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REVIEW ARTICLE

# CDKL5 Deficiency Disorder-Related Epilepsy: A Review of Current and Emerging Treatment

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**Abstract**
Cyclin-dependent kinase-like 5 (*CDKL5*) deficiency disorder (CDD) is a developmental and epileptic encephalopathy with infantile-onset epilepsy. Most individuals with CDD develop refractory epilepsy with multiple seizure types. Management of seizures in CDD remains challenging for clinicians given the highly refractory nature of seizures and the limited number of disease-specific studies that offer a high level of evidence. Epileptic spasms are the most common seizure type in CDD and are more often refractory to standard first-line treatment than are spasms of other etiologies. In other seizure types, the effectiveness of antiseizure medications is limited and wanes over time. Ketogenic diet and palliative surgical treatments have both had mixed results in observational studies. When treating refractory seizures in CDD, we recommend carefully balancing seizure control and treatment-related side effects to optimize each individual's overall quality of life. Clinical trials of medications targeting epilepsy in CDD have been conducted, and additional investigational small molecules, gene therapy, and other disease-modifying therapies are in development for CDD.

## 1 Introduction

Cyclin-dependent kinase-like 5 (*CDKL5*) deficiency disorder (CDD) is a developmental and epileptic encephalopathy (DEE) with infantile-onset epilepsy, global developmental delay with subsequent intellectual and motor disabilities, and cortical visual impairment as major features [1–4]. The first clinical report of CDD in 2003 described two girls with infantile spasms, hypsarrhythmia, and global developmental delay due to balanced translocation on Xp22.3 causing a breakage of *CDKL5* [5]. Initially identified as the early-onset seizure variant of Rett syndrome, the spectrum and phenotypes of CDD that emerged proved it to be an independent disorder [3, 4, 6] garnering a specific *International Classification of Diseases, Tenth Revision, Clinical Modification* code (G40.42). CDD, an X-linked disease, is more prevalent in girls, with a female-to-male ratio of approximately 4:1 [6, 7]. Overall, boys have more severe developmental impairment and lower quality of life than girls, although this varies because of a high rate of somatic mosaicism in males [8–10].

**Key Points**

Anti-seizure medications tend to lose effectiveness with time in individuals with cyclin-dependent kinase-like 5 (*CDKL5*) deficiency disorder (CDD).

Balance treatment side effects with caution in CDD, focusing on quality of life.

Clinical trials or expanded access programs are ongoing for CDD, and disease-modifying therapies are in development.

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Epilepsy in CDD has been described in three stages (Fig. 1), starting with early infantile-onset generalized tonic or tonic-clonic seizures, with variable pharmaco-responsiveness [11, 12]. The median age of seizure onset has been reported from 4 weeks to 2 months; 90% of individuals with CDD present with seizures by 3 months of age [6, 11–13]. Early infantile electroencephalograms (EEGs) may be normal or accompanied by a slow background with or without epileptiform activities [11]. In contrast to other severe early infantile-onset epileptic encephalopathies, CDD is rarely associated with a burst-suppression pattern on EEG [11]. In this first phase, a subset of individuals experience a transient period of seizure freedom, known as a honeymoon period [11]. There is wide variability in reports of a honeymoon period, defined as seizure freedom lasting at least 1 month (median duration 4–6 months), described in 14–100% of individuals (38% when pooled across four studies), with median onset of 20–24 months [11–14]. In the second stage,

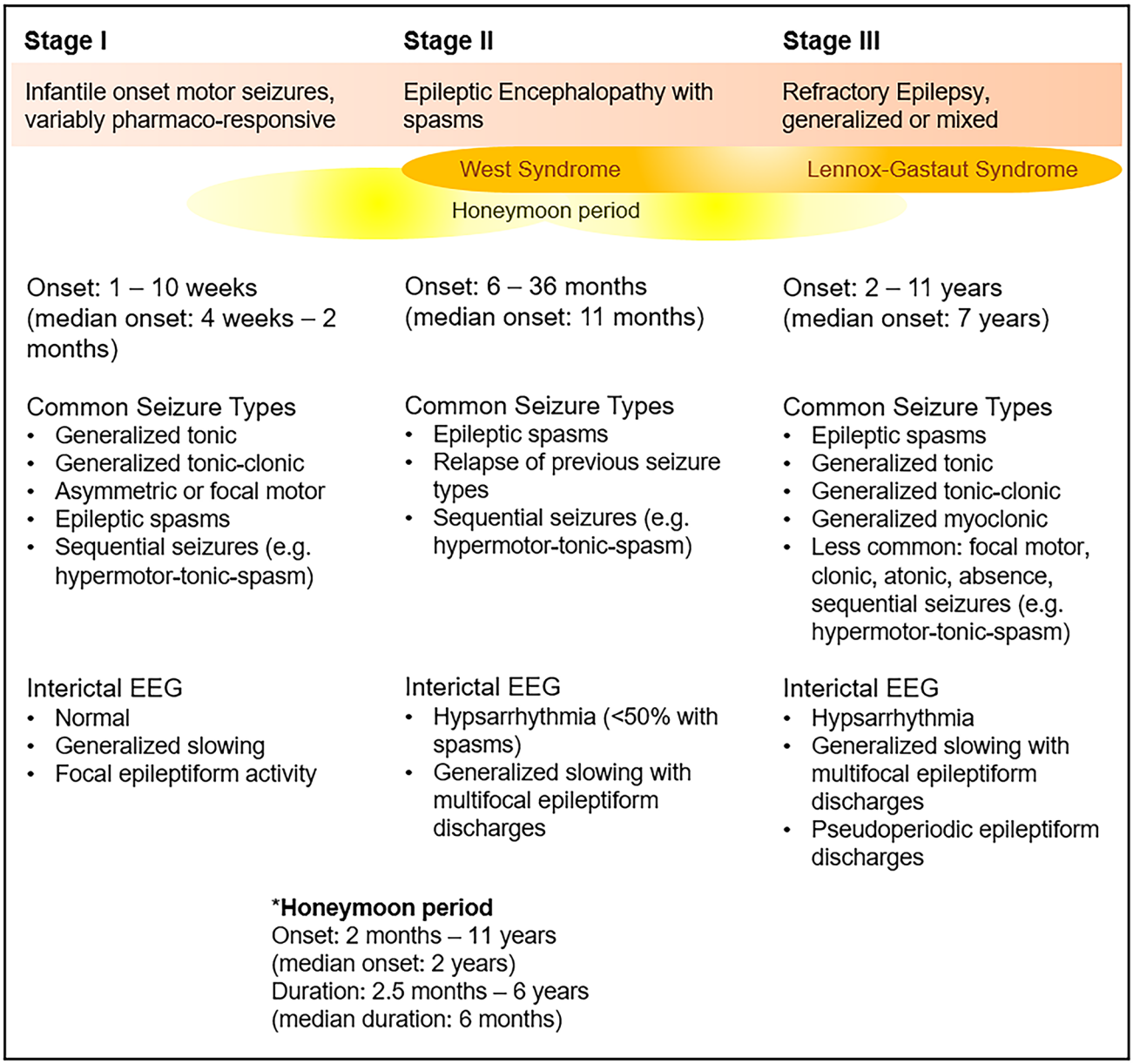


**Fig. 1** Three stages of epilepsy in *CDKL5* deficiency disorder (CDD). During the initial stage, the EEG may be normal, and hypsarrhythmia may not be present at the onset of spasms. In later stages, hypsarrhythmia and generalized slowing with multifocal epileptiform discharges are common. A portion of individuals may experience a honeymoon period. Epileptic encephalopathy and refractory generalized or mixed epilepsy are common in later stages, and a subset of individuals are diagnosed with West syndrome or Lennox–Gastaut syndrome. Sequential seizures with multiple motor phases are common in all three stages [7, 11, 13]. *EEG* electroencephalogram

there is relapse of previous seizures and onset of epileptic spasms [11]. While epileptic spasms are the most common seizure type in CDD, only about half of those with spasms have hypsarrhythmia captured on EEG at any point [12]. In the third and final stage, spasms may continue or evolve to other seizure types, and most individuals with CDD continue to have generalized or mixed focal and generalized seizures [7, 11]. In children and adults, EEGs have shown multifocal and/or generalized interictal epileptiform discharges, including pseudoperiodic epileptiform discharges, focal or generalized slowing, and at times high amplitude background [7, 11]. Other common types of seizures include generalized tonic, generalized tonic-clonic, generalized myoclonic, and focal seizures, and less commonly clonic, atonic, and absence seizures [6, 12, 15]. Unique sequential seizures with multiple distinct motor and nonmotor phases in a single seizure have been reported, including hypermotor-tonic-spasm and similar variations [12, 16], hyperkinetic-spasm [17], tonic-clonic-spasm [18], and tonic-spasm-myoclonic [19]. Three case reports documented reflex seizures triggered by diaper change, noise, light, or water immersion [20–22]. Sudden unexpected death in epilepsy (SUDEP) has also been reported, and while the frequency of SUDEP in CDD is not established, the highly refractory nature of epilepsy in CDD puts many individuals with CDD at high risk for SUDEP [23–25].

Our goal is to discuss a treatment approach in the context of this highly refractory DEE. We synthesize the current observational and clinical trial data on the treatment of epilepsy in CDD, and—given the limited number of studies with high level of evidence—also aim to provide expert opinions from the CDKL5 Centers of Excellence. We conclude with a review of emerging therapies in development.

## 2 Treatment Approach for Epilepsy in *CDKL5* Deficiency Disorder (CDD)

In DEEs, epileptiform activity may interfere with normal brain function and negatively impact an individual's development above what may be attributable to the underlying condition [26]. However, in certain DEEs with underlying genetic causes, including CDD, whether improving seizure control or epileptiform activities leads to better development has been debatable [13, 27, 28]. A multicenter retrospective study in 2016 of individuals with CDD found no improvement in cognitive function despite significant reduction of seizures [27]. While an association between better functional abilities and fewer seizures in individuals with CDD has been observed, whether better function results from improved seizure control or is an epiphenomenon of a less severe genotype remains to be answered [13].

When approaching epilepsy management in CDD, it is critical to consider seizures in the context of each individual's broader neurodevelopmental disorder and each family's priorities for quality of life. Seizure control in and of itself is not necessarily the highest priority for optimizing quality of life [9, 29], and we must consider the extent to which additional attempts to minimize seizures may benefit individuals with CDD compared with the risk of side effects from medications or nonmedication approaches to treatment.

### 2.1 Impact of Seizure Burden on Quality of Life

Families and caregivers of individuals with CDD have identified seizures as the second most burdensome symptom, after global developmental delay, and as an important factor in determining quality of life [29, 30]. Seizures in CDD are prevalent and frequency is high, with approximately two-thirds of individuals having daily seizures and nearly one-third experiencing five or more seizures per day [6, 13]. Frequent seizures can lead to a prolonged recovery period and somnolence, limiting communication, interaction, mobility, and participation in support services [30]. Those with reflex seizures and hypersensitivity to stimuli can experience a negative impact on their behavioral and emotional wellbeing [30]. Factors such as postictal sedation, need for rescue medication, and frequency of seizure-related emergency room visits or hospitalization may all play a role in how much seizures negatively influence an individual's quality of life. Having more than five seizures per day and a high hospital admission rate was associated with lower quality of life scores [9].

### 2.2 Benefits and Side Effects of Antiseizure Medications

Nearly three-quarters of individuals with CDD take two or more antiseizure medications (ASMs) simultaneously [9, 13]. In a 2021 retrospective report with data on 168 individuals with CDD, the median number of ASMs prescribed per individual over their lifetime was six (range 0–18) [15]. ASMs are the most commonly used medications in CDD. While some do help decrease the seizure burden, others may provide only transient or partial benefit for seizures and cause a negative impact on cognition and motor function [15, 27, 29]. Families have reported that sedating effects from ASMs, causing lethargy and decreased engagement in daily activities, negatively impact quality of life and in certain instances outweigh the positive effects associated with seizure control [9, 29, 30]. Treatment with monotherapy compared with polytherapy with three or more medications was associated with higher quality of life scores [9].

### 2.3 Balance of Seizure Control and Quality of Life

A 2021 study assessing quality of life in children with CDD, based on questionnaires completed by 129 families registered with the International CDKL5 Disorder Database, found that functional impairment, including lack of ability to sit, use hands, and communicate, had the greatest adverse impact on quality of life [9]. At the 2019 US Patient-Focused Drug Development Meeting for CDD, caregivers ranked the following in the top three most desirable targets for new CDD treatment development: developmental milestones (76% [35/46]), improved language abilities (54% [25/46]), and improved social communication (35% [16/46]) [29]. Only 30% (14/46) rated reduced seizures in the top three priorities [29]. These results highlight aspects to consider when using available treatments for epilepsy.

In the CDKL5 Centers of Excellence, we tend to be cautious about the high burden of medication side effects. Brief seizures that do not impact alertness and interaction may be better tolerated than escalating doses of ASMs that may cause sedation, impair cognitive function, and worsen hypotonia and dysphagia. Withdrawing medications when seizures are active can be challenging but may be necessary to avoid increasing polypharmacy. Simplifying the ASM regimen may minimize complex drug–drug interactions affecting pharmacokinetics and absorption; rarely does simplifying a regimen worsen seizure control more than transiently, in our experience. Thus, the art of epilepsy management in CDD, as in other severe refractory epileptic encephalopathies, necessitates a careful balancing act to optimize each individual's ability to interact with family and others.

## 3 Treatment for CDD-Associated Infantile Spasms

Epileptic spasms are present at any point in time in 82% of individuals with CDD, and as the initial seizure type in 23% [12]. In addition, more than one-third of individuals with CDD report seizures with multiple phases that include epileptic spasms, often combined with tonic seizures [12]. Epileptic spasms in this population are highly refractory and may continue into childhood and adulthood [7, 12]. In one early case series, only three of eight individuals with CDD and epileptic spasms responded to high-dose corticosteroids [11]. Data presented at the 2020 American Neurological Association meeting from three CDKL5 Centers of Excellence showed that response to first-line pharmacologic treatments for infantile spasms in individuals with CDD was low when compared with infantile spasms of other etiologies from the National Infantile Spasms Consortium (NISC) database [31, 32] (Table 1). A sustained response at 3 months was rare in the CDD cohort [31]. A ketogenic diet for refractory spasms initially had similar response rates between both cohorts at approximately 20%, but the response rate in individuals with CDD at 3 months was 17% (2/12) compared with 38% (15/40) in the comparison group [31]. Future research should focus on an alternative first-line therapy specific for epileptic spasms in CDD.

## 4 Antiseizure Medications in CDD

### 4.1 Observational Studies of Currently Available Medications

Four large studies have investigated the benefits of different ASMs approved by the US FDA [14, 15, 27, 33] (Table 2). Three were multicenter retrospective observational studies with effectiveness defined as a >50% seizure reduction at variable time points [14, 15, 27], and the other was a questionnaire-based study that asked caregivers what they considered to be "the most effective medication" [33]. Levetiracetam was one of the top five most used ASMs in all studies, and topiramate, phenobarbital, valproic acid, and vigabatrin were among the top five most used ASMs in three of the four studies [14, 15, 27, 33]. Clobazam, lamotrigine, valproic acid, and vigabatrin were each in the top five most effective ASMs in at least three of the four studies, none of which differentiated responses by seizure types [14, 15, 27, 33]. This excludes ASMs used in fewer than ten individuals per study, as well as adrenocorticotropin hormone (ACTH) and corticosteroids, which are discussed separately. Two studies looked into the percentage of responders to ASMs longitudinally and demonstrated a decline in the effectiveness of ASMs over the course of 2–9 months [15, 27].

One small case series reported a more than 90% decrease in seizure frequency in five individuals with a combined use of vigabatrin and zonisamide [18]. Data on the use of sodium channel blockers are mixed, ranging from seizure exacerbation to seizure freedom lasting ≥ 3 years [14, 15, 27, 29, 34]. In one multicenter retrospective observational study in 2021, six of 19 individuals with CDD reported a > 50% reduction in seizure frequency at 6 months with sodium channel blockers [34]. However, caution may be advised if using sodium channel blockers in infants, given the potential risk of these medications inducing infantile spasms in high-risk populations, including those with CDD [35]. Levetiracetam and cannabidiol have also been anecdotally reported to exacerbate the seizure burden in CDD in certain situations [14, 15, 27, 29, 36].

### 4.2 Cannabidiol

Following randomized double-blinded placebo-controlled trials, Epidiolex® (purified cannabidiol) was approved by the FDA in 2018 for Dravet syndrome and Lennox–Gastaut

**Table 1** Treatment response of infantile spasms in CDD is worse for standard first-line medications than for a non-CDD population from the NISC database [32]

| Treatment | CDD Treated % (N) | NISC Treated % (N) | CDD 14-day response % (N) | NISC 14-day response % (N) | CDD 1-month response % (N) | NISC 1-month response % (N) | CDD 3-month response % (N) | NISC 3-month response % (N) |
|---|---|---|---|---|---|---|---|---|
| ACTH | **38** (17/45) | **60** (225/376) | **24** (4/17) | **63** (138/219) | | | **0** (0/8) | **59** (128/217) |
| Prednisolone | **40** (17/43) | **30** (111/376) | **12** (2/17) | **53** (51/97) | | | **0** (0/6) | **54** (45/84) |
| Vigabatrin | **67** (30/45) | **53** (197/375) | **27** (7/26) | **42** (78/184) | | | **11** (2/19) | **42** (78/184) |
| Ketogenic diet | **53** (24/45) | **14** (51/376) | | | **20** (4/20) | **19** (5/27) | **17** (2/12) | **38** (15/40) |

Data are presented as % (*N*). Individuals included in the analysis had infantile spasms onset between 2 months and 2 years of age. Exclusion criteria were tuberous sclerosis complex, trisomy 21, and unknown etiology with normal development. The CDD cohort showed poorer response to all first-line treatments. Early response of the CDD cohort to a ketogenic diet for refractory spasms was similar to that of the non-CDD group, but the response rate was lower in the CDD cohort at 3 months [31]

*ACTH* adrenocorticotropic hormone, *CDD CDKL5* deficiency disorder cohort, *NISC* non-CDD cohort from National Infantile Spasms Consortium

syndrome [37, 38]. Use of Epidiolex® and other non-FDA-approved cannabidiol derivatives has gained popularity in CDD, with 20% of individuals reporting current use and 36% reporting use at some point in their treatment course [9, 15]. The perceived benefit of cannabidiol was also significant, with 54% (38/70) of caregivers reporting sustained benefit in seizure control and another 16% (11/70) reporting some temporary benefit, according to an analysis of caregivers' questionnaires [36]. When used as an adjuvant treatment to clobazam, Epidiolex® reportedly granted one individual with CDD total seizure freedom at 8 weeks [39]. However, other observational and retrospective studies provided variable results (Table 3). In open-label studies of Epidiolex® including individuals with CDD [40, 41], disease-specific long-term outcomes were variable, with the primary long-term extension study reporting only one of five individuals with CDD who remained in the study having a > 50% reduction in sustained motor seizures at 24 months [41]. An overlapping study of individuals with four genetic conditions reported that 53% (9/17) of individuals with CDD had a ≥ 50% reduction in motor seizures at 48 weeks [42]. A 2021 retrospective report from the CDKL5 Centers of Excellence that evaluated seizure response to Epidiolex® in individuals with CDD reported a ≥ 50% reduction in at least one seizure type in 29% (4/14) and 21% (3/14) at 2 weeks and 3 months, respectively [15]. Currently, there is not enough evidence for Epidiolex® to conclude whether it is more effective in certain seizure types.

### 4.3 Ganaxolone

At the time of writing, ganaxolone was the only ASM approved specifically for CDD by the FDA. Ganaxolone is a synthetic analog of endogenous allopregnanolone, a progesterone-derived neurosteroid [43]. Neurosteroids are allosteric modulators of gamma-aminobutyric acid (GABA)-A receptors with a binding site distinct from that of benzodiazepines [43]. Both allopregnanolone and ganaxolone showed early promising results for the treatment of status epilepticus and focal seizures but ultimately failed to show efficacy [43–45]. In CDD, the results of a randomized, placebo-controlled, double-blinded phase III trial (NCT03572933) showed a statistically significant reduction in bilateral tonic, generalized tonic-clonic, bilateral clonic, focal to bilateral tonic-clonic, and atonic seizures with 17-week use of ganaxolone (median 32 vs. 4%) [46]. The percentage of individuals with a ≥ 50% reduction in seizures was also higher for ganaxolone (25 vs. 10%), although this did not reach statistical significance [46]. Clinical global impression scales also tended to be better with ganaxolone without reaching statistical significance [46]. Adverse events and serious adverse events occurred at a similar rate in the treatment and placebo groups (88 vs. 86% for adverse events, and 12 vs. 10% for serious adverse events), with common side effects including somnolence, fever, and upper respiratory tract infection [46]. An expanded access program for ganaxolone in CDD (NCT04678479) was subsequently established for compassionate use. Ganaxolone was approved by the FDA

**Table 2** Summary of antiseizure medications used for CDD-related epilepsy based on data from four large observational studies: clobazam, lamotrigine, valproic acid, and vigabatrin were more commonly in the top five most effective antiseizure medications, but the response rate declines over time

| Study type (LoE) | Seizure reduction criteria | ACTH/cortico-steroid[a] | CBZ/OXC | CLB | LTG | LVT | PB | RFM | TPM | VGB | VPA | ZNS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Retrospective observational (4) [27] | > 50% at 3 mo | 19 (5/26) | 10 (3/29) | **24** (4/17) | **22** (5/23) | 16 (5/31) | 8 (2/26) | 8 (1/13) | 16 (5/31) | **32** (8/25) | **21** (7/34) | **18** (2/11) |
| | > 50% at 12 mo | 0 (0/26) | **7** (2/29) | 0 (0/17) | **9** (2/23) | 0 (0/31) | **8** (2/26) | 0 (0/13) | 3 (1/31) | 4 (1/25) | **9** (3/34) | 0 (0/18) |
| Caregiver survey (4) [33] | "Effective" not defined | 11 (1/9) | 0 (0/7) | **43** (6/14) | **15** (2/13) | **11** (3/27) | 0 (0/21) | 0 (0/1) | 7 (1/15) | **52** (12/23) | **19** (5/27) | 29 (2/7) |
| Retrospective observational (4) [14] | ≥ 50% | 41 (9/22)[b] | 0 (0/21) | 0 (0/22) | **5** (1/21) | 0 (0/21) | 0 (0/19) | 0 (0/5) | 0 (0/20) | 50 (1/2) | **7** (2/28) | 0 (0/23) |
| Retrospective observational (4) [15] | ≥ 50% for 2 wk | 38 (15/40) | 19 (5/26) | **48** (12/25) | **40** (6/15) | 14 (8/56) | **37** (13/35) | **47** (7/15) | 26 (10/38) | **56** (15/27) | 36 (9/25) | 0 (0/13) |
| | ≥ 50% for 3 mo | 0 (0/40) | 8 (2/26) | **36** (9/25) | 13 (2/15) | 5 (3/56) | 9 (3/35) | **27** (4/15) | 13 (5/38) | **33** (9/27) | **28** (7/25) | 0 (0/13) |

Data are presented as % (*N*). Levetiracetam was commonly used, but clobazam, lamotrigine, vigabatrin, and valproic acid were most consistently effective for seizure reduction. Response rate to ASMs declined over time when reported longitudinally. Bold text indicates the top five most effective medications, excluding ACTH and corticosteroids, each with a minimum ten or more sample size, from each study. LoE is sourced from the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653)

*ACTH* adrenocorticotropic hormone, *ASMs* antiseizure medications, *CBZ/OXC* carbamazepine or oxcarbazepine, *CDD CDKL5* deficiency disorder, *CLB* clobazam, *LoE* level of evidence, *LTG* lamotrigine, *LVT* levetiracetam, *mo* month(s), *PB* phenobarbital, *RFM* rufinamide, *Retrospective observational* study, *TPM* topiramate, *VGB* vigabatrin, *VPA* valproic acid, *wk* week(s), *ZNS* zonisamide

[a]Response was not differentiated by seizure types (spasms vs. other seizure types)

[b]ACTH effects were reported to be short lived

**Table 3** Summary of observational and clinical trial data for cannabidiol and investigational medications for CDD-related epilepsy: cannabidiol results were highly variable, ganaxolone showed benefit in a phase III trial and is now US FDA approved, and fenfluramine showed promise in a phase II trial

| Treatment | Study type (LoE) | Seizure outcome in CDD |
|---|---|---|
| Cannabidiol | Caregiver Survey (4) [36] | "Improved" in 54% (38/70); "temporary improved" in 16% (11/70) |
| Cannabidiol (Epidiolex®) | OLP (4)[a] in refractory epilepsy [41] | >50% reduction in motor[b] seizures in 20% (1/5) at 24 months |
| Cannabidiol (Epidiolex®) | OLP (4) in genetic syndromes [42] | 41% (median, $n = 11$) reduction of convulsive[c] seizures at week 12<br>60% (median, $n = 10$) reduction of convulsive[c] seizures at week 48<br>≥ 50% reduction of convulsive[c] seizures in 41% (7/17) at week 12<br>≥ 50% reduction of convulsive[c] seizures in 53% (9/17) at week 48 |
| Cannabidiol (Epidiolex®) | RO (4) [15] | ≥ 50% reduction in at least one seizure type for 2 weeks in 29% (4/14)<br>≥ 50% reduction in at least one seizure type for 3 months in 21% (3/14) |
| Ganaxolone | RCT (2) (phase III, 2020) [46] | 32% (median, $n = 50$) reduction in motor seizures at 17 weeks<br>(vs. 4% in placebo, $p = 0.002$) |
| Fenfluramine | OLP (4) (phase II, 2021) [66] | 90% (median, $n = 5$) reduction in generalized tonic-clonic seizures<br>55% (median, $n = 2$) reduction in tonic seizures<br>71% ( $n = 1$) reduction in myoclonic seizures |
| Soticlestat | OLP (4) (phase II, 2021) [73][d] | 14% (median, $n = 12$) reduction in motor seizures |
| Ataluren | RCT (2) (phase III, 2021) [74] | No improvement at 12 weeks |

Data on cannabidiol were mixed, possibly because of the different outcome measures used in the different studies. Ganaxolone was approved by the US FDA for CDD-related epilepsy in individuals aged ≥ 2 years in March 2022. Fenfluramine phase II results were promising, and a phase III trial is in process. LoE was sourced from the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653)

*CDD CDKL5* deficiency disorder, *LoE* level of evidence, *OLP* open-label prospective study, *RO* retrospective observational study, *RTC* randomized, placebo-controlled, double-blinded study

[a]Long-term follow-up study from a short-term efficacy analysis of Epidiolex® in intractable childhood onset epilepsy including eight individuals with CDD [40]

[b]Motor seizures included tonic, clonic, atonic, and myoclonic-absence seizures

[c]Convulsive seizures were defined as countable motor seizures lasting >3 s

[d]Presented at the 2021 annual American Academy of Neurology meeting

for CDD-related epilepsy in individuals aged ≥ 2 years in March 2022 and is expected to be available in the second half of 2022.

### 4.4 Immune-Modulating Therapies

There is a lack of clear evidence to recommend immune-modulating or anti-inflammatory therapy in pediatric epilepsy, with certain exceptions such as infantile spasms and autoimmune-associated epilepsy [47–49]. Rare case reports describe successful reduction in seizures with corticosteroids in genetic epilepsy, including in Angelman syndrome [50]. In CDD, three of the four large studies mentioned in Sect. 4.1 reported either ACTH or corticosteroids as among the top five most used ASMs [14, 15, 27, 33]. However, these reports did not differentiate as to whether the observed effects were on epileptic spasms or on other seizure types, and details on the duration or titration schedules of these therapies are limited [14, 15, 27, 33]. Regardless, the benefits of ACTH or corticosteroids on reducing seizure burden appeared to be transient at best [14, 15, 27, 33]. Two observational studies with longitudinal data both showed a decline in response rate to zero over 2–9 months after the initial response rate of 19 and 38% [15, 27]. However, in one of the two studies, the authors noted that discontinuation of medication, as is typical for corticosteroids or ACTH after a short course, would place the medication in the nonresponder category [27]. The third observational study specifically reported that the response to ACTH was transient, and only 11% (1/9) of parents and caregivers in the questionnaire-based study considered corticosteroids as "the most effective medication" [14, 33]. Only in one small case series was high-dose prednisolone noted to be particularly effective, with a > 75% reduction of seizures in five of eight individuals with CDD who were diagnosed with either West syndrome or Lennox–Gastaut syndrome [51].

Literature on the use of intravenous immunoglobulin (IVIG) is limited to one case series presented at the 2017 annual American Epilepsy Society meeting [52]. Of the three individuals with CDD who were treated with corticosteroids followed by IVIG, all three had a reported reduction in both seizure frequency and duration with corticosteroids, and one became free of motor seizures during the 8-month course of IVIG [52]. Overall, while ACTH, corticosteroids, or IVIG could be considered in CDD in select situations at

the clinician's judgment, more evidence is needed to decide on their indication, dose, and duration of therapy.

## 5 Diet Therapy

The ketogenic diet provides a nonpharmacologic approach to seizure management. Studies have estimated that a ketogenic diet is used in approximately one-fifth to one-third of individuals with CDD, with more than one-half of individuals with CDD reporting the use of a ketogenic diet at some point [9, 15, 30, 53]. A ketogenic diet is often initiated after 1 year of age, with one study showing the median age of diet initiation of 2 years and another study reporting a median time between seizure onset and diet initiation of 4 years [15, 53]. The literature on the benefits of a ketogenic diet in CDD shows mixed results (Table 4). Three large studies (total $N = 171$) have reported an at least 50% response rate of either a $\geq 50\%$ reduction in seizure frequency or perceived benefits from caregivers, along with variable benefits on behavior, cognition, and quality of life [15, 33, 53]. On the other hand, five smaller studies (total $N = 47$) showed poorer outcomes [14, 27, 54–56]. Overall, more studies on the ketogenic diet, including its use in infants and longitudinal follow-up, are warranted.

## 6 Surgical Treatments

Data on surgical intervention in CDD are sparse. Resective surgeries in genetic epilepsy are more effective in those with focal epilepsies related to variants in the phosphoinositide 3-kinase pathway and Gap Activity Toward Rag 1 complexes [57]. Focal resective surgeries or hemispherectomies in CDD would be expected to be palliative at best and are generally not recommended. One individual with CDD had persistent seizures after a functional hemispherectomy performed prior to the genetic diagnosis [15].

Palliative surgeries, including vagus nerve stimulator (VNS) and corpus callosotomy, have been performed, likely with a bias toward those with more severe epilepsy. A study on quality of life in individuals with CDD showed that one-quarter of individuals with CDD had a VNS placed [9]. Three studies (total $N = 64$, not accounting for possible overlap) reported an overall reduction in seizure burden of 63–75% with VNS in individuals with CDD [15, 33, 58] (Table 5). The benefits of VNS in reducing seizure burden related to CDD have also been reported individually [1, 59–61]. On the other hand, the 2021 multicenter retrospective study from Japan reported three individuals with CDD with VNS implantation and another three individuals with CDD who underwent corpus callosotomy, none of whom achieved a $\geq 50\%$ reduction in seizure frequency [14]. There are reports of at least short-term benefits of corpus callosotomy for seizure control in six individuals, including a

**Table 4** Observational studies on the effectiveness of a ketogenic diet in CDD demonstrate mixed results but more benefits in a larger case series and caregiver surveys

| Study type (LoE) | Outcome |
|---|---|
| Caregiver survey (4) [53] | Positive perceived effects on seizure characteristics in 59% (61/104)<br>Positive behavioral changes in 25% (26/104)<br>Worsening seizures in 8% (8/104) |
| Retrospective observational (4) [15] | $\geq 50\%$ reduction in seizure frequency in 50% (22/44)<br>Subjective cognitive benefit in 25% (11/44)<br>Worsening seizures in 11% (6/54) |
| Caregiver survey (4) [33] | "Effective" for seizure control in 52% (12/23)<br>Fewer antiseizure medications in 36% (5/14)<br>Fewer rescue medications in 33% (6/18)<br>Improved quality of life in 53% (10/19) |
| Retrospective observational (4) [27] | $\geq 50\%$ reduction of seizure in 17% (2/12) at 3 months<br>$\geq 50\%$ reduction of seizure in 8% (1/12) at 12 months |
| Retrospective observational (4) [55] | "Effective" for seizure control in 10% (1/10) |
| Retrospective observational (4) [54] | $\geq 90\%$ reduction of seizure in 0% (0/10) |
| Retrospective observational (4) [14] | $\geq 50\%$ reduction of seizure in 10% (1/10) |
| Retrospective observational (4) [56] | "Significant reduction" in seizure frequency and duration in 20% (1/5) |

Results are mixed, but larger studies support the use of a ketogenic diet for seizure control. LoE was sourced from the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653)

*CDD CDKL5* deficiency disorder, *LoE* level of evidence

**Table 5** Vagal nerve stimulator demonstrates improvements in three of four retrospective case series and caregiver surveys for CDD-related epilepsy

| Study type (LoE) | Outcome |
|---|---|
| Caregiver survey (4) [58] | Improvement in seizure activity in 69% (25/36)<br>Reduction in duration in 72% (18/25)<br>Reduction in frequency in 68% (17/25)<br>Reduction in intensity in 60% (15/25) |
| Retrospective observational (4) [15] | Improvement in seizure activity in 63% (10/16)<br>Reduction in seizure duration in 12% (2/16)<br>Reduction in seizure frequency in 43% (7/16)<br>Reduction in seizure intensity in 18% (3/16) |
| Caregiver survey (4) [33] | "Effective" for seizure control in 75% (9/12)<br>Fewer antiseizure medications in 17% (2/12) after 1 year<br>Fewer rescue medications in 17% (2/12) after 1 year<br>Improved quality of life in 75% (9/12) after 1 year |
| Retrospective observational (4) [14] | ≥ 50% reduction of seizure in 0% (0/3) |

VNS may be effective for seizure reduction in select refractory cases. LoE was sourced from the Oxford Centre for Evidence-Based Medicine (http://www.cebm.net/index.aspx?o=5653)

*CDD CDKL5* deficiency disorder, *LoE* level of evidence, *VNS* vagal nerve stimulator

> 50% reduction in at least four individuals, one of whom also had a VNS [15, 51, 55].

The use of deep brain stimulation or responsive neurostimulation for individuals with CDD has not been reported thus far. A preclinical study conducted in *Cdkl5*$^{+/-}$ mice found that chronic forniceal deep brain stimulation rescued hippocampal memory deficits, restored synaptic plasticity, and relieved feedforward inhibition, raising the possibility that deep brain stimulation could be used in the future to enhance the function of neural circuitry in individuals with CDD [62].

## 7 Investigational Drugs

### 7.1 Fenfluramine

Fenfluramine is a serotonergic agent originally developed as an appetite suppressant in combination with phentermine but was withdrawn from the market in 1997 because of complications related to valvular heart disease [63]. Since then, fenfluramine has reemerged as an effective ASM for its significant reduction of convulsive seizures in Dravet syndrome [64] as well as drop seizures in Lennox–Gastaut syndrome, as presented at the 2020 annual American Epilepsy Society meeting [65]. The FDA subsequently approved fenfluramine under a risk evaluation and mitigation strategy for Dravet syndrome in June 2020 and for Lennox–Gastaut syndrome in March 2022. In CDD, a phase II open-label trial investigated the benefits of fenfluramine for convulsive seizures, defined as tonic-clonic, tonic, atonic, clonic, or focal motor seizures lasting ≥ 3 s [66]. In six individuals with four or more convulsive seizures per month, a 14-week course of fenfluramine showed a 90% median reduction ($n = 5$) for tonic-clonic seizures, 55% median reduction ($n = 2$) for tonic seizures, and 71% reduction ($n = 1$) for myoclonic seizures [66]. Clinically meaningful improvement and improvement in quality of life were reported as secondary outcome measures [66]. Echocardiograms performed at 6 weeks did not reveal signs of valvular heart disease [66]. The safety profile related to this potential adverse event has also been monitored in trials in Dravet syndrome, showing only trace, also known as physiologic, mitral or aortic regurgitation [64, 67, 68]. The phase III trial of fenfluramine for Lennox–Gastaut syndrome, presented at the 2020 annual American Epilepsy Society meeting, also reported no cases of valvular heart disease [65]. Overall, the degree of seizure reduction in these data is notable, but the efficacy and safety profile of this treatment in CDD will be best established through the ongoing phase III double-blinded, placebo-controlled, clinical trial (NCT05064878).

### 7.2 Soticlestat

Soticlestat (TAK-935/OV-935), a cholesterol 24-hydroxylase inhibitor largely expressed in neurons, converts cholesterol to 24(S)-hydroxycholesterol for excretion [69]. 24(S)-hydroxycholesterol has various functions, including being a direct positive allosteric modulator of N-methyl-D-aspartate (NMDA) signaling [69–71]. Thus, soticlestat provides a novel mechanism of action as a potential ASM. A phase Ib/IIa randomized double-blinded, placebo-controlled trial followed by an open-label study showed a 36% reduction in bilateral motor seizure frequency in individuals with DEE at the end of the open-label phase [72]. Common adverse events included dysarthria, lethargy, upper respiratory

infection, fatigue, and headache; treatment-related emergent or serious adverse events included gait disturbance, lethargy, asthenia, and seizure clusters [72]. A subsequent phase II open-label study in individuals with CDD and 15q duplication syndrome, presented at the 2021 annual American Academy of Neurology meeting, showed a 14% decrease in median ($n = 12$) seizure frequency in CDD [73]. In total, 11 of 12 families and 8 of 12 clinicians reported improvement in the global impression of change scale, a secondary outcome measure [73]. No treatment-related serious adverse events occurred [73]. An open-label extension phase II trial to study long-term safety and tolerability (NCT03635073) is ongoing, and additional trials in other epileptic encephalopathies are also in recruitment (NCT04940624 and NCT04938427).

## 8 Disease-Modifying and Other Targeted Therapies in Development

Disease-modifying therapies for CDD are in development. A randomized placebo-controlled phase II trial of ataluren, a drug that promotes a premature stop codon read-through, failed to show improvement in seizure frequency or quality of life in 15 individuals with CDD or Dravet syndrome [74]. Protein replacement therapy and virus-mediated gene transfer have been investigated in animal models of CDD, with promising results [75, 76]. *CDKL5* gene delivery via an adenovirus vector demonstrated partial improvement in subsets of testing parameters representative of autistic behavior and motor coordination in *Cdkl5* knockout (KO) mice [75]. Systemic infusion of a TAT-CDKL5 fusion protein rescued various neuroanatomical and behavioral defects in *Cdkl5*-null mice, including breathing pattern and visual responses, and intracerebrocortical infusion of TAT-*CDKL5* restored hippocampal development, hippocampus-dependent memory, and breathing pattern [76]. In a conditional rescue mouse model, restoration of *Cdkl5* after the early stages of brain development ameliorated a majority of CDD-related loss-of-function behavioral impairments (including hyperactivity, anxiety-related phenotypes, autistic-like behaviors, motor impairments, and learning and memory deficits) and aberrant NMDA receptor signaling, suggesting the potential for a broad therapeutic window for disease reversal in CDD [77].

Other possible pharmacologic approaches for the treatment of CDD have been studied in mouse models. Sertraline, a selective serotonin reuptake inhibitor, has been studied in *Cdkl5* KO female mice, with promising effects, including normalization of locomotion, stereotypic and autistic-like features, and spatial memory [78]. Memantine, a noncompetitive NMDA receptor antagonist, significantly mitigated behavioral deficits in Dlx-cKO mice, a model with selective ablation of *CDKL5* expression in forebrain GABAergic neurons, and selectively ameliorated autistic-like features in a novel mouse CDD model bearing a known pathogenic nonsense variant, p.R59X [79]. Treatment with a combined glycogen synthase kinase 3-beta/histone deacetylase inhibitor restored synapse development, neuronal survival, and microglia overactivation, and improved the motor and cognitive abilities of *Cdkl5* KO mice [80]. Another study suggested that neuroinflammatory processes contribute to the pathogenesis of CDD and showed that treatment with luteolin, a natural anti-inflammatory flavonoid, recovered microglia alterations and neuronal survival and maturation in *Cdkl5* KO mice [81].

To date, CDD-related phenotypes in mice are mostly reproducible, including several cardinal elements of the human disease, such as learning and memory impairments, motor deficits, and autistic-like behaviors [77]. However, although animal models of CDD have shown evidence of hyperexcitability, spontaneous seizures have been exhibited only in aged female heterozygous *Cdkl5* mutant mice as epileptic spasms [82]. Additional research will thus be needed before considering a human trial phase for any of these compounds, although each sheds additional light on the underlying biology of the disorder.

## 9 Limitations and Future Direction

The majority of available literature related to epilepsy management in CDD are retrospective studies, surveys, case series, and case reports. These lack systematically collected quantifiable objective measurements and a pretreatment period to establish baseline seizure burden for comparison post-treatment. In addition, while it is important to select ASMs based on seizure types, observational studies in CDD have largely not been able to differentiate treatment responses by specific seizure types. This limitation poses a particular challenge in interpreting treatment data of ACTH and corticosteroids for their use in epileptic spasms and other seizure types. Thus, caution is needed when interpreting these data for clinical use.

As emphasized throughout the manuscript, seizure reduction is only a part of many factors that contribute to the overall quality of life in individuals with CDD. Yet, most clinical trials in epilepsy rely on reduction in seizure count as their primary outcome measure, and there is a need for other objective quantifiable measures that reflect other aspects of quality of life in individuals with CDD. The ongoing clinical trial readiness project for CDD, funded through the National Institute of Neurological Disorders and Stroke (NINDS, 1U01NS114312-01A1), as well as the observational study in CDD (CANDID) are important steps toward defining these outcome measures for CDD. The FDA approval for ganaxolone as a CDD-specific medication highlights the enthusiasm and hope in the *CDKL5*

community for better therapies. Additional clinical trials in small molecules, gene therapy, and other disease-modifying therapies will be expected in the coming years, which we anticipate will change the treatment approach to CDD.

## Declarations

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