 years on medications, and seizure resolution, defined as no seizure relapse following termination of AEDs [28]. Zafeiriou, et al [8], reported that 134/178 of their patients with cerebral palsy and epilepsy could discontinue antiepileptic drugs successfully after a 3-year seizure-free period. In approximately a 5 year follow-up period, the majority (86%) did not experience relapse [8]. Newer data from Tsubouchi, et al [28], indicated that 34/72 (47%) of that patient cohort with epilepsy and CP achieved remission of epilepsy at median age of 11 years. In 53 patients who were followed beyond 10 years of age, the proportion who achieved seizure remission was even higher, (64%; 34/53). Additionally, 10/34 (30%) of their patients successfully discontinued anti-seizure medications. They found a high remission proportion in patients with a perinatal etiology of CP. None of the patients with low voltage background activity or background slow waves experienced remission. Additionally, spastic quadriplegia was associated with low rate of remission [28]. Finally, population-based data published by Jonsson, et al [29], reported an increased incidence of epilepsy in patients with CP from childhood to adulthood (9% to 18%), but 6/13 (46%) of the children with CP and epilepsy no longer fulfilled criteria for epilepsy as adults

[29]. Authors have postulated that with maturation, there is a reduction in glutamate receptors and synaptic excitation and an increase in inhibitory input (mediated through an increase in GABA receptors), which may contribute to remission of epilepsy from childhood to adulthood, and that this maturation process may take longer in children with CP [28]. While there is no established consensus regarding when anti-seizure medication should be weaned in patients with epilepsy and cerebral palsy, the long-term data suggests that in patients who have achieved at least 2-3 years of seizure freedom with medication, medication weaning may be successful. Further research is needed to clarify the ideal candidates and timing for weaning medications in patients with cerebral palsy.

5. EEG Features

Children with cerebral palsy often have abnormal electroencephalogram (EEG) findings, even in the absence of previous clinical seizures. In a study of 151 patients with cerebral palsy, of the 70 patients without a history of clinic seizures, only 23 (34.3%) had normal EEG tracings. The most common abnormalities seen in patients without epilepsy were generalized and asynchronous slow waves, seen in 28 (40%). Generalized epileptiform abnormalities were also seen in 23 (32.9%), and focal and multifocal abnormalities were seen in 4 (5.8%) of that cohort [30].

The majority of patients with cerebral palsy and epilepsy also have abnormal interictal EEGs. Three studies that specifically examined EEG findings in children with cerebral palsy and epilepsy, found that over 80% of patients with both epilepsy and CP have abnormal EEGs [8, 30, 31]. The abnormalities, however, are largely non-specific and most commonly include generalized background slowing, focal or generalized epileptiform activity [18, 23, 31]. A study by Zafeiriou, et al. compared a subset of patients who have epilepsy and CP with patients who have epilepsy without CP; the group with CP and epilepsy had a higher incidence of abnormal interictal EEGs, focal epileptiform, and generalized epileptiform activity and more common focal or diffuse background slowing [8]. Similar findings were noted in a study including 146 children with CP and epilepsy, which reported abnormal EEGs in 88% of the patient cohort. Of those, generalized background slowing (34%), focal (36%) and generalized (29%) epileptiform activity were the most common findings, with relatively fewer patients showing multifocal epileptiform discharges (9%), hypsarrhythmia (4%), and focal background slowing (19%). The same study found that focal slowing, focal and multifocal epileptiform abnormalities were the features most associated with a risk for refractory epilepsy [18].

In a cohort of 74 children with epilepsy and CP the interictal findings in the majority of children with quadriplegia and diplegia showed generalized EEG abnormalities [23]. This finding may reflect deep and diffuse lesions. About 43% of (7/16) of the children with hemiplegic CP had focal abnormalities. While many seizure types occurring in patients with cerebral palsy are described as generalized, the EEG studies tend to support a focal onset of seizures with a rapid bilateral spread in most cases. Background slowing, especially focal, is typically attributed to a focal structural or functional abnormality and may be associated with a higher risk for drug-resistant epilepsy.

6. Management

Anti-seizure medications (ASM) are the mainstay of treatment in patients with epilepsy and cerebral palsy. There are many available anti-seizure medications (Table 1), and the detailed

review of each medication is beyond the scope of this article. The selection of an appropriate medication regimen should be based upon the seizure type, EEG findings, epilepsy syndrome-if applicable, and side effect profile. The goal should be to optimize safety and quality of life, while minimizing seizures and side effects. Poor control of seizures in a child with CP is associated with an increased risk of mortality, sudden unexpected death in epilepsy, and increased psychosocial burden [18].

Table 1 Common anti-seizure medications in children with epilepsy and special considerations in children with CP [32].

Antiseizure Medication	Primary Mechanism of Action	Common Side Effects	Special considerations
Brivaracetam	Binding SV2A	Somnolence, dizziness, fatigue	1. Broad spectrum medication 2. Interactions: Clearance is induced by enzyme inducing medications. It may increase carbamazepine and phenytoin concentrations
Carbamazepine	Na channel blockade	Sedation, dizziness, ataxia, diplopia, tremor, impaired cognitive functioning. Rarely may be associated with rash, SJS, hyponatremia, reduced blood counts, elevated liver enzymes	1. Enzyme inducer-reduces levels of drugs metabolized by CYP enzyme system; multiple drug-drug interactions 2. Potential teratogenicity 3. May exacerbate absence, myoclonic and atonic seizures; abrupt withdrawal may be associated with severe rebound seizures 4. Other indications include treatment of acute mania, bipolar disorder, and trigeminal neuralgia 5. Long-term may be associated with reduced bone mineral density, and weight gain
Cannabidiol	Enhances GABA, modulation of intracellular Ca	Diarrhea, elevated liver enzymes, decreased appetite sleepiness, vomiting	1. May counteract chronic constipation 2. Studies ongoing regarding possibility of reducing anxiety and depression [33] 3. High potential for medication interactions, particularly with clobazam-increases clobazam active metabolite levels

			4. Specifically approved for use in Dravet syndrome, Lennox-Gastaut syndrome, and TSC
Clobazam	Enhances GABA	Drowsiness, nystagmus, incoordination, unsteadiness, dysarthria, worsening constipation, sialorrhea	1. Interactions through CYP2C19; susceptible to inhibition from felbamate, cannabidiol, cenobamate resulting in increased sedation and accumulation 2. Broad spectrum, and effective against multiple seizures types, including use in LGS 3. Caution in patients with risk for aspiration [34]
Eslicarbazepine acetate	Na channel blockade	Dizziness, fatigue, diplopia, ataxia, nausea, vomiting, headache Rare: Rash, hyponatremia	1. Once daily dosing 2. Weak inducer of CYP3A4, potentially decreases plasma concentrations of estrogens, and weak inhibitor of CYP2C19, potentially increasing plasma concentration of phenytoin 3. May worsen generalized seizures
Ethosuximide	Blocking T-type Ca channels	Nausea, abdominal pain, anorexia, diarrhea, drowsiness, insomnia, nervousness, dizziness, fatigue, ataxia, behavior changes Rarely may be associated with rash, SJS, systemic lupus erythematosus, changes in blood counts, autoimmune thyroiditis	1. Narrow-spectrum medication for control of absence seizures
Felbamate	NMDA antagonism, blocking Na channels,	Anorexia, nausea, vomiting, insomnia, irritability,	1. Broad-spectrum medication 2. Inhibitor of CYP2C19, CYP1A2, and beta oxidation; inhibits metabolism of phenobarbital,

	enhancing GABA	headache weight loss Rare, potentially lethal aplastic anemia and hepatic failure	phenytoin, valproate, carbamazepine epoxide, N-desmethylclobazam, warfarin 3. Reduces OCP efficacy 4. Due to rare severe reaction, reserved for severe epilepsy where treatment benefits outweigh the risks
Fenfluramine	Enhancing serotonin	Decreased appetite, fatigue, somnolence, weight loss Was previously withdrawn from market when used at high doses for weight loss, as valvular heart disease and pulmonary hypertension were noted. These have not been seen at lower doses	1. Indicated for seizures associated with Dravet syndrome and LGS 2. Has many medication interactions, particularly stiripentol and clobazam increase serum concentrations of fenfluramine 3. Requires periodic echocardiograms to monitor for the development of pulmonary hypertension and valvulopathy
Gabapentin	Binding alpha-2-delta subunit of Ca channels	Drowsiness, dizziness, ataxia, tiredness, weight gain, cognitive slowing, mood lability, peripheral edema	1. Narrow-spectrum medication, effective against focal seizures, may worsen generalized seizure types like myoclonus 2. Also approved for treatment of postherpetic neuralgia, restless leg syndrome, and may be beneficial for headache treatment 3. Antacids may interfere with absorption, but otherwise no known interactions
Lacosamide	Na channel blockade	Dizziness, nausea, vomiting, diplopia, fatigue, sedation May cause a dose-dependent prolongation of the PR interval	1. Effective against focal onset and generalized tonic clonic seizures. Typically not effective against myoclonic or absence seizures 2. Caution in patients with cardiac conduction problems
Lamotrigine	Na channel blockade	Dizziness, diplopia, ataxia, nausea,	1. Broad spectrum medication with efficacy against multiple

		headache, tremor, rash Tends to be less sedating and with fewer cognitive side effects when compared with other ASM May widen QRS interval and slow ventricular conduction, which can induce arrythmias and sudden death in patients with structural heart disease or myocardial ischemia	seizure types including in the setting of LGS, and absence seizures 2. Estrogen and pregnancy increase clearance 3. Also approved for use in treatment of bipolar disorder 4. Requires slow titration due to risk of SJS-limits use in patients with frequent seizures 5. Multiple medication interactions; metabolism induced by inducers, inhibited by valproic acid
Levetiracetam	Binding SV2A	Somnolence, dizziness, weakness, irritability, hostility, depression, anxiety, rarely psychosis	1. Broad spectrum medication 2. No significant pharmacokinetic interactions 3. Irritability and mood side effects may limit use in some people
Oxcarbazepine	Na channel blockade	Sedation, dizziness, ataxia, diplopia, tremor Rarely may be associated with rash, SJS, hyponatremia, reduced blood counts, elevated liver enzymes	1. Weak inducer of CYP3A4, reduces efficacy of OCPs at high doses 2. May exacerbate myoclonic and absence seizures; abrupt withdrawal may be associated with severe seizures 3. May be used off label for treatment of behavior disorders [35, 36]
Perampanel	AMPA antagonism	Dizziness, somnolence, headache, fatigue, ataxia, blurred vision. High incidence of	1. Effective against focal and generalized tonic-clonic seizures 2. Long half-life allows once daily dosing 3. Accelerates the metabolism of levonorgestrel, a progesterone

		aggression and hostility resulted in black box warning	component of OCPs
Phenobarbital	Enhancing GABA	Sedation, decreased concentration, hyperactivity, depression	1. Long-term use may be associated with decreased bone density 2. May negatively impact cognitive ability 3. Risk of teratogenicity, cardiac malformations in exposed fetus 4. Most frequently used in neonatal seizures in the US
Phenytoin	Na channel blockade	Ataxia, dysarthria, diplopia, nystagmus, sedation, rash IV phenytoin associated with burning pain, purple glove syndrome IV fosphenytoin, phenytoin may be associated with arrhythmias	1. Poor bioavailability when given with nasogastric feeds, calcium, antacids 2. Enzyme inducer-reduces efficacy of drugs metabolized by P450 enzyme system 3. Multiple drug-drug interactions 4. May exacerbate absence or myoclonic seizures 5. Long-term use may be associated with gingival hyperplasia, acne, hirsutism, cerebellar atrophy, decreased bone mineral density, anemia, peripheral neuropathy
Pregabalin	Binding alpha-2-delta subunit of Ca channels	Dizziness, fatigue, weight gain, peripheral edema	1. Narrow-spectrum medication, effective against focal seizures, may worsen generalized seizure types like myoclonus and absence seizures 2. Also approved for treatment of postherpetic neuralgia, diabetic peripheral neuropathy, fibromyalgia, neuropathic pain associated with spinal cord injury 3. No known medication interactions
Rufinamide	Na channel blockade	Dizziness, fatigue, somnolence, headache, vomiting. May shorten QT	1. Broad spectrum medication, indicated specifically for treatment of Lennox-Gastaut syndrome 2. Interactions including with

		interval	valproate, which increases rufinamide levels by up to 70% 3. Caution in patients with cardiac conduction abnormalities
Stiripentol	Enhancing GABA	Nausea, decreased appetite, weight loss, drowsiness, agitation, tremor, dysarthria, insomnia	1. Indicated as adjunctive treatment in patient with Dravet syndrome 2. High potential for medication interactions, requires careful consideration of other medication doses
Topiramate	Blocking Na channels, AMPA/glutamate antagonism, enhancing GABA	Cognitive slowing, decreased attention and memory, word-finding difficulties, sedation, fatigue, dizziness, ataxia, depression, decreased appetite, weight loss, hyperthermia, oligohydrosis, metabolic acidosis Rare side effects include kidney stones, angle closure glaucoma	1. Broad spectrum medication, but not effective against absence seizures 2. Also approved for migraine prophylaxis and used off label for weight loss and bipolar disorder 3. Reduces efficacy of OCPs at doses above 200mg per day 4. Teratogenicity risk associated with defects including oral clefts 5. Caution when used with valproate as the combination may result in hyperammonemia 6. Caution with ketogenic diet, due to elevated risk for metabolic acidosis
Valproate	Blocking Na channels, enhancing GABA, blocking T-type Ca channels	Nausea, vomiting, weight gain, tremor, fatigue, hair loss, confusion, edema, poor attention Dose dependent thrombocytopenia, hepatotoxicity, endocrine effects-PCOS, insulin resistance, rarely pancreatitis	1. Potent inhibitor, reduces the clearance of medications like phenobarbital, lamotrigine, rufinamide, carbamazepine 2. Effective against focal and generalized seizure types 3. High teratogenic risk; risk for reduced verbal IQ, cognitive dysfunction, autism with intrauterine exposure 4. Specific formulations are used for migraine prophylaxis and treatment of bipolar disorder
Vigabatrin	Enhancing GABA	Sedation, fatigue, dizziness, ataxia, irritability,	1. Narrow spectrum used for focal seizures and infantile spasms, particularly with TSC. It may

		psychosis, depression, weight gain. Can cause an irreversible concentric visual field loss, the risk of which increased with increased daily dose and duration of therapy	worsen absence and myoclonic seizures. 2. Periodic visual assessment is recommended at baseline and every 3 months
Zonisamide	Na channel blockade, blocking T-type Ca channels	Sedation, ataxia, dizziness, nausea, fatigue, irritability, anorexia. Weight loss and cognitive slowing can occur. Rarely rashes such as SJS, kidney stones, oligohidrosis, hyperthermia, metabolic acidosis	1. Broad spectrum medication 2. Long half-life may be an advantage, allows once daily dosing, and reduces impact of missed dose 3. In the US, it is not approved for use in children

ASM: Anti-seizure medications, LGS: Lennox-Gastaut syndrome, OCP: Oral contraceptive pills, PCOS: polycystic ovary syndrome, SJS: Stevens-Johnson syndrome, TSC: tuberous sclerosis complex

In children with focal seizures, narrow-spectrum medications such as oxcarbazepine, carbamazepine, gabapentin, pregabalin, and vigabatrin may be utilized. Knowledge of seizure type, however, is important, as those medications may exacerbate generalized seizure types. Broad-spectrum medications such as levetiracetam, lamotrigine, phenytoin, topiramate, felbamate, zonisamide, valproic acid, phenobarbital, lacosamide (now also approved as adjunctive therapy for primary generalized tonic-clonic seizures) and clobazam, may be effective against focal or generalized seizure types, and may also be used when seizure type is unclear. Although considered amongst broad-spectrum anti-seizure drugs, it is important to recognize that in some cases lamotrigine has been associated with exacerbation of myoclonic seizures, and phenobarbital can trigger absence seizures in some patients. Hence it is important to educate the primary caretaker to be watchful of the activities such as absence events and myoclonic jerks, which can be subtle and missed due to underlying spasticity, movement disorders and other impairments.

If a specific epilepsy syndrome is identified, the medication therapy should be tailored to the treatment of that syndrome. Infantile Spasms syndrome, for example, is an infantile epileptic encephalopathy characterized by clusters of infantile spasms. Children typically present between 4 months and 2 years of age with infantile spasms, hypsarrhythmia and

developmental regression. First-line treatments include ACTH, oral corticosteroids, and vigabatrin [37]. Lennox-Gastaut syndrome (LGS) is an epileptic encephalopathy that typically begins in early childhood and is characterized by multiple seizure types, intellectual disability, and specific EEG features, such as slow spike-wave activity. West syndrome may evolve to LGS. The seizures in this syndrome are characteristically difficult to control with medications and polytherapy is often required. The currently indicated anti-seizure medications for LGS in the United States are lamotrigine, topiramate, felbamate, rufinamide, clobazam, cannabidiol, and fenfluramine. Valproic acid, levetiracetam, zonisamide, lacosamide, perampanel and clonazepam are also commonly used as adjunctive therapy [12, 38, 39]. Cannabidiol (brand name Epidiolex), has received a lot of recent attention due to the potential beneficial effects on anxiety and depression, which often occur co-morbidly with epilepsy. Unpublished pilot study data presented at Society for Neuroscience conference in November, 2021 on eight pediatric patients using cannabidiol for treatment of epilepsy also suggested benefits in mood and depression, but larger studies will be needed to confirm this benefit [33]. If childhood absence epilepsy is identified ethosuximide, valproic acid and lamotrigine are typically utilized as first-line therapies [40].

Medication interactions and side effects are important considerations when choosing an anti-seizure medication (ASM) regimen. Patients with cerebral palsy often have other co-morbid medical problems that require daily medication(s). They also have a higher risk for refractory epilepsy, making them more likely to require multiple ASMs for seizure control [41]. The subgroup of children at the highest risk for refractory seizures also have a higher risk for intellectual disability and may not be able to adequately express when they experience adverse effects. It is, therefore, critical to be cognizant of potential side effects, particularly when using multiple medications from the same class, or with similar side effect profiles. Common side effects among anti-seizure medications may include fatigue, somnolence, dizziness, balance difficulties, change in appetite, and abdominal pain. These side effects may be difficult to recognize in non-verbal children, who may manifest non-specific symptoms of irritability, aggression, frequent falls or refusal to walk. Hence a detailed account of the baseline status of the child prior to starting the medication and monitoring changes after starting the ASMs are vital in management. Drug combinations that may be particularly challenging include combinations of sodium channel blocking agents, such as oxcarbazepine, lamotrigine, and lacosamide, as these can cause dizziness, ataxia, falls, vision disturbances and EKG changes. Likewise, phenobarbital and valproic acid can cause excessive weight gain and fatigue. Enzyme inducers, such as carbamazepine and phenytoin, require escalation of other medication doses [42].

Anti-seizure medications may also be chosen with other medical comorbidities in mind. Children with cerebral palsy are at risk for behavior challenges. The ASMs that tend to have the most benefit on mood and behavior include valproic acid, lamotrigine, oxcarbazepine, and carbamazepine. Topiramate or zonisamide may be chosen in children who are obese or overweight to help with weight loss. Topiramate, valproic acid, and lamotrigine may be utilized in children with comorbid migraines to help both with headaches and seizures. On the other hand, zonisamide and topiramate are typically avoided in children with a history of nephrolithiasis and cognitive difficulties. Children with spastic quadriparesis may be at higher risk to develop osteoporosis and fractures, due to non-weight bearing status. Several ASMs, including carbamazepine, valproic acid, phenytoin, and phenobarbital may impact bone health, increasing

the risk for osteoporosis and fractures, and avoided in such patients if possible, especially if the child is non ambulatory as these patients have lower baseline bone density [43]. CP patients with impaired motor skills are at higher risk for falls, so medications that cause significant dizziness or ataxia, or that significantly increase the risk for fractures may not be ideal to use as first-line. Finally, in children with hepatic or renal dysfunction, the metabolism of ASMs should be evaluated to determine if dose adjustments or alternative medications should be considered.

Children who continue to have seizures despite 2 or more well-chosen medications are considered to have medically refractory epilepsy and are less likely to have seizures completely controlled by medication alone [27]. Epilepsy surgery can be the most effective way to treat seizures in children with focal refractory focal epilepsy. The advancements in recent surgical, imaging, and EEG techniques, have shown promising results in the field of epilepsy surgery [44]. Many patients with cerebral palsy have diffuse, or multifocal areas of injury, which may preclude them from focal surgical resection. Patients with focal or unilateral lesions, however, may do very well with epilepsy surgery. In a case series of 6 children with unilateral cerebral palsy and hemispheric encephaloclastic lesions who were treated with hemispherectomy, all children had an Engel Class 1 outcome for seizures with an improvement in cognition, quality of life, a reduction in anti-seizure medications [45]. Epilepsy surgery, however, can negatively impact language, motor and neurocognitive functions. Hence, surgical options should be approached with caution and should be offered only if in line with the family's and patient's goals & expectations.

Alternative strategies including ketogenic diet therapy, vagus nerve stimulator (VNS), and palliative surgical procedures like corpus callosotomy, or neurostimulation techniques should also be considered alone or in combination. Patients with refractory epilepsy should be evaluated early in the course to optimize the benefits i.e. reduction of seizure burden and potential cure. Data regarding vagus nerve stimulation for childhood-onset refractory epilepsy from Russo, A., et al. in 2021 [46], for example, suggests that early vagus nerve stimulator implantation within 5 years of seizure onset was a predictor of favorable clinical outcome in that pediatric patient cohort. In those patients, a >50% seizure reduction was reported in 25.8% of their patient cohort at 1 year, and 5.2% were seizure-free with vagus nerve stimulator [46]. Long-term outcomes in pediatric patients with VNS for refractory epilepsy suggests even better efficacy, with approximately 50% of patients experiencing 50% or greater reduction in seizure frequency, and overall good patient tolerance of therapy [47]. The ketogenic diet is a high fat, low carbohydrate diet that has shown success for aiding in management of refractory epilepsy. A long-term study of 140 patients who were maintained on ketogenic diet, found that about 56% achieved at least a 75% reduction in seizures on diet, and of those, 20% were seizure-free on ketogenic diet [48]. Smaller studies of pediatric patients specifically looked at ketogenic diet efficacy in patients with malformations of cortical development and acquired structural epileptic encephalopathies also found benefit in those patients [49, 50]. Corpus callosotomy is a palliative procedure that is utilized for multifocal or generalized epilepsy, particularly in patients with drop attacks. In published case series of pediatric patients who underwent corpus callosotomy, it was reported that the majority of patients had a meaningful decrease in seizure frequency. The factors associated with a better outcome after corpus callosotomy included younger age at surgery and onset of seizures, the presence of drop attacks, slow spike-wave patterns on EEG, and reduced synchronicity of postoperative discharges [51]. Of the patients who respond to

corpus callosotomy, the number of anti-seizure medications can typically be reduced at some point following surgery [52].

As children with CP and epilepsy are at higher risk of status epilepticus, the establishment of an abortive plan is imperative. Currently approved abortive medications for prolonged seizures or clusters of seizures include rectal diazepam, intranasal midazolam, and intranasal diazepam. Selection of the abortive medication is mainly based on the patient's age, clinical condition, and the comfort level of the caregiver in administering the medication (intranasally vs. rectally). Rectal diazepam is FDA approved from the age of 2 years, intranasal diazepam is FDA approved for use in children ages 6 and above, and intranasal midazolam is FDA approved for use in patients 12 years and older [53, 54]. Intranasal formulations are less invasive and may be easier to administer. For example, in patients who have limited mobility, are large, or have significant spasticity with scissoring of the legs, moving the patient and removing clothing to administer the rectal preparation may be challenging. Patients and caregivers should also be educated about when to seek medical attention. It is helpful to establish a seizure action plan, which is individualized and specifies the patient's seizure type(s), the definition of a seizure emergency in the particular patient, advises when to administer a rescue medication, and when to call for emergency help [55].

In addition to a discussion with the patient and caregivers regarding epilepsy, ASM, side effects, adherence with a medication regimen, and abortive medications, education about sudden unexpected death in epilepsy (SUDEP), should be incorporated into the visit. A detailed discussion about goals of care and expectations should be established. Caregivers should be aware that SUDEP typically affects 1 in 4,500 children each year with epilepsy [56]. Leading risk factors include uncontrolled generalized tonic clonic seizures, and nocturnal seizures. Successfully controlling generalized tonic clonic seizures is associated with a decreased risk for SUDEP. Adherence with the recommended medications to control seizures should be emphasized [56]. Facts regarding the risks of SUDEP in children with epilepsy should be discussed with patients and their families, including information about mitigating risk factors through optimally managing seizures, and particularly preventing generalized tonic clonic seizures.

7. Conclusion

Cerebral palsy is a static encephalopathy caused by an early insult to the brain, which results primarily in a motor dysfunction. Epilepsy is a common co-morbid condition that occurs frequently in children who are more severely impacted by cerebral palsy, and in children with CP and intellectual disability. When compared to children with epilepsy alone, children with CP and epilepsy are more likely to be refractory to treatment, require multiple medications to prevent seizures, experience status epilepticus, and are more likely to require life-long anti-seizure medications. The EEG findings in children with CP and epilepsy are relatively non-specific, and most commonly include generalized background slowing, focal or generalized epileptiform abnormalities.

Treatment for epilepsy in CP begins with prophylactic anti-seizure medication. There are many available ASMs, and the initial choice typically is based upon seizure type, epilepsy syndrome, side effect profiles and co-morbid conditions. The goal of treatment is to minimize seizures and side

effects. Side effects should be closely monitored, as children with CP, particularly with co morbid intellectual disability, may not be able to adequately express the effects of their medications. Early evaluation for surgical candidacy should be considered in refractory patients, as surgical options may be curative. Caregiver education plays a vital role in the management of these patients and should be tailored individually. Seizure action plans are a useful tool to help with parental education. Further research is needed to reduce further the incidence of cerebral palsy, clarify ideal ASM regimens, identify which children with cerebral palsy are most likely to successfully wean from ASM, and the most appropriate time to initiate weaning.

Author Contributions

Dr. Amanda Weber was responsible for project outline, manuscript drafting and editing, and creation of the table to supplement the text. Dr. Prabhu Patil was responsible for project outline, manuscript drafting and editing.

Competing Interests

The authors have declared that no competing interests exist.

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