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RESEARCH ARTICLE

International consensus on diagnosis and management of Dravet syndrome

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Abstract

Objective: This study was undertaken to gain consensus from experienced physicians and caregivers regarding optimal diagnosis and management of Dravet syndrome (DS), in the context of recently approved, DS-specific therapies and emerging disease-modifying treatments.

Methods: A core working group was convened consisting of six physicians with recognized expertise in DS and two representatives of the Dravet Syndrome Foundation. This core group summarized the current literature (focused on clinical presentation, comorbidities, maintenance and rescue therapies, and evolving disease-modifying therapies) and nominated the 31-member expert panel (ensuring international representation), which participated in two rounds of a Delphi process to gain consensus on diagnosis and management of DS.

Results: There was strong consensus that infants 2–15 months old, presenting with either a first prolonged hemiclonic seizure or first convulsive status epilepticus with fever or following vaccination, in the absence of another cause, should undergo genetic testing for DS. Panelists agreed on evolution of specific comorbidities with time, but less agreement was achieved on optimal management. There was also agreement on appropriate first- to third-line maintenance therapies, which included the newly approved agents. Whereas there was agreement for recommendation of disease-modifying therapies, if they are proven safe and efficacious for seizures and/or reduction of comorbidities, there was less consensus for when these should be started, with caregivers being more conservative than physicians.

Significance: This International DS Consensus, informed by both experienced global caregiver and physician voices, provides a strong overview of the impact of DS, therapeutic goals and optimal management strategies incorporating the recent therapeutic advances in DS, and evolving disease-modifying therapies.

KEYWORDS

cannabidiol, developmental and epileptic encephalopathy, disease-modifying treatment, fenfluramine, *SCN1A*, stiripentol

1 | INTRODUCTION

Dravet syndrome (DS) is an infantile onset developmental and epileptic encephalopathy associated with drug-resistant, lifelong seizures and comorbidities including intellectual disability, behavior concerns, sleep disorders, and gait problems. Nearly all cases are due to pathogenic variants in *SCN1A* that result in haploinsufficiency of $Na_v1.1$, the alpha-1 subunit of the sodium channel.[1]

Prior consensus papers from North America[2] and Europe[3] summarized treatment options; however, these preceded the recent approval of three DS-specific therapies, pharmaceutical-grade cannabidiol (Epidiolex, Epydiolex)[4] by the US Food and Drug Administration (FDA) in June 2018 and the European Medicines Agency (EMA) in September 2019, fenfluramine[5,6] by the FDA in June 2020 and the EMA in December 2020, and stiripentol,[7] which has been available in many European countries but was approved by the FDA in August 2018.

Furthermore, disease-modifying therapies (DMTs) are on the horizon. STK-001, an antisense oligonucleotide that restored $Na_v1.1$ to wild-type levels and decreased both seizures and mortality in Dravet mice,[8] is currently in human trials. Genetic therapies are also being pursued. ETX-101, an adenovirus vector containing an engineered transcription factor designed to upregulate *SCN1A* coupled with a highly conserved, human regulatory sequence to constrain expression to γ-aminobutyric acid (GABA)ergic inhibitory interneurons, led to significant seizure reduction and reduced risk of sudden death in Dravet mice[9,10] and will likely start human trials shortly.

The aims of our study were to gain international consensus from both physicians and caregivers with extensive expertise in DS regarding optimal diagnosis and management, in the context of newly approved therapies. We also aimed to determine the potential role for DMTs, if these are shown to be both safe and highly efficacious.

Key Points

- Dravet syndrome is an early onset, developmental and epileptic encephalopathy associated with drug-resistant seizures and multiple comorbidities
- Genetic studies are suggested in developmentally normal, 2–15-month-old children presenting with a single prolonged hemiclonic seizure or focal/generalized status epilepticus of unknown etiology in the context of vaccination or fever
- Valproic acid, clobazam, stiripentol, and fenfluramine may be considered as first- or second-line maintenance therapies for seizures due to DS
- Several disease-modifying therapies are in clinical development; provided these are safe and efficacious, there is consensus for recommending their use in persons with Dravet syndrome

2 | MATERIALS AND METHODS

The concept of this study was proposed by the Executive and Scientific Directors of the Dravet Syndrome Foundation (DSF; M.A.M. and V.H.) and discussed with E.C.W.

2.1 | Identification of the core working group

A core working group was convened, consisting of six physicians with recognized expertise in DS, four of whom were members of the DSF Medical Advisory Board (K.G.K., I.E.S., J.S., E.C.W.), and three of whom practiced outside of North America (R.N., I.E.S., J.W.), and two individuals representing the DSF (M.A.M., V.H.). This core working group reviewed the existing literature, created the initial Delphi survey, and nominated physicians and caregivers from around the world for the expert panel.

2.2 | Literature review

Five focus areas were identified: (1) clinical presentation (including seizure semiology, electroencephalography [EEG], magnetic resonance imaging [MRI], and genetic studies), (2) comorbidities (cognition, behavior, autism, gait, sleep, other medical concerns, sudden unexpected death in epilepsy [SUDEP] and mortality, vaccinations), (3) maintenance therapies (medications, diet, surgery, neuromodulation), (4) DMTs, and (5) rescue therapies, management of status epilepticus, and transition to adult care. Two physician members of the core working group summarized the literature in each area, through April 2021, and a collated, referenced literature review was sent to the entire core group for feedback. Following revisions, the final summary was provided to each expert panelist before completion of the surveys.

2.3 | Establishing the expert panel

Members of the core working group provided nominations for physicians who were clinically recognized for their expertise in the management of DS for the expert

panel. Nominees were divided into specific regions with quotas for each region as follows: Europe/UK ($n = 6$), North America ($n = 5$), South/Central America ($n = 2$), Asia ($n = 4$), Africa ($n = 1$), and Australia/New Zealand ($n = 2$). Core working group members anonymously ranked physician nominees from each region, and the top-ranked candidates were invited to join the expert panel. To enhance diversity, no more than one panelist from each center was included, and we ensured representation from different countries within each region. All physicians accepted the invitation to participate. Members of the core working group (excepting study facilitators E.C.W. and V.H.) were also included as members of the expert panel.

Caregiver expert panelists were selected by the DSF, through their connections with other international DS patient advocacy groups, and included three from Europe/UK, three from North America, two from Asia, and one each from South America, Africa, and Australia/New Zealand.

In the first Delphi round, each expert panelist was asked how long they had worked with/cared for persons with DS. Physicians were asked the number of persons with DS they had ever and were currently managing and whether they saw only children, only adults, or both. Caregivers were asked how many people with DS they were familiar with.

2.4 | Delphi questionnaires

A two-round Delphi process[11] was utilized. The first questionnaire was created by the study facilitators based on literature review and feedback from the core working group and was sent to the expert panel using a Survey Monkey link. Panelists were instructed to answer questions based on both the literature review and their own expertise and were given 4 weeks to complete each round with two reminders sent, as needed.

Caregivers and physicians received similar Delphi questionnaires; however, topics focusing on specific laboratory study results were sent to physicians only.

The first round was comprised of:

- Statements where the literature suggested consensus. Panelists rated their overall agreement ranging from 1 to 9, where 1 is strongly disagree and 9 is strongly agree, with an option of "no opinion." Free text comments were encouraged, particularly for any statements rated as 6 or lower.
- Open-ended questions. Panelists were asked to estimate the proportion of cases they were aware of that manifested specific features, and to provide free text answers to specific questions (criteria for defining seizure control, when medication should be changed, optimal first- and second-line therapies, experience with surgical therapies, neuromodulation, anticipated benefits of DMTs, transition to adult care).
- Rating of specific medications based on their efficacy for certain seizure types, tolerability, and durability of response.

The study facilitators collated results, evaluated areas where consensus was not achieved in Round 1, refined statements based on panelist comments (where appropriate), and included these in Round 2. Additionally, based on the open-ended questions from Round 1, they proposed several additional statements in Round 2.

Consensus was determined only for statements when more than half of the target group provided responses, defined as at least 11 physicians and at least five caregivers. Absent responses or "no opinion" were grouped and considered as "no response." Consensus was defined as Strong if 80% or more of panelists providing an opinion rated the statement as 7 or higher and as Moderate if 67% or more of panelists rated the statement as 7 or higher. Statements that did not reach this level of agreement were interpreted as "no consensus."

3 | RESULTS

All physicians ($n = 20$) and nine of 11 caregivers participated in both Delphi rounds. One caregiver participated in the first round only, and another did not participate in either. Ninety percent of physicians and 89% of caregivers had >10 years, and all had >5 years of experience with DS. The proportion of cases that panelists cared for is shown in Figure 1. Of physicians, 15 (75%) saw predominantly children, four (20%) saw both adults and children, and one (5%) saw only adults.

3.1 | Clinical presentation, seizures, and diagnostic testing

Table 1 summarizes where consensus was reached regarding clinical presentation of DS. Genetic studies should be performed in a developmentally normal, 2–15-month-old child presenting with a single prolonged (5–29 min) hemiclonic seizure or focal/generalized status epilepticus (≥30 min) of unknown etiology in the context of vaccination or fever (Strong). There was Moderate consensus for genetic testing with (1) a single prolonged generalized tonic–clonic seizure in a child aged 2–5 months associated with fever or vaccination; (2) a single, prolonged generalized convulsive seizure (5–29 min) in a child aged

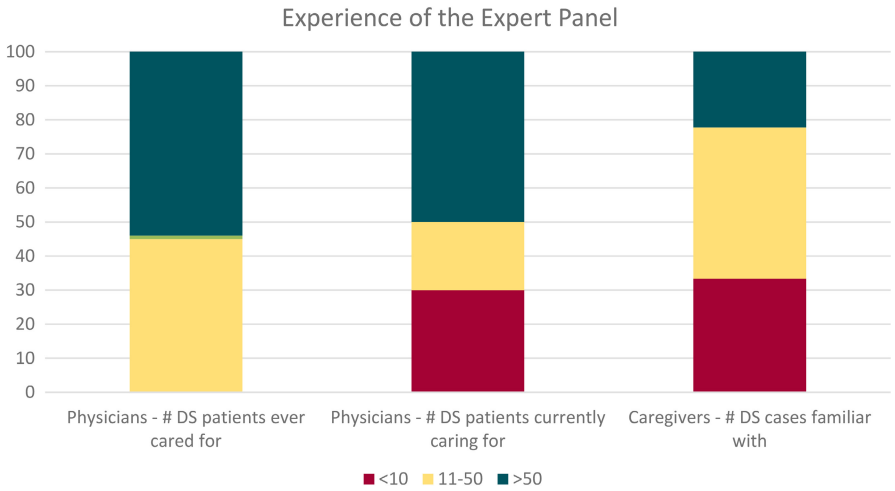

FIGURE 1 Expertise of the physician and caregiver panel. Shown are the percentage of physicians who have ever cared for or are currently caring for <10, 11–50, or >50 persons with Dravet syndrome (DS) and the percentage of caregivers who are familiar with <10, 11–50, or >50 persons with DS

TABLE 1 Clinical presentation: in a developmentally normal child, who presents with seizures of unknown cause (normal magnetic resonance imaging, normal laboratory studies, ± normal cerebrospinal fluid studies), genetic testing to exclude DS should be performed with the following seizure types

	Age 2–5 months			Age 6–15 months		
Seizure	**Without fever**	**With fever**	**After vaccination**	**Without fever**	**With fever**	**After vaccination**
Single seizure						
Prolonged (5–29 min) GTCS	63%[a]	74%[b]	74%[b]	63%[a]	58%[a]	68%[b]
Prolonged (5–29 min) hemiclonic seizure	68%[b]	84%[c]	95%[c]	68%[b]	84%[c]	89%[c]
Focal or generalized convulsive status epilepticus (≥30 min)	74%[b]	84%[c]	89%[c]	74%[b]	84%[c]	89%[c]
Recurrent seizures						
Recurrent brief (<5 min) convulsive seizures	63%[a]	58%[a]		58%[a]	58%[a]	
Recurrent brief (<5 min) hemiclonic seizures	68%[b]	74%[b]		79%[b]	79%[b]	
Recurrent prolonged focal or generalized convulsive seizures (5–29 min)	89%[c]	100%[c]		84%[c]	95%[c]	
Recurrent focal or generalized convulsive status epilepticus (≥30 min)	89%[c]	95%[c]		89%[c]	95%[c]	

Note: Based on 19 physician responses.

Abbreviations: DS, Dravet syndrome; GTCS, generalized tonic–clonic seizure.

[a]Responses indicate no consensus for genetic testing for DS.

[b]Responses indicate Moderate consensus for genetic testing for DS.

[c]Responses indicate Strong consensus for genetic testing for DS.

6–15 months following vaccination; or (3) a single episode of afebrile convulsive status epilepticus or a single, prolonged afebrile hemiclonic seizure in a child aged 2–15 months.

In children presenting with recurrent seizures of unknown etiology, genetic testing is indicated in those 2–15 months old with recurrent prolonged focal or generalized convulsive seizures with or without fever (including status epilepticus; Strong), in children 6–15 months old with recurrent brief hemiclonic seizures without fever (Strong), and in infants 2–15 months old with recurrent, brief, hemiclonic seizures with or without fever (Moderate).

Table 2 summarizes consensus regarding seizure types, evolution with time, and diagnostic studies. Myoclonic and focal impaired awareness seizures are seen in more than half of cases before age 5 years (Strong to Moderate). Although some seizures abate with time, brief generalized tonic–clonic seizures persist in most adults (Strong).

SCN1A pathogenic variants are present in >85% of cases (Strong). The initial MRI is normal, but a minority

TABLE 2 Consensus regarding seizure types and evolution with time and diagnostic testing

Other seizure types: frequency and age at presentation

Myoclonic seizures

- Seen in 50–90% of cases (**PHYSICIANS**: $n = 19$, 84%; ***caregivers***: $n = 7$, 71%).
- Typically begin between 1 and 3 years of age (**PHYSICIANS**: $n = 19$, 89%; ***caregivers***: $n = 6$, 67%), but all physicians and 4/5 caregivers who responded indicated they may be seen in the first year of life.

Absence seizures

- No consensus on whether these are seen in majority of cases or not (*physicians* or *caregivers*).
- Typically begin between 1 and 5 years of age (**PHYSICIANS**: $n = 19$, 89%; **CAREGIVERS**: $n = 5$, 80%), but 53% of physicians and 1/3 caregivers who responded indicated they could begin in the first year of life.

Focal impaired awareness seizures

- Seen in more than half of cases (***physicians***: $n = 19$, 74%; **CAREGIVERS**: $n = 5$, 100%).
- Typically, onset is between 1 and 5 years (**PHYSICIANS**: $n = 14$, 86%; caregivers[a]: $n = 4$, 75%), but 57% of physicians and 1/3 caregivers indicated they could begin in the first year of life.

Atonic seizures

- Seen in fewer than half of cases (**PHYSICIANS**: $n = 19$, 100%; caregivers[a]: $n = 2$, 100%).
- Typically, onset is between ages 1 and 5 years (**PHYSICIANS**: $n = 14$, 93%; caregivers[a]: $n = 1$, 100%), but 8% of physicians and 1/3 caregivers indicated they could begin in the first year of life.

Tonic seizures

- Seen in fewer than half of cases (***physicians***: $n = 19$, 79%); seen in more than half of cases (**CAREGIVERS**: $n = 6$, 83%).
- No consensus for typical age at onset (*physicians* or *caregivers*), and only 7% of physicians but 4/4 caregivers indicated they could begin in the first year of life.

Nonconvulsive (obtundation) status epilepticus

- Seen in 10%–49% of cases (**PHYSICIANS**: $n = 19$, 84%; caregivers[a], $n = 4$, 50%).
- Usually starts in the first decade of life (**PHYSICIANS**: $n = 14$, 93%; caregivers[a]: $n = 2$, 100%), but only 29% of physicians and 0/2 caregivers indicated this could begin in the first year of life.

Persistence of seizure types into adulthood

- Myoclonic seizures:
  a. Persist in fewer than half of cases into adulthood (**PHYSICIANS**: $n = 14$, 86%; *caregivers*: $n = 6$, 50%)
- Absence seizures:
  a. Persist in fewer than half of cases into adulthood (**PHYSICIANS**: $n = 14$, 86%; ***caregivers***: $n = 6$, 67%)
- Atonic seizures:
  a. Persist in fewer than half of cases into adulthood (**PHYSICIANS**: $n = 14$, 100%; **CAREGIVERS**: $n = 5$, 100%)
- Tonic seizures:
  a. Persist in fewer than half of cases into adulthood (**PHYSICIANS**: $n = 15$, 80%)
  b. Persist in more than half of cases into adulthood (***caregivers***: $n = 7$, 71%)
- Brief (<5 min) generalized tonic–clonic seizures:
  a. Persist in more than half of cases into adulthood (**PHYSICIANS**: $n = 15$, 93%; **CAREGIVERS**: $n = 7$, 86%)
- Focal impaired awareness seizures:
  a. No consensus (*physicians* or *caregivers*)
- Brief (<5 min) focal motor seizures:
  a. No consensus (*physicians*)
  b. Persist in fewer than half of cases into adulthood (***caregivers***: $n = 6$, 67%)
- Prolonged (5–29 min) convulsive seizures
  a. Persist in fewer than half of cases into adulthood (**PHYSICIANS**: $n = 14$, 86%; ***caregivers***: $n = 7$, 71%)
- Convulsive status epilepticus (≥30 min):
  a. Persists in fewer than half of cases into adulthood (**PHYSICIANS**: $n = 15$, 93%; **CAREGIVERS**: $n = 6$, 100%)
- Nonconvulsive status epilepticus:
  a. Persists in fewer than half of cases into adulthood (**PHYSICIANS**: $n = 14$, 100%; caregivers[a]: $n = 3$, 67%)

Genetic testing

- Provided the cost of an epilepsy gene panel is similar to *SCN1A* targeted testing, an epilepsy gene panel is the preferred genetic study for young children with suspected DS (**PHYSICIANS**: $n = 20$, 90%).
- *SCN1A* pathogenic variants are detected in >85% of DS patients (**PHYSICIANS**: $n = 19$, 95%).

(Continues)

TABLE 2 (Continued)

Neuroimaging

- Brain MRI is typically normal at diagnosis (**PHYSICIANS**: $n = 19$, 100%).
- With time, variable degrees of cortical atrophy may be seen on MRI; however, this may not be recognized, as serial MRI is typically not performed in persons with DS (**PHYSICIANS**: $n = 20$, 85%).
- Hippocampal sclerosis may develop over time in a minority of cases (**PHYSICIANS**: $n = 19$, 100%).

EEG

- With the exception of postictal slowing, the EEG background is typically normal prior to 12 months of age (**PHYSICIANS**: $n = 19$, 100%).
- In persons 5 years and older, background slowing is present in most cases (**PHYSICIANS**: $n = 19$, 89%).
- Interictal discharges are seen in fewer than half of cases before 12 months of age (**PHYSICIANS**: $n = 19$, 95%).
- Interictal discharges are seen in most cases by 5 years of age (**PHYSICIANS**: $n = 19$, 100%).
- Interictal discharges may be focal, multifocal, and/or generalized (**PHYSICIANS**: $n = 19$, 100%).
- Up to half of persons with DS show a photoparoxysmal response on EEG at some point over their disease course. This finding may be age dependent and abate with time (**PHYSICIANS**: $n = 20$, 80%).
- Recorded seizures are often "falsely generalized," meaning that changes may appear bilateral on EEG early in a seizure that is clinically focal, or may appear bilateral at onset and then become and remain asymmetric (**PHYSICIANS**: $n = 18$, 94%).
- Recorded seizures may be "unstable," meaning that the epileptiform discharge changes topographically, moving from one brain region to another during the same seizure (**PHYSICIANS**: $n = 17$, 88%).
- A minority of adolescents with DS may develop bifrontal spike-and-slow-wave with generalized polyspikes in sleep, which correlate with axial tonic seizures (***physicians***: $n = 18$, 67%).

Note: Bold and all-capital text indicates Strong consensus; bold and italic text indicates Moderate consensus; nonbold and italic text indicates no consensus.

Abbreviations: DS, Dravet syndrome; EEG, electroencephalography; MRI, magnetic resonance imaging.

[a]Consensus was not determined for statements where >50% of the group did not provide a response.

show variable degrees of cortical atrophy or hippocampal sclerosis with time (Strong). The EEG is often normal before 12 months of age but demonstrates background slowing and epileptiform discharges in most cases by age 5 years (Strong). "Falsely generalized" and "unstable" recorded seizures are unique ictal patterns (Strong).

3.2 | Comorbidities, vaccination recommendations, and transition to adult care

Development is considered normal before 18 months, although subtle delays may be appreciated prior to that time (physicians: Strong; caregivers: Moderate), but intellectual disability is usually present by 3 years of age and becomes more apparent with time (physicians and caregivers: Strong; Table 3).

Attention problems are present in most children by school age (physicians and caregivers: Strong) and psychostimulants are considered both safe (physicians: Strong) and effective (physicians: Moderate). Internalizing problems such as depression and anxiety are more prevalent with increasing age and present in most adults (physicians and caregivers: Strong). There was disagreement between physicians and caregivers regarding the prevalence of autistic features; caregivers reported such symptoms in a majority of children (Strong), whereas physicians indicated that most lacked autistic features (Moderate).

Gait problems (ataxia or crouch gait) are seen in half of school-aged children and most teens and young adults (Strong) and may resemble Parkinsonian features in adulthood. There was limited consensus on optimal management, with only modest benefits reported for physiotherapy or carbidopa–levodopa.

Sleep problems occur in most persons (Strong); however, optimal management is less clear. Most panelists had experience using melatonin, a minority with clonidine, and very small numbers with other agents. Both melatonin and clonidine were reported to be modestly effective by most respondents.

Families of persons with DS must be counseled about the significant risk of SUDEP at the time of diagnosis (Strong). Caregivers reported higher patient use of seizure-monitoring devices than physicians. The effectiveness of such devices to detect seizures was rated as 7 (interquartile range [IQR] = 6–9) and 6 (IQR = 5–7) by caregivers and physicians, respectively, on a scale of 1–9, where 1 is ineffective and 9 is highly effective.

Persons with DS should receive all routine vaccines (physicians: Strong; caregivers: Moderate), an annual influenza vaccine (physicians and caregivers: Moderate), and the COVID-19 vaccination (physicians: Strong; caregivers: Moderate). Antipyretics are recommended to reduce risk of vaccine-associated fever (Strong), but there was no consensus among physicians on the use of additional seizure medications around vaccination, and moderate consensus among caregivers against this practice.

Regarding transition of care to an adult provider, both physicians and caregivers identified the importance of a knowledgeable adult provider, clear communication between pediatric and adult providers around the time of transition, family education with a focus on progressive transition, and a comprehensive transition document prepared by the pediatric provider (Strong). Barriers to successful transition included lack of adult providers with expertise in DS (Strong), lack of appropriate structure in the adult setting to provide holistic care (Strong), limited involvement of parents or caregivers in clinical decisions on the adult side (caregivers: Moderate; physicians: no consensus), and reluctance of families to transition as they are bonded to the pediatric team (physicians: Moderate; caregivers: no consensus).

3.3 | Seizure control, maintenance therapies, disease-modifying treatment, and management of seizure emergencies

3.3.1 | Goals for seizure control

Important goals of seizure control are to maximize quality of life for the patient and their family (Strong) and to limit side effects of medication (Strong; Table 4). Control of convulsive seizures should be prioritized over nonconvulsive seizures, given their greater impact on quality of life and higher association with SUDEP (physicians: Strong; caregivers: no consensus).

There was general agreement between physicians and caregivers regarding when a new therapy should be considered. A medication deemed to be less effective or to have led to greater side effects should be tapered if a prolonged period of seizure freedom is achieved (physicians: Strong; caregivers: no consensus).

3.3.2 | Maintenance therapies

Valproic acid is an appropriate first-line drug, and clobazam can be considered as either the initial or second antiseizure medication (ASM; Strong). Further consensus for other first-line therapies included fenfluramine (physicians: Strong; caregivers: Moderate), and stiripentol (physicians: Moderate; caregivers: Strong). Pharmaceutical-grade cannabidiol was supported either as first- or second-line treatment (caregivers: Strong; physicians: no consensus). There was modest consensus among caregivers, but no consensus among physicians to support topiramate as first-, second-, or third-line therapy. Lamotrigine is contraindicated in children with DS (Moderate). Figure 2 summarizes consensus regarding therapy.

Based on physician ratings (Table S1), valproic acid, clobazam, stiripentol, and fenfluramine were perceived as most efficacious for focal or generalized convulsive seizures. For absence seizures, both valproic acid and ethosuximide rated highly, and for myoclonic seizures, valproate was rated most efficacious. Physicians and caregivers were also asked to rate tolerability of ASMs, on a scale of 1–9, where 1 is poorly tolerable and 9 is highly tolerable (Table S2). Therapies with good tolerability (rated as 7 or higher) by both physicians and caregivers included valproic acid and fenfluramine. Therapies most commonly associated with improved alertness and/or behavior included ketogenic diet (73% improved), fenfluramine (54% improved), and pharmaceutical-grade cannabidiol (50% improved; Table S3). Conversely, those most correlated with worsening alertness and/or behavior included clobazam (78% worsened), topiramate (68% worsened), clonazepam (61% worsened), and levetiracetam (52% worsened).

Dietary therapy should be considered after failure of three or four ASMs (Strong; Table 4). The classical ketogenic diet was recommended for children 6 years and younger (Moderate) and the modified Atkins diet for teens and adults (Strong).

Interestingly, there was moderate consensus among physicians and caregivers that specific therapies stood out from others due to higher efficacy and/or better tolerability, and among those who responded affirmatively to this statement, fenfluramine was the only therapy with consensus (Strong).

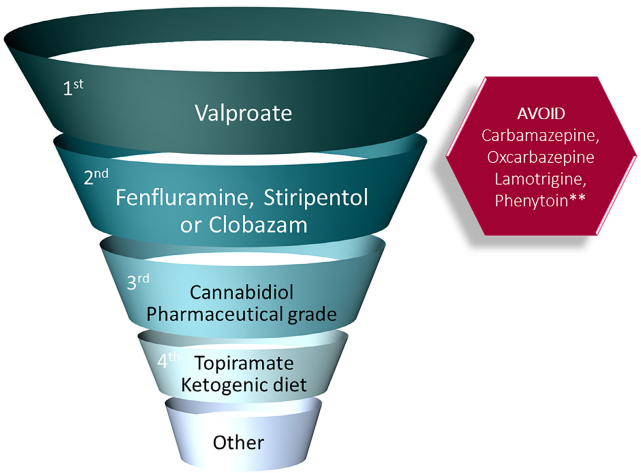

FIGURE 2 Therapeutic algorithm for maintenance therapies for management of seizures in Dravet syndrome. There was consensus for use of valproic acid as first-line therapy, and for use of clobazam, fenfluramine, or stiripentol as first- or second-line therapy. There was also consensus for contraindicated medications. **Phenytoin may be helpful for status epilepticus. "Other" includes vagal nerve stimulation, levetiracetam, zonisamide, bromides, clonazepam, and ethosuximide (for absences)

TABLE 3 Comorbidities, development, vaccination recommendations, and transition

Development

- Development is usually normal prior to 18 months of age, although subtle delays may be appreciated prior to that time in a minority of cases (**PHYSICIANS**: $n = 20$, 90%; ***caregivers***: $n = 10$, 70%).
- Subtle delays are typically evident between 18 and 36 months (**PHYSICIANS**: $n = 19$, 100%; ***caregivers***: $n = 9$, 78%).
- Intellectual disability (developmental quotient < 70) is present in most children aged 3 year and older (**PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 89%).
- Degree of intellectual disability worsens with time, with most young adults having moderate to severe intellectual disability (**PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 89%).
- Most children exhibit stagnation (lack of or slower progression) as opposed to true regression (loss of skills; **PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 89%).
- Encephalopathy and regression can occur following a bout of prolonged febrile status epilepticus in a minority of cases (**PHYSICIANS**: $n = 19$, 100%; ***caregivers***: $n = 9$, 78%).
- Social skills are better preserved than communication skills (**PHYSICIANS**: $n = 18$, 83%; *caregivers*: $n = 9$, 44%).
- The following factors are correlated with poor developmental outcome:
  a. Younger age at onset of DS (**PHYSICIANS**: $n = 18$, 89%; ***caregivers***: $n = 9$, 78%)
  b. Greater number of convulsive status epilepticus (>30 min) episodes (**PHYSICIANS**: $n = 19$, 95%; ***caregivers***: $n = 9$, 78%)
  c. Greater duration of longest convulsive status epilepticus event (**PHYSICIANS**: $n = 17$, 82%; ***caregivers***: $n = 9$, 78%)
  d. Longer use of contraindicated medications (i.e., sodium channel blockers including lamotrigine) in early life (**PHYSICIANS**: $n = 18$, 83%; **CAREGIVERS**: $n = 8$, 100%)
  e. Delay in use of optimal therapies (**PHYSICIANS**: $n = 18$, 83%; ***caregivers***: $n = 9$, 78%)
  f. Appearance of absence and/or myoclonic seizures in the first year of life (**PHYSICIANS**: $n = 16$, 94%; **CAREGIVERS**: $n = 7$, 86%)
  g. Appearance of tonic seizures (*physicians*: $n = 14$, 57%; caregivers[a]: $n = 4$, 75%)
  h. Higher frequency of interictal discharges on EEG if the first year of life (**PHYSICIANS**: $n = 14$, 82%; caregivers[a]: $n = 2$, 100%)
  i. Early motor delay (***physicians***: $n = 19$, 74%; *caregivers*: $n = 9$, 56%)
  j. Greater number or longer episodes of nonconvulsive status epilepticus (*physicians*: $n = 17$, 59%; ***caregivers***: $n = 8$, 75%)
  k. Specific types of *SCN1A* variants (*physicians*: $n = 18$, 28%; *caregivers*: $n = 7$, 57%)

Attention problems, autism, and behavior problems

- Attention problems are present in most school-aged children and teens with DS (**PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 100%).
- Stimulant medications are safe to use in persons with DS with significant attention problems (**PHYSICIANS**: $n = 18$, 94%; caregivers[a]: $n = 2$, 100%).
- Stimulant medications are effective in persons with DS with significant attention problems (***physicians***: $n = 17$, 76%; caregivers[a]: $n = 3$, 67%).
- Internalizing behaviors (depression, anxiety) are seen in a minority of preschool children but become more common with age and are present in more than half of adults (**PHYSICIANS**: $n = 18$, 83%; **CAREGIVERS**: $n = 8$, 100%).
- Externalizing behaviors (aggression, impulsivity) are seen in more than half of persons at the following ages:
  a. Preschool children (*physicians*: $n = 18$, 56%; **CAREGIVERS**: $n = 7$, 86%)
  b. School-aged children (***physicians***: $n = 18$, 67%; **CAREGIVERS:** $n = 7$, 86%)
  c. Teens (*physicians*: $n = 18$, 61%; **CAREGIVERS**: $n = 7$, 86%)
  d. Adults (*physicians*: $n = 13$, 46%; *caregivers*: $n = 7$, 43%)
- Prevalence of autistic features in children with DS:
  a. Preschool children: ***physicians***: $n = 18$, 72% stated prevalence of autistic features was <50%; **CAREGIVERS**: $n = 9$, 89% stated prevalence of autistic features was >50%.
  b. School-aged children: ***physicians***: $n = 19$, 68% stated prevalence of autistic features was <50%; **CAREGIVERS**, $n = 8$, 100% said prevalence of autistic features was >50%.
- Children with DS are at risk of autism spectrum disorder and concerns may be more apparent to parents/caregivers than neurology providers. Providers should query families for these concerns at regular follow-up visits (**PHYSICIANS**: $n = 19$, 84%; *caregivers*: $n = 8$, 60%).
- Less than half of preschool and school-aged children with DS have undergone a formal evaluation for autism (**PHYSICIANS**: $n = 18$, 83%; **CAREGIVERS**: $n = 8$, 100%).
- Current resources limit the number of at-risk children who undergo formal evaluation for autism, leading to probable underdiagnosis of autism in DS (**PHYSICIANS**: $n = 19$, 89%; ***caregivers***: $n = 10$, 70%).

TABLE 3 (Continued)

Gait problems and parkinsonian features

- Gait abnormalities including ataxia or crouch gait are noted in approximately half of school-aged (age 6–11 years) children with DS (**PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 89%).
- Gait abnormalities are seen in the majority of teens and young adults with DS (**PHYSICIANS**: $n = 18$, 100%; **CAREGIVERS**: $n = 9$, 100%).
- Parkinsonian features including bradykinesia, rigidity, parkinsonian gait (stooped, stiff, unsteady), and postural instability are seen in a majority of adults with DS; however, resting tremor is typically absent (**PHYSICIANS**: $n = 13$, 92%; **CAREGIVERS**: $n = 7$, 86%).
- Therapies prescribed for gait disorders:
  a. Physiotherapy and/or occupational therapy prescribed by 12/18 physicians and used by 6/8 caregivers. Median benefit reported by physicians was 5 and by caregivers was 6, on a scale of 1–9, where 1 is no benefit and 9 is marked benefit.
  b. Sinemet (physicians: only 6 had ever tried Sinemet and only 4 treated more than 5 patients. Of physicians who had tried Sinemet, median reported benefit was 5 on a scale of 1–9).

Speech

- Most/all children with DS should be routinely referred for speech assessment and therapy (**PHYSICIANS**: $n = 19$, 79%; **CAREGIVERS**: $n = 8$, 88%).
- Speech therapy is at least moderately beneficial for teens and adults with DS (*physicians*: $n = 15$, median score of 6 on a scale of 1–9; *caregivers*: $n = 9$, median score of 7 on a scale of 1–9).

Sleep problems

- Sleep problems are seen in a majority of persons with DS and can include increased nocturnal wakening, snoring, insomnia, and/or excessive daytime somnolence (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 10$, 90%).
- Questions regarding sleep should be routinely asked as part of continuing care of a person with DS (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 8$, 100%).
- A formal sleep study should be considered if a clinical history of a possible sleep disorder is obtained (**PHYSICIANS**: $n = 18$, 89%; ***caregivers***: $n = 8$, 75%).
- Attention to sleep hygiene is important in managing sleep problems associated with DS (**PHYSICIANS**: $n = 19$, 100%; *caregivers*: $n = 10$, 60%).
- Melatonin may be considered for persons with difficulty with initiating and maintaining sleep, but there are limited data on its efficacy (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 6$, 100%).
- Benefits of melatonin for sleep:
  a. 18 physicians had experience using melatonin, median efficacy = 6.5 of 9 on a scale of 1–9, where 1 is no benefit and 9 is highly effective.
  b. 6 caregivers had experience with melatonin, median efficacy = 6.5 of 9.
- Benefits of clonidine for sleep:
  a. 7 physicians had experience using clonidine, median efficacy = 7 of 9.
  b. 3 caregivers had experience using clonidine, median efficacy = 6 of 9.

Autonomic dysfunction

- Routine cardiac testing is not required for persons with DS (***physicians***: $n = 19$, 79%).
- There is no consistent therapy that is effective for dysautonomia (**PHYSICIANS**: $n = 11$, 82%).

SUDEP

- Persons with DS have a significant risk of SUDEP. Families must be made aware of this potential risk at diagnosis (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 9$, 100%).
- Risk of SUDEP will be at least mildly to moderately reduced due to recently approved seizure medications that have shown improved efficacy for DS (**PHYSICIANS**: $n = 16$, 88%; *caregivers*: $n = 6$, 50%)
- Use of monitoring devices for seizures:
  a. 68% of physicians did not routinely recommend the use of seizure monitoring devices for their patients with DS, but 74% would support a family's request for such a device.
  b. 31% of physicians reported that >50% of their patients used a seizure monitoring device.
  c. 67% of caregivers reported that >50% of persons with DS used a seizure monitoring device.
  d. Effectiveness of monitoring devices for seizure detection was rated by physicians ($n = 15$) as 6 (IQR = 5–7) and by caregivers ($n = 8$) as 7 (IQR = 6–9) on a scale of 1–9, where 1 is ineffective and 9 is highly effective.
- There was no consensus among physicians or caregivers that any particular monitoring device was more efficacious than another.

(Continues)

TABLE 3 (Continued)

Vaccinations
• Persons with DS should receive all routine vaccinations (**PHYSICIANS**: $n = 19$, 84%; ***caregivers***: $n = 9$, 78%).
• Persons with DS should receive an annual influenza vaccination (***physicians***: $n = 19$, 79%; ***caregivers***: $n = 9$, 78%).
• Routine use of antipyretic medication around vaccinations should be considered to reduce likelihood of seizures (**PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 89%).
• Routine use of additional antiseizure medication (such as benzodiazepines) around vaccinations should be considered to reduce the likelihood of seizures (*physicians*: $n = 19$, 53%; ***caregivers***: $n = 9$, 67% that this should NOT be done).
• Persons with DS who are eligible should receive the COVID-19 vaccination (**PHYSICIANS**: $n = 19$, 95%; ***caregivers***: $n = 9$, 78%).
Transition of care to adult neurology
• The following factors are key to successful transition to adult care for persons with DS:
a. Identifying a competent adult provider who understands DS (**PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 100%)
b. Clear communication between the pediatric and adult neurology providers around the time of transition (**PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 100%)
c. Education of the family with a focus on progressive transition that occurs over a prolonged period, rather than a single transfer of care (**PHYSICIANS**: $n = 19$, 89%; **CAREGIVERS**: $n = 8$, 100%)
d. Creation of a detailed transition document by the pediatric provider that summarizes the subject's medical course, comorbidities, and social supports, which is given to the adult provider (**PHYSICIANS**: $n = 19$, 95%; **CAREGIVERS**: $n = 9$, 100%)
• The following factors are significant barriers in successful transition to adult care for persons with DS:
a. Lack of adult providers with expertise in DS (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 9$, 100%)
b. Reluctance of families to transition as they are very bonded to their pediatric team (***physicians***: $n = 19$, 79%; *caregivers*: $n = 8$, 63%)
c. Lack of appropriate infrastructure in the adult setting to provide holistic care to a young adult with DS (**PHYSICIANS**: $n = 18$, 89%; **CAREGIVERS**: $n = 9$, 100%)
d. Limited involvement and/or inclusion of parents/caregivers in care decisions once transition to an adult provider has occurred (*physicians*: $n = 18$, 56%; ***caregivers***: $n = 7$, 71%)

Note: Bold and all-capital text indicates Strong consensus; bold and italic text indicates Moderate consensus; nonbold and italic text indicates no consensus.

Abbreviations: DS, Dravet syndrome; EEG, electroencephalogram; IQR, interquartile range; SUDEP, sudden unexpected death in epilepsy.

[a]Consensus was not determined for statements where >50% of the group did not provide a response.

Regarding artisanal marijuana, there was strong consensus from physicians, but no consensus from caregivers against the recommendation of nonpharmaceutical grade cannabidiol. Only a minority of respondents indicated they had experience with the use of low-dose tetrahydrocannabinol, with none reporting efficacy.

Although vagus nerve stimulation was considered a therapeutic option, there was Strong consensus that valproic acid, clobazam, stiripentol, and ketogenic diet, and Moderate consensus that fenfluramine, cannabidiol, and topiramate should be trialed prior to such therapy. Vagus nerve stimulation typically results in a <50% reduction in seizures (Strong) and use of the magnet has a low to modest impact on stopping seizures. Corpus callosotomy has no therapeutic role in DS (Moderate), and temporal lobectomy should not be considered (Strong).

Figure S1 documents the proportion of physicians who had personal experience using the various therapies for DS.

3.3.3 | Disease-modifying therapies

Assuming DMTs are safe, there was universal consensus among physicians and caregivers for recommendation of a DMT that results in greater seizure reduction than the current best therapy and reduces cognitive and other comorbidities. In such cases, there was consensus from physicians (Moderate), but not caregivers, that this should be started as early as possible.

If a DMT resulted in greater seizure reduction than the current best therapy, but had no impact on comorbidities, there was still consensus for recommendation (physicians: Strong**;** caregivers: Moderate), but no consensus for first-line use.

Conversely, if a DMT reduced cognitive and other comorbidities, but had no greater impact on seizure control than the current best therapy, there was still consensus to recommend this therapy (physicians: Strong; caregivers: Moderate), and consensus from only physicians to start as soon as possible (Moderate).

There was consensus that neither current seizure frequency nor degree of intellectual disability in a preschool or early school-aged child should impact the decision to offer DMTs. Additionally, if DMTs were proven efficacious and safe in clinical trials in younger patients, there was consensus from physicians (Moderate), but not caregivers, to consider their use in persons too old to qualify for the original clinical trial.

3.3.4 | Management of seizure emergencies

All persons with DS need a home rescue medication (Strong). For prolonged convulsive seizures that persist despite benzodiazepines, either intravenous valproate or levetiracetam should be the next therapeutic choices (Strong). Intravenous phenytoin or fosphenytoin could be considered after these agents if the seizure persists (Strong).

4 | DISCUSSION

The recommendations in this paper reflect those of the first International DS Consensus, which included both expert physicians and caregivers, from all continents. Our methodology utilized the Delphi methodology, a rigorous process to gather consensus regarding a disease.[11]

Over the past 10 years, DS has been diagnosed at younger ages, due to improved awareness by child neurologists and increased access to genetic testing, which is becoming part of routine clinical care in many regions.[12,13] Expedient diagnosis is critical to avoid contraindicated therapies that may exacerbate seizures and negatively impact development,[14] and importantly, to allow timely access to DMTs, if these are shown to be efficacious and safe in clinical trials. *SCN1A* variants can present with a range of epilepsy phenotypes, and several prediction models combining both clinical and genetic information have been developed that allow more confident early diagnosis of DS.[1,15] There was consensus from our expert panel regarding clinical presentations that should mandate genetic testing for DS, including infants 2–15 months old with either a first prolonged hemiclonic seizure or convulsive status epilepticus of unknown cause, with fever or following vaccination. Although we found strong consensus for where a diagnosis of DS should be considered, this does not preclude testing in other settings, as DS can present up to 19 months of age, with afebrile brief seizures and in the setting of developmental delay.[16]

Although there was strong consensus that specific comorbidities evolve with time, including intellectual

TABLE 4 Seizure control endpoints, maintenance therapies, and management of status epilepticus

Goals for seizure control

- In DS, it is appropriate to accept infrequent, brief convulsive seizures with the main goal focused on avoiding prolonged convulsive seizures and status epilepticus (***physicians***: $n = 19$, 79%; *caregivers*: $n = 9$, 56%).
- Convulsive seizures have a greater impact on quality of life and SUDEP, and thus should be prioritized above nonconvulsive seizures (**PHYSICIANS**: $n = 19$, 84%; *caregivers*: $n = 9$, 56%).
- One of the goals of seizure control should be limitation of side effects from ASMs (**PHYSICIANS**: $n = 19$, 89%; **CAREGIVERS**: $n = 9$, 100%).
- One of the goals of seizure control should be maximizing quality of life for the patient and their family (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 9$, 89%). The definition of seizure control varies with age (*physicians*: $n = 19$, 58%; ***caregivers***: $n = 9$, 78% state it is NOT dependent on age).

Factors that should prompt consideration of a new therapy

- Prolonged seizures or status epilepticus should lead to a review of current maintenance therapies. A new maintenance therapy could be added, but the potential for benefit and risk of adverse effects must be considered. Addition of a therapy with higher documented efficacy may be reasonable; however, adding a therapy with limited efficacy, in someone who has already trialed the more effective therapies, may not be indicated (***physicians***: $n = 19$, 74%; ***caregivers***: $n = 8$, 75%).
- Prolonged seizures or status epilepticus should lead to review of the home rescue therapy and seizure action plan (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 9$, 89%).
- Addition of a new therapy should be considered with frequent convulsive seizures (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 9$, 89%).
- Addition of a new therapy should be considered with frequent nonconvulsive seizures (**PHYSICIANS**: $n = 19$, 89%; ***caregivers***: $n = 9$, 78%).
- Addition of a new therapy should be considered with emergence of a new seizure type (***physicians***: $n = 19$, 68%; ***caregivers***: $n = 9$, 78%).
- A recently approved, new effective therapy for DS should be considered for persons with suboptimal seizure control (**PHYSICIANS**: $n = 19$, 95%; ***caregivers***: $n = 9$, 78%).

Factors that should prompt consideration of tapering off medication, other than intolerable side effects

- A therapy that does not result in improved seizure control despite achieving maximum tolerated dose should be strongly considered for tapering (**PHYSICIANS**: $n = 19$, 100%; *caregivers*: $n = 9$, 56%[a]).
- When a newer therapy has been added with improved seizure control, tapering off a less effective one should be considered (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 8$, 88%).
- In a person with DS who is on several antiseizure therapies and who has achieved a prolonged period of seizure control, it is appropriate to consider tapering off one of the therapies deemed to be either least effective or associated with more significant side effects (**PHYSICIANS**: $n = 19$, 100%; *caregivers*: $n = 9$, 56%).

(Continues)

TABLE 4 (Continued)

Maintenance ASMs

- What is the maximal number of ASMs that are reasonable to use together in a person with DS? Physicians: median = 3, IQR = 3–4; caregivers: median 3, IQR = 3–4.
- How many of your current patients are presently treated with the following number of ASMs (physicians only)?
  a. One ASM only: 8%
  b. Combination of 2 ASMs: 22%
  c. Combination of 3 ASMs: 48%
  d. Combination of 4 ASMs: 21%
  e. Combination of >4 ASMs: 7%
- What is the role of each of the following medications in persons with DS?
  a. Valproic acid
     - Should be used 1st line (**PHYSICIANS**: $n = 18$, 83%; **CAREGIVERS**: $n = 9$, 100%)
  b. Clobazam:
     - Should be used 1st or 2nd line (**PHYSICIANS**: $n = 18$, 83%; **CAREGIVERS**: $n = 9$, 89%)
  c. Fenfluramine
     - Should be used 1st or 2nd line (**PHYSICIANS**: $n = 19$, 84%; ***caregivers***: $n = 8$, 75%)
  d. Stiripentol
     - Should be used 1st or 2nd line (***physicians***: $n = 17$, 71%; **CAREGIVERS**: $n = 9$, 100%)
  e. Cannabidiol (pharmaceutical grade)
     - Should be used 1st or 2nd line (*physicians*: $n = 16$, 31%; **CAREGIVERS**: $n = 7$, 86%)
     - Should be used 1st, 2nd, or 3rd line (**PHYSICIANS**: $n = 16$, 81%)
  f. Topiramate
     - Should be used 1st, 2nd, or 3rd line (*physicians*: $n = 14$, 64%; ***caregivers***: $n = 8$, 75%)
- One or two of the currently available medications stand out from the other therapies due to better efficacy and/or improved tolerability (***physicians***: $n = 19$, 74%; ***caregivers***: $n = 8$, 75%).
  a. Of respondents who responded positively to this question, there was consensus for fenfluramine (**PHYSICIANS**: $n = 14$, 93%; **CAREGIVERS**: $n = 6$, 83%). However, no other medications received even moderate consensus.

Lamotrigine

- Lamotrigine should be considered contraindicated in children with DS (***physicians***: $n = 19$, 79%).
- Lamotrigine may have a very limited role in adults with refractory seizures due to DS, but should not be used until all appropriate 1st, 2nd, and 3rd line agents have been trialed. If started, careful observation is needed to ensure it is not exacerbating seizures (**PHYSICIANS**: $n = 19$, 100%).
- In an adult with DS on lamotrigine with good seizure control, tapering off lamotrigine may rarely lead to an exacerbation of seizures (**PHYSICIANS**: $n = 13$, 92%).

Non-pharmaceutical grade medical marijuana

- Non-pharmaceutical grade CBD is not recommended for treatment of DS (**PHYSICIANS**: $n = 16$, 81%; *caregivers*: $n = 8$, 62.5%).
- Only 16% of physicians and 37% of caregivers indicated they had experience using low-dose THC, but all stated they did not see improved benefit with THC.

Drug–drug interactions

- The dose of clobazam should be reduced when cannabidiol is added (if the patient is not already on stiripentol; *physicians*: $n = 15$, 60%).
- The dose of clobazam should be reduced when stiripentol is added (if the patient is not already on cannabidiol; ***physicians***: $n = 17$, 76%).
- The dose of valproic acid should be reduced when stiripentol is added (*physicians*: $n = 17$, 41%).
- When using stiripentol, both clobazam and valproic acid are recommended as cotherapies (**PHYSICIANS**: $n = 17$, 82%).

Fenfluramine

- How much of a concern is cardiac valvulopathy or pulmonary hypertension with fenfluramine (scored from 1–9, where 1 = no concern and 9 = extreme concern)? Physicians: median score = 3/9, IQR = 2–5; caregivers: median score = 3/9, IQR = 2–7.
- Serotonin syndrome:
  a. Fenfluramine could be used with caution in combination with a serotonergic agent (physicians[b]: $n = 7$, 71%). However, only 2 physicians had combined fenfluramine with a serotonergic agent; neither had noted symptoms of serotonin syndrome.

TABLE 4 (Continued)

Medications that impact appetite
- Topiramate was identified by 63% of physicians and 50% of caregivers as a medication that most impacts appetite.
- Stiripentol was identified by 58% of physicians and 67% of caregivers as a medication that most impacts appetite.
- Fenfluramine was identified by 47% of physicians and 50% of caregivers as a medication that most impacts appetite.
- Pharmaceutical-grade CBD was identified by 37% of physicians and 17% of caregivers as a medication that most impacts appetite.
- Valproic acid was identified by 21% of physicians and 33% of caregivers as a medication that most impacts appetite.

Bloodwork monitoring while on ASMs

Valproic acid
- Patients on valproic acid do not need routine drug levels drawn. However, valproic acid levels should be strongly considered in the presence of poor seizure control or with possible dose-dependent side effects (***physicians***: $n = 19$, 74%).
- CBC and liver enzymes should be routinely monitored periodically in all patients on valproic acid (***physicians***: $n = 19$, 74%).

Cannabidiol
- Liver enzymes ± CBC should be routinely monitored in all patients on cannabidiol (***physicians***: $n = 19$, 68%).

Stiripentol
- Liver enzymes and CBC should be routinely monitored in all patients (*physicians*: $n = 19$, 53%).

Dietary therapy
- Dietary therapy should not be used first line before any ASMs are tried (***physicians***: $n = 19$, 79%; *caregivers*: $n = 8$, 38%).
- Dietary therapy should be considered after failure of 1–2 ASMs (*physicians*: $n = 19$, 42%; *caregivers*: $n = 9$, 56%).
- Dietary therapy should be considered after failure of 3–4 ASMs (**PHYSICIANS**: $n = 19$, 84%; **CAREGIVERS**: $n = 7$, 86%).
- In infants aged <2 years, the classical ketogenic diet is the recommended option (***physicians***: $n = 15$, 73%).
- In children 2–6 years, the classical ketogenic diet is the recommended option (***physicians***: $n = 16$, 75%).
- In school-aged children, the classical ketogenic diet (*physicians*: $n = 16$, 56%) or modified Atkins diet are the recommended options (*physicians*: $n = 16$, 56%).
- In adolescents, the modified Atkins diet is the recommended option (**PHYSICIANS**: $n = 15$, 87%).
- In adults, the modified Atkins diet is the recommended option (physicians[b]: $n = 9$, 89%).

Vagus nerve stimulation and epilepsy surgery
- For families willing to consider vagus nerve stimulation and where resources are available to place that device, the following therapies should be tried prior to placing that device:
  a. Valproate (**PHYSICIANS**: $n = 19$, 100%)
  b. Clobazam (**PHYSICIANS**: $n = 19$, 100%)
  c. Fenfluramine (***physicians***: $n = 13$, 77%)
  d. Stiripentol (**PHYSICIANS**: $n = 13$, 92%)
  e. Topiramate (***physicians***: $n = 13$, 77%)
  f. Cannabidiol, pharmaceutical grade (***physicians***: $n = 13$, 77%)
  g. Ketogenic diet, if feasible for the family (**PHYSICIANS**: $n = 19$, 84%)
- Vagus nerve stimulation in persons with DS usually leads to a <50% reduction in seizure frequency (**PHYSICIANS**: $n = 12$, 100%; **CAREGIVERS**: $n = 5$, 100%).
- How beneficial is the magnet at stopping seizures in persons with DS (scored from 1–9, where 1 is not effective and 9 is highly effective)? Physicians: median score = 3.5; caregivers: median score = 6.

Other epilepsy surgical procedures
- There is no role for corpus callosotomy in DS (***physicians***: $n = 14$, 79%).
  a. 2 physicians were aware of a total of 3 persons who had undergone callosotomy for atonic seizures. Of these, 2 had improvement in atonic seizure frequency (1 only transiently).
  b. 2 caregivers were aware of 2 persons who had undergone callosotomy. One was reported to have reduced atonic seizures, whereas the other did not benefit.
- There is no role for temporal lobectomy in DS (**PHYSICIANS**: $n = 13$, 92%).
  a. 7 physicians were aware of a total of 16 patients who had undergone temporal lobectomy. Only one was reported to have a mild reduction in seizures, whereas the rest did not benefit.

(Continues)

TABLE 4 (Continued)

Disease-modifying therapies

Assuming a disease-modifying therapy was proven to be safe, there were no barriers to access, and cost was not prohibitive:

- A disease-modifying therapy is recommended if it leads to greater reduction in seizures than the current best therapy AND has an impact on reducing cognitive and other comorbidities (**PHYSICIANS**: $n = 18$, 100%; **CAREGIVERS**: $n = 9$, 100%):
  a. Would use as early as possible (***physicians***: $n = 18$, 72%; *caregivers*: $n = 9$, 44%)
  b. Would use at some point before trying a 3rd ASM (**PHYSICIANS**: $n = 18$, 89%; **CAREGIVERS**: $n = 9$, 89%)
- A disease-modifying therapy is recommended if it leads to greater reduction in seizures than the current best therapy, even if it has NO impact on comorbidities (**PHYSICIANS**: $n = 18$, 83%; ***caregivers***: $n = 8$, 75%):
  a. Would use as early as possible (*physicians*: $n = 15$, 47%; *caregivers*: $n = 6$, 50%)
  b. Would use at some point before trying a 3rd ASM (***physicians***: $n = 15$, 67%; **CAREGIVERS**: $n = 6$, 100%)
- A disease-modifying therapy is recommended if it has an impact on reducing cognitive and other comorbidities, even if it has NO greater impact on seizures than the current best therapy (**PHYSICIANS**: $n = 18$, 89%; ***caregivers***: $n = 8$, 75%):
  a. Would use as early as possible (***physicians***: $n = 16$, 69%; *caregivers*: $n = 6$, 17%)
  b. Would use at some point before trying a 3rd ASM (**PHYSICIANS**: $n = 16$, 88%; ***caregivers***: $n = 6$, 67%)
- If studies of disease-modifying therapy in infants and preschool children showed an impact on both seizures and comorbidities, but studies had not been performed in older persons with DS, such therapies should be considered for use in older children and adults with moderate to severe intellectual disability (***physicians***: $n = 17$, 71%; *caregivers*: $n = 8$, 50%).
- In a preschool or early school-aged child, current seizure frequency would not impact the decision to recommend disease-modifying treatment (**PHYSICIANS**: $n = 12$, 83%; **CAREGIVERS**: $n = 6$, 100%).
- In a preschool or early school-aged child, degree of intellectual disability would not impact the decision to recommend these therapies (**PHYSICIANS**: $n = 12$, 83%; ***caregivers***: $n = 6$, 67%). If both gene therapy and antisense oligonucleotides were safe and effective, gene therapy is the preferred option, as only one treatment is needed (**PHYSICIANS**: $n = 10$, 80%; caregivers[b]: $n = 2$, 50%).

Seizure emergencies

- All persons with DS should have a home rescue medication (**PHYSICIANS**: $n = 19$, 100%; **CAREGIVERS**: $n = 10$, 100%).

Status epilepticus (physicians only)

- In a patient with DS presenting with a prolonged convulsive seizure that has not responded to 2 appropriate doses of benzodiazepines, the optimal next option is:
  a. IV valproic acid load (assuming the child is not already on maintenance valproate with high therapeutic levels; *physicians*: $n = 19$, 63%)
  b. IV phenytoin or fosphenytoin load (*physicians*: $N = 19$, 47%)
  c. IV levetiracetam load (*physicians*: $n = 19$, 37%)
- In a patient with DS presenting with a prolonged convulsive seizure that has not responded to 2 appropriate doses of benzodiazepines, the following are NOT recommended as the optimal next option:
  a. IV midazolam infusion (***physicians***: $n = 19$, 79%)
  b. IV phenobarbital load (**PHYSICIANS**: $n = 19$, 89%)
  c. IV lacosamide load (**PHYSICIANS**: $n = 19$, 100%)
- In a patient with DS presenting with a prolonged convulsive seizure that has not responded to 2 appropriate doses of benzodiazepines, the following agents are appropriate to use either first or second line as acute treatment:
  a. IV valproic acid load (assuming the child is not already on maintenance valproate with high therapeutic levels; **PHYSICIANS**: $n = 19$, 95%)
  b. IV levetiracetam load (**PHYSICIANS**: $n = 19$, 84%)
  c. IV phenytoin or fosphenytoin load (*physicians*: $n = 19$, 63%)
  d. IV midazolam infusion (*physicians*: $n = 19$, 58%)
  e. IV phenobarbital load (*physicians*: $n = 19$, 53%)
- Phenytoin or fosphenytoin are NOT considered contraindicated when used as acute treatment for prolonged seizures in DS (**PHYSICIANS**: $n = 19$, 89%).

Note: Bold and all-capital text indicates Strong consensus; bold and italic text indicates Moderate consensus; nonbold and italic text indicates no consensus.

Abbreviations: ASM, antiseizure medication; CBC, complete blood count; CBD, cannabidiol; DS, Dravet syndrome; IQR, interquartile range; IV, intravenous; SUDEP, sudden unexpected death in epilepsy; THC, tetrahydrocannabinol.

[a]3/9 caregivers who did not agree commented that certain ASMs may lead to improvement in comorbidities, and that alone may be reason to continue them even if seizures are not improved.

[b]Consensus was not determined for statements where >50% of the group did not provide a response.

disability, attention problems, gait abnormalities, and sleep problems, agreement on their optimal management was limited. There was only moderate consensus from physicians, and no consensus from caregivers, that psychostimulants were effective for attention problems. Whereas most panelists reported modest benefit with melatonin for sleep disorders,[17] the majority lacked experience with other agents. Further work is needed to define

optimal management strategies for these comorbidities, which markedly impact quality of life.

We found several areas in which caregivers and physicians expressed discordant opinions, with caregivers reporting higher rates of both autistic features and externalizing behaviors than physicians. The prevalence of autism in studies of children with DS that employed formal autism-specific instruments ranges from 22% to 46%.[18] However, autism appears to be underrecognized, as in a recent study, clinically significant social communication deficits were noted in 67%, of whom only 44% had been diagnosed with autism.[19] These findings suggest that behavioral comorbidities in children with DS may be underdiagnosed and untreated, despite their significant negative impact on quality of life. These findings support the need for periodic formal evaluation by neuropsychology, developmental pediatrics, or child psychiatry for children with DS.

In the 5 years since the North American consensus publication, there have been three new ASMs approved for the treatment of seizures associated with DS, each with robust, class 1 evidence documenting efficacy and well-described side effect profiles.[4–7] These studies allow clinicians to have data-driven discussions with families about expected outcomes regarding seizure reduction and long-term durability of this response. The demonstrated efficacy of these "DS-specific" medications strongly supports their use earlier in the treatment paradigm.

Most young children with suspected or genetically proven DS are still started on a more conventional ASM as opposed to one of these "DS-specific" medications. In many ways, this is justified and practical due to lack of access to and the expense of such therapies. It can be challenging to start one of the newer DS-specific ASMs, as they only have labeling as adjunctive therapy from 1 or 2 years of age. Patients with DS often have some beneficial response to a conventional ASM; the decision to add or change therapy should be predicated on the overall goal of minimizing seizures and side effects, acknowledging that for most patients, complete seizure freedom remains unrealistic. To automatically switch to one of the DS-specific medications may not be indicated if the patient is controlled on their current regimen. However, we should redefine our expectations of seizure control, and no longer accept seizures every 1–2 months as the best we can do.

A rescue plan for seizure emergencies remains an important part of a comprehensive treatment plan. Although there was widespread consensus regarding the early use of benzodiazepines for convulsive seizures, the specific agents and formulations should be tailored to each patient. Some patients may respond to one benzodiazepine more favorably than another, and these observations remain important in arriving at an individualized seizure action plan. This should include a home rescue plan followed by an emergency department plan, and for the latter, despite phenytoin's primary mechanism of action being a sodium channel blocker, there was consensus that phenytoin/fosphenytoin is not contraindicated as a treatment for status epilepticus.

Although treatment is often focused on seizure reduction, both clinicians and caregivers agree that non-seizure-related comorbidities must also be addressed. Thankfully, some of these recent DS-specific therapy trials have also demonstrated improvements in non-seizure-related outcomes such as executive function,[20] and it remains to be seen whether earlier use of "DS-specific" ASMs will have more favorable impact on long-term outcomes. Although a recent study suggested that fenfluramine may be associated with reduced risk of SUDEP,[21] further research is needed.

As comorbidities remain an important determinant of overall quality of life, DMTs that go beyond seizure management are needed. These types of therapeutics are in various stages of development, and although their perceived role is speculative, our findings highlight the current climate and state of the art looking forward. One clinical trial is underway with an antisense oligonucleotide (ASO) that, in an *SCN1A* mouse model, restored the haploinsufficient state to that of wild type, resulting in reduced incidence of seizures and SUDEP.[8] This specific ASO is being studied in multiple ascending doses in children 2–18 years of age with DS caused by pathogenic *SCN1A* variants (ClinicalTrials.gov identifier: NCT04442295) and has the potential not only to reduce seizures but also to improve other comorbidities. There was universal consensus to recommend a DMT if it addresses both comorbidities and seizures; however, in that scenario, there was only Moderate consensus from physicians to prescribe such therapy as soon as possible. This is likely due to the lack of clinical safety and efficacy outcome data in this first in-human trial; perceptions and opinions will likely evolve as more data become available. Future data will also shed light on whether there is an optimal age to intervene with a DMT. Within the DS community, there has been concern regarding the intrathecal route of administration and potential exclusion from participation in future trials should gene therapy not work, which may have led to greater hesitation from caregivers. Taken altogether, these developments are moving toward a precision-based treatment approach for persons with DS, and importantly today, clinicians and caregivers should never feel it is too late to optimize care using all available treatments.

Transition to adult care is important; adult patients with DS develop additional adult medical issues that pediatricians are poorly equipped to manage. However,

panelists noted numerous barriers to this process. There is a critical need for knowledgeable adult providers and specialized clinics focused on adults with developmental and epileptic encephalopathies, such as DS, to assume this role. A recent transition guide to help with transition from pediatric to adult practice for persons with DS has been published.[22]

One of the most significant limitations of our study was that not all new therapies are approved worldwide and current trials of DMTs are being performed in a limited number of settings. The use and order of selection of ASMs is based on which drugs are available in each expert's country and patient population, so each expert's experience is understandably colored by accessibility issues. Furthermore, as DMTs are still in clinical trials, opinions on their utility are purely theoretical. A further limitation, implicit to all Delphi processes, is that conclusions may not be based on the most recent evidence, but rather the consensus view. It takes time for novel scientific insights to filter to the clinical domain if they differ from current teaching.

We believe that this International DS Consensus, informed by both experienced global caregiver and physician voices, provides a strong overview of the impact of DS, therapeutic goals, and optimal management strategies, taking into account the recent therapeutic advances and evolving DMTs. We hope these results will impact clinical practice by identifying who to screen and how to manage seizures and comorbidities to improve outcomes in persons with DS.

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CONFLICT OF INTEREST

E.C.W. has served as a paid consultant for Encoded Therapeutics, Eisai, Epygenix, and BioMarin. She is Editor-in-Chief of Epilepsy.com. K.G.K. has received research funding from Zogenix, Encoded, Eisai, and West Pharmaceuticals. She has participated on data and safety monitoring boards for GW Pharmaceuticals and Epygenix, and has received consulting funds from BioMarin, Zogenix, Encoded, Eisai, Stoke, and Biocodex. R.N. has served as principal investigator in clinical trials for Novartis, Nutricia, Eisai, UCB, GW Pharma, and LivaNova. She has received consulting and lecturer honoraria from Biogene, BioMarin, Praxis, GW Pharma, Zogenix, Novartis, Nutricia, Stoke, Ionis, Targeon, Neuraxpharma, Takeda, Nutricia, Biocodex, Advicennes, and Eisai. She has received unrestricted research grants from Eisai, UCB, LivaNova, and GW Pharma and academic research grants from EJP-RD (Horizons 2020). I.S. has served on scientific advisory boards for UCB, Eisai, GlaxoSmithKline, BioMarin, Nutricia, Rogcon, Chiesi, Encoded Therapeutics, Knopp Biosciences, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, LivaNova, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, BioMarin, and Eisai; has served as an investigator for Zogenix, Zynerba, Ultragenyx, GW Pharma, UCB, Eisai, Xenon Pharmaceuticals, Anavex Life Sciences, Ovid Therapeutics, Epygenix, Encoded Therapeutics, and Marinus; has consulted for Zynerba Pharmaceuticals, Atheneum Partners, Ovid Therapeutics, Care Beyond Diagnosis, Epilepsy Consortium, and UCB; and is a Non-Executive Director of Bellberry. She may accrue future revenue on pending patent WO61/010176 (filed 2008): Therapeutic Compound; has a patent for *SCN1A* testing held by Bionomics and licensed to various diagnostic companies; has a Patent Molecular Diagnostic/Theranostic Target for Benign Familial Infantile Epilepsy (BFIE) (PRRT2) 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID: 2012-009). J.W. has received an honorarium for activities as Associate Editor for *Epilepsia*. J.S. has served as a paid consultant for the Epilepsy Study Consortium, Encoded Therapeutics, Greenwich Biosciences, Epygenix Therapeutics, Invitae, and Longboard, and has stock options in Epygenix. Neither of the other authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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