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Original Article

Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel

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ABSTRACT

OBJECTIVES: To establish standards for early, cost-effective, and accurate diagnosis; optimal therapies for seizures; and recommendations for evaluation and management of comorbidities for children and adults with Dravet syndrome, using a modified Delphi process. **METHODS:** An expert panel was convened comprising epileptologists with nationally recognized expertise in Dravet syndrome and parents of children with Dravet syndrome, whose experience and understanding was enhanced by their active roles in Dravet syndrome associations. Panelists were asked to base their responses to questions both on their clinical expertise and results of a literature review that was forwarded to each panelist. Three rounds of online questionnaires were conducted to identify areas of consensus and strength of that consensus, as well as areas of contention. **RESULTS:** The panel consisted of 13 physicians and five family members. Strong consensus was reached regarding typical clinical presentation of Dravet syndrome, range of electroencephalography and magnetic resonance imaging findings, need for genetic testing, critical information that should be conveyed to families at diagnosis, priorities for seizure control and typical degree of control, seizure triggers and recommendations for avoidance, first- and second-line therapies for seizures, requirement and indications for rescue therapy, specific recommendations for comorbidity screening, and need for family support. Consensus was not as strong regarding later therapies, including vagus nerve stimulation and callosotomy, and for specific therapies of associated comorbidities. Beyond the initial treatment with benzodiazepines and use of valproate, there was no consensus on the optimal in-hospital management of convulsive status epilepticus. **CONCLUSIONS:** We were able to identify areas where there was strong consensus that we hope will (1) inform health care providers on optimal diagnosis and management of patients with Dravet syndrome, (2) support reimbursement from insurance companies for genetic testing and Dravet syndrome–specific therapies, and (3) improve quality of life for patients with Dravet syndrome and their families by avoidance of unnecessary testing and provision of an early accurate diagnosis allowing optimal selection of therapeutic strategies.

Keywords: Dravet syndrome, diagnosis, genetic testing, questionnaire, guidelines

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Dravet syndrome is a distinctive, early-life epilepsy with a reported incidence of 1 in 15,700 to 1 in 40,900.[1-3] A high degree of clinical suspicion is needed for this diagnosis, because magnetic resonance imaging (MRI) is typically normal and the electroencephalography (EEG) findings are nonspecific. However, the early clinical presentation of Dravet syndrome is unique, with the onset of recurrent, convulsive seizures, which are often prolonged and triggered by fever, in a developmentally normal infant.

Variants in the *SCN1A* gene, which codes for the α-1 subunit of the neuronal, voltage-gated sodium channel, are found in as many as 85% of individuals who are clinically diagnosed with Dravet syndrome.[3] *SCN1A* mutations may also be found in less severe epilepsy types such as genetic epilepsy with febrile seizures plus and more severe forms of epilepsy such as migrating focal seizures[4]; therefore careful clinical correlation is needed.[5]

The goal of prophylactic treatment in Dravet syndrome is cessation of prolonged convulsions, reduction in overall seizure frequency, and minimization of treatment side effects. However, medications are only partly effective,[6] and essentially all patients develop multiple comorbidities over time[7,8] because of the underlying channelopathy,[9] recurrent seizures, and side effects of polypharmacy.[9,10] Furthermore, persons with Dravet syndrome have a significantly higher premature mortality because of status epilepticus, accidents, and sudden unexpected death in epilepsy (SUDEP).[7,8,11,12] There is often considerable delay in the diagnosis of Dravet syndrome,[13] which results in unnecessary, costly, and, at times, invasive testing, and use of ineffective therapies, which can exacerbate seizures, increase the risk of status epilepticus, and worsen cognitive outcome.[6,14,15]

The literature regarding the diagnosis and optimal management of Dravet syndrome is limited, and no current guidelines or consensus statements exist regarding specific indications and investigations for Dravet syndrome, prophylactic or abortive treatments for seizures, or screening recommendations for specific comorbidities. To develop consensus on these issues, we performed a literature review and established a North American Expert Panel, consisting of both epileptologists (pediatric and adult) and parents/caregivers who have had significant involvement with the lay Dravet syndrome organizations (Dravet Syndrome Foundation and Dravet Canada). A consensus-building process was employed, i.e., a modified Delphi process,[16] to establish standards for early, cost-effective, and accurate diagnosis; optimal therapies for seizures; and recommendations for evaluation and management of comorbidities for children and adults with Dravet syndrome. It is our hope that such recommendations will be valuable for both clinicians and families.

Methods

The concept of this study was proposed by two members of the Pediatric Epilepsy Research Consortium (A.T.B. and E.C.W.) and then discussed in further detail with the Executive Director and Members of the Medical Advisory Board of the Dravet Syndrome Foundation and the President of the Intractable Childhood Epilepsy Alliance, who provided input on the study design and content.

Identification of the study participants

Expert panel

An initial core panel was convened, which consisted of five pediatric epileptologists on the Medical Advisory Board of the Dravet Syndrome Foundation, a Canadian pediatric epileptologist with extensive clinical expertise in Dravet syndrome, and two parents of children with Dravet syndrome, who through their leadership roles in Dravet syndrome organizations, know of numerous other children and families affected by this disorder.

These eight core panelists were asked to nominate other North American clinicians with expertise in the management of patients with Dravet syndrome and nominations were collated. Nominees included 39 pediatric epileptologists and one adult epileptologist who runs an adult Dravet clinic. There was uniform consensus from the panel to include this individual, given her unique expertise in the care of adults with Dravet syndrome. Core panelists ranked the remaining pediatric epilepsy nominees based on their expertise on Dravet syndrome, and the top-ranked eight agreed to participate in the panel (three from Canada, four from the United States).

In addition, core panelists identified three other family/caregiver panelists, all of whom have a child with Dravet syndrome and are active in one of the lay organizations.

Thus the expert panel ultimately comprised 14 physicians and five family members/caregivers, and their credentials are summarized in Supplementary Table 1.

Study facilitator

The study facilitator (A.T.B.) collated responses from the expert panel into a series of statements reflecting the position of the entire group (including the range of opinions and reasons for those opinions). The facilitator determined if consensus had been reached, if further clarification was needed, or if opinions were too diverse to achieve consensus. Subsequent iterations were designed to clarify points where consensus could, or could not, be reached.

Methodology

Literature review

The six physician members of the core panel reviewed the literature on Dravet syndrome regarding diagnosis and genetic testing, clinical presentation and evolution, long-term outcome, comorbidities, and prophylactic and abortive seizure treatment, with each main topic being assigned to two reviewers. The results of this literature review were collated into a single document, which was distributed to each member of the expert panel before study onset. The articles included in this literature review are indicated in the Reference section of this paper or in Supplementary Table 2 if not referred to in this article. The evidence from the literature in each area surveyed was graded using the American Academy of Neurology Classification of Evidence (http://tools.aan.com).

Questionnaires

Review of clinician expertise and perceived strength of the medical literature. Panelists indicated the total number of patients with Dravet syndrome that they had seen or evaluated in the past (physicians) or had personal knowledge about their clinical course, evaluation, and management (family members/caregivers). Physician panelists indicated the number of patients with Dravet syndrome that they currently follow, both as the primary epilepsy provider and as the consulting provider. All panelists were asked to rate their personal experience as extensive, moderate, or little. The following topics were addressed:

- Diagnosis: clinical presentation, development, imaging, EEG, and genetic testing
- Treatment: daily maintenance therapies, including antiepileptic medications, dietary therapies, surgical therapies including vagus

nerve stimulation, rescue medications, steroids/verapamil, and cannabidiol/marijuana
- Comorbidities: orthopedic and gait issues, sleep, gastrointestinal and endocrine issues, dysautonomia, and SUDEP

Creation of questionnaires. A three-round Delphi approach was conducted to generate the recommendations included in these standards. Initially, members of the core panel were asked to identify critical or controversial issues regarding the diagnosis, evolution, and management of patients with Dravet syndrome. A draft was created based on the evidence, amended after feedback from core panelists, and then distributed as iteration #1 to the expert panel (19 members) as a web-based electronic questionnaire utilizing CLIRINX. Panelists were asked to complete the questionnaire within a 3-week period, and reminders were sent electronically after 2 and 3 weeks if responses were not received.

Following the analysis of iteration #1, a second electronic questionnaire, iteration #2, was created and forwarded to panelists to confirm areas of consensus and clarify areas where consensus was not yet reached. To confirm consensus, panelists were asked to indicate their agreement with specific statements (strongly agree, agree, somewhat agree, neutral, somewhat disagree, disagree, strongly disagree, or do not know). For any response less than "agree," they were asked to provide comments to support their position. A final questionnaire, iteration #3, was sent out after the analysis of iteration #2, asking for responses following a similar format. Although most questions were posed to the entire group, as families had significant clinical expertise based on their personal experience and interactions with other families, those items that focused on distinguishing Dravet from other epilepsy types and specific questions regarding interpretation of EEG and MRI were posed solely to physicians.

Consensus was defined as *strong* if more than 75% strongly agreed or agreed; as *moderate* if more than 75% strongly agreed, agreed, or somewhat agreed; as *modest* if less than 75% strongly agreed, agreed, or somewhat agreed and none disagreed; and as *no consensus* if less than 75% strongly agreed, agreed, or somewhat agreed and some disagreed at any level. For areas where there was no consensus, we evaluated whether the disagreement was solely from physicians or family members or from both.

Following the analysis of all data from iterations #1-#3, a final summary of the evidence and recommendations was forwarded to all 18 panelists and they were invited to submit any final feedback.

Results

The expertise of panel members is summarized in Figs 1 and 2.

Round 1 received 18 responses (13/14 physicians and 5/5 family members/caregivers). Questions covered 11 areas of diagnosis (age at seizure onset; seizure types: mandatory, typical but not mandatory, neither typical nor unusual, atypical or exclusionary, and typical ages of presentation; seizure triggers; seizure frequency; common misdiagnoses; development; neurological examination findings; family history; imaging findings; EEG findings; genetic testing and essential components of clinical counseling around a diagnosis of Dravet syndrome), eight areas regarding treatment (priorities for seizure control, strategies to reduce seizure triggers, prophylactic antiepileptic medications, dietary therapies, surgical therapies, rescue medications, management of status epilepticus, and alternative therapies), and eight areas regarding comorbidities (developmental and behavioral screening and intervention, screening and management of gait and orthopedic concerns, sleep disorders, gastrointestinal symptoms, dysautonomia and cardiac

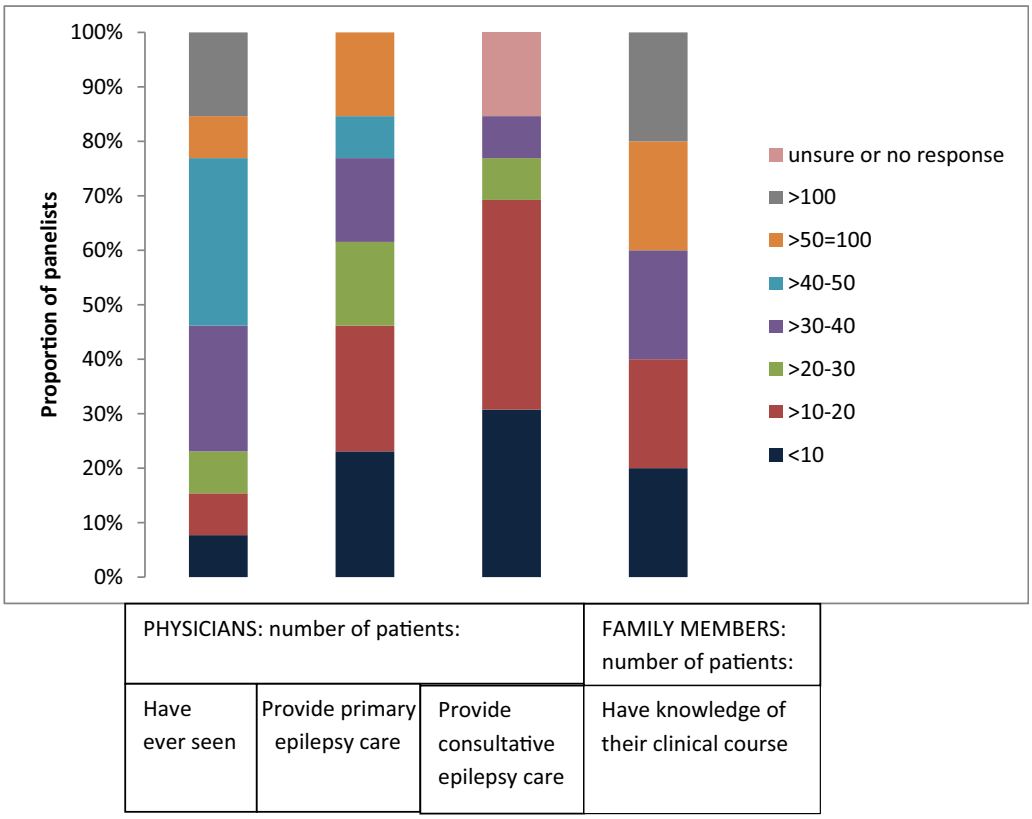

FIGURE 1.
Panel expertise. (The color version of this figure is available in the online edition.)

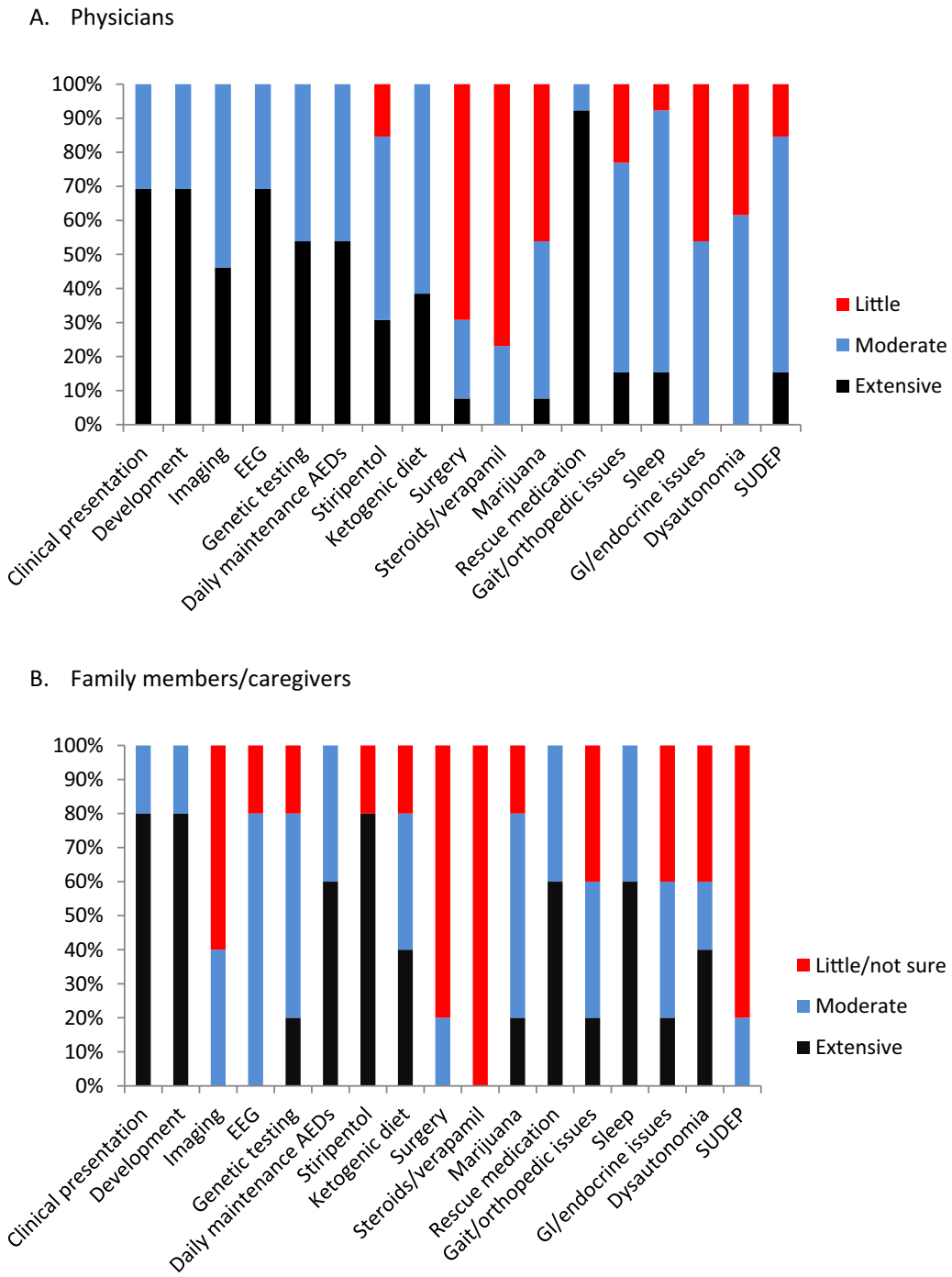

FIGURE 2.
Extent of personal experience in each area. (A) Physicians. (B) Family members/caregivers. AED, antiepileptic drug; EEG, electroencephalography; SUDEP, sudden unexpected death in epilepsy. (The color version of this figure is available in the online edition.)

symptoms, SUDEP prevention strategies and seizure detection devices, and home care and family support).

All 18 panelists who completed round 1 also completed rounds 2 and 3 and provided feedback on the draft consensus statement.

Round 2 consisted of two sections. The first section consisted of statements that represented majority opinions from round 1, and respondents were asked to indicate their level of agreement with each statement (strongly agree, agree, somewhat agree, neutral, somewhat disagree, disagree, or strongly disagree). For responses of neutral or any level of disagreement, respondents were asked to provide specific comments regarding their concerns with the statement. The second section included multiple choice questions and aimed to clarify opinion in specific areas.

Round 3 also consisted of two sections. The first section comprised a series of statements that represented a majority opinion from round 2, and respondents were asked to

indicate their level of agreement with each statement (strongly agree, agree, somewhat agree, neutral, somewhat disagree, disagree, or strongly disagree). For responses of neutral or any level of disagreement, respondents were asked to provide specific comments regarding their concerns with the statement. The second section comprised a limited number of forced choices regarding indications for genetic testing (four scenarios—would you order genetic testing—yes/no/do not know) and the specific type of genetic testing to order (*SCN1A* sequencing, followed by deletion/duplication testing if negative, an Epilepsy Gene Panel, or no preference—both choices are reasonable).

Data from all three rounds were then summarized into a draft consensus statement, indicating areas where consensus was reached and strength of consensus (strong, moderate, modest, versus no consensus), as well as areas of contention, and forwarded to all panelists for their final written feedback.

Diagnostic issues

The initial presentation of Dravet syndrome in a young child is quite characteristic. In older, previously undiagnosed, children and adults in whom the early childhood history is not available, the diagnosis can be more challenging. The panel identified key clinical features that suggest the diagnosis of Dravet syndrome at specific ages (Table 1). The presence of such features should prompt genetic testing.

Table 2 further summarizes the group's consensus on diagnostic issues.

Benefits of early diagnosis

The literature review did not provide any evidence regarding the benefits of early diagnosis of Dravet syndrome. However, based on their clinical experience, panelists believed that earlier diagnosis improves long-term outcome for patients overall (moderate), with improved cognition and seizure control.

Misdiagnoses

Children with Dravet syndrome may be misdiagnosed with myoclonic atonic epilepsy, Lennox-Gastaut syndrome, myoclonic epilepsy in infancy, genetic epilepsy with febrile seizures plus, atypical febrile seizures, lesional focal epilepsy, and mitochondrial disorders (strong). Conversely, those with myoclonic atonic epilepsy, myoclonic epilepsy in infancy, and PCDH19-associated epilepsy may be misdiagnosed with Dravet syndrome (strong).

Genetic testing

There was strong consensus that genetic testing should be pursued for all patients with a clinical picture suggestive of Dravet syndrome and on the specific types of genetic testing to order. Moderate to strong consensus was reached regarding the specific clinical scenarios that should or should not mandate genetic testing for Dravet syndrome, with one noted exception. There was no consensus regarding the need for genetic testing for a child aged less than 12 months with normal early development, a normal MRI, and no known seizure etiology who presents with more than two prolonged (more than 15 minutes) generalized febrile seizures (72.2% strongly agreed/agreed/somewhat agreed that testing should be done, 5.6% indicated they did not know, and 22.2% strongly disagreed/disagreed/somewhat disagreed).

What information should be conveyed to the family at the time of diagnosis

Strong consensus was achieved regarding the breadth of topics that should be addressed during genetic counseling and in the education of families of newly diagnosed patients.

TABLE 1.
Characteristic Clinical Presentation of Dravet Syndrome

Presentation in Young Children
- Typical onset between 1 and 18 months (strong)
- Recurrent generalized tonic-clonic or hemiconvulsive seizures, which are mandatory for diagnosis. These are often prolonged but may be shorter (strong)
- Myoclonic seizures are typically seen by age 2 years (strong). Obtundation status, focal dyscognitive seizures, and atypical absences are also typical but usually occur after age 2 years (strong). Typical absences and epileptic spasms are atypical (strong)
- Hyperthermia, which may be associated with vaccination, triggers seizures in most patients (strong); other triggers may include flashing lights, visual patterns, bathing, eating, and overexertion
- Normal development and neurological examination at onset (strong)
- Normal MRI and nonspecific EEG findings at onset (strong)

Presentation in Older Previously Undiagnosed Children and Adults, If Details of the Early Childhood History Are Not Available
- Persisting seizures, which include focal and/or generalized convulsive seizures, and, in many cases, myoclonic, focal, atypical absence and tonic seizures (strong). Recurrent status epilepticus and obtundation status become less frequent with time and may not be seen in adolescence and young adulthood
- Hyperthermia as a seizure trigger (strong) may become less problematic in adolescence and adulthood
- Seizure exacerbation with the use of sodium channel agents (strong)
- Intellectual disability, which is typically evident by age 18-60 months (strong)
- Abnormalities on neurological examination, which are typically evident by age 3-4 years and include crouched gait, hypotonia, incoordination, and impaired dexterity (strong)
- An MRI that is typically normal but may show mild generalized atrophy and/or hippocampal sclerosis (strong)
- An EEG that shows diffuse background slowing, often with multifocal and/or generalized interictal discharges. A photoparoxysmal response may be seen (strong)

Abbreviations:
EEG = Electroencephalography
MRI = Magnetic resonance imaging

TABLE 2.
Diagnostic Issues: Summary of Consensus of Expert Panel

	AAN Class of Evidence*	Finding	Strength of Agreement
Timing of diagnosis			
Benefits of early diagnosis	IV[17]	Early diagnosis improves long-term outcome for patients with Dravet syndrome	Moderate
Clinical presentation			
Age at onset	II[7,18-21]	Age at onset of seizures in Dravet syndrome is typically between 1 and 18 months	Strong
		Onset between 18 and 24 months is rare but still consistent with the diagnosis	Strong
Seizure types and typical ages of presentation	II[7,18-20,22]	Within the first 2 years of onset, generalized tonic-clonic or hemiconvulsive seizures are *mandatory* for diagnosis; although these are often prolonged, shorter convulsions are also typical	Strong
		Myoclonic seizures are *typical but not mandatory* and are seen in the majority by age 2 years	Strong
		Obtundation status is *typical but not mandatory*, usually occurs in children older than 2 years, but may be seen earlier	Strong
		Focal dyscognitive seizures are *typical but not mandatory*, usually occur in children older than 2 years, but may be seen earlier	Strong
		Atypical absences are *typical but not mandatory*, and usually occur in children older than two years of age, but may be seen earlier	Strong
		Tonic seizures are *neither typical nor unusual* in older patients but are atypical before age 2 years	Strong
		Typical absences and epileptic spasms are *atypical/exclusionary*	Strong
Seizure triggers	II[8,18-22]	Hyperthermia triggers seizures in most patients	Strong
Misdiagnoses†	NA	Children with Dravet syndrome are commonly to sometimes misdiagnosed with myoclonic atonic epilepsy, Lennox-Gastaut syndrome, myoclonic epilepsy in infancy, genetic epilepsy with febrile seizures plus, atypical febrile seizures, lesional focal epilepsy, and mitochondrial disorders	Strong
		Children with myoclonic atonic epilepsy, myoclonic epilepsy in infancy, and PCDH19-associated epilepsy are commonly to sometimes misdiagnosed as Dravet syndrome	Strong
Neurodevelopment	II[7-10,19-21,23-25]	Development is normal at the time of seizure onset	Strong
		Virtually all patients ultimately develop intellectual disability	Strong
		Delays are typically evident by age 18 to 60 months	Strong
		Regression for a period lasting longer than 2 to 4 weeks may be seen following a prolonged seizure	Strong
Neurological examination	II[7,8,20,21,26]	Abnormalities on the neurological examination are seen in most patients with time	Strong
		Such abnormalities are typically evident by age 3 to 4 years	Strong
		Hypotonia and crouch gait are the most common motor abnormalities	Strong
		Fine motor deficits include incoordination and impaired dexterity	Strong
Family history	III[7,18-21]	A first-degree family history of epilepsy or febrile seizures is present in less than one quarter of cases	Strong
Investigations			
Neuroimaging†	II[7,20,27-29]	The MRI is typically normal	Strong
		Findings that may be seen with time and still consistent with the diagnosis include:	
		Generalized atrophy	Strong
		Hippocampal sclerosis	Strong
		Malformations of cortical development and dysembryoplastic neuroepithelial tumors are considered *atypical or exclusionary*	Strong
EEG†	II[7,8,19,20,30-32]	Background:	
		≤2 years: can be either diffusely slow or normal	Strong
		>2 years: diffuse slowing is typical	Strong
		Interictal discharges:	
		Can be focal, multifocal, and/or generalized	Strong
		Between 2 to 12 years, discharges are seen in more than half of cases	Strong
		In teens and adults, discharges are present in over 75% of cases	Strong
		Photoparoxysmal response:	
		Seen in up to half of children ≤12 years	Strong
		A photoparoxysmal response is present in one quarter or fewer of teens and adults	Strong
Genetic testing	III/IV[5,33,34]	Should be pursued for all patients with a clinical picture suggestive of Dravet syndrome	Strong
		Greater availability of genetic testing has resulted in earlier diagnosis—most children are now diagnosed within 24 months of seizure onset	Strong
		For patients with a clinical history highly suggestive of Dravet syndrome:	
		Either specific *SCN1A* sequencing, followed by testing for deletions and duplications if sequencing is negative, or a larger epilepsy gene panel should be performed†	Strong but No Consensus that one is superior
		A chromosomal microarray is not required†	Strong
		If the clinical history is less distinct or if atypical clinical features are present:	
		An epilepsy gene panel is preferable to specific *SCN1A* testing†	Strong

(*continued on next page*)

TABLE 2. (*continued*)

	AAN Class of Evidence*	Finding	Strength of Agreement
		A chromosomal microarray could be considered†	No consensus
		A karyotype is not needed in the evaluation of a patient with suspected Dravet syndrome†	Strong
		Genetic testing should be pursued in the following situations, provided the child's early development is normal, the MRI does not show a causal lesion, and the seizure etiology remains unknown:	
		Child aged <12 months with ≥2 prolonged (>15 min) focal febrile seizures, affecting opposite sides of the body. Testing could be done by either specific *SCN1A* sequencing, followed by testing for deletions and duplications if sequencing is negative, or an epilepsy gene panel	Strong
		Child aged <12 months with >2 prolonged (>15 minute) focal febrile seizures, affecting same side of body. Testing could be done by either specific *SCN1A* sequencing, followed by testing for deletions and duplications if sequencing is negative, or an epilepsy gene panel	Strong
		Child aged <12 months with ≥2 prolonged (>15 minute) febrile seizures, at least one of which was focal and one of which was generalized. Testing could be done by either specific *SCN1A* sequencing, followed by testing for deletions and duplications if sequencing is negative, or an epilepsy gene panel	Strong
		Child 12-35 months with ≥1 prolonged (>15 minutes) febrile seizure before age 18 months and myoclonic and/or atypical absence seizures refractory to one or more antiepileptic drug. Testing could be done by either specific *SCN1A* sequencing, followed by testing for deletions and duplications if sequencing is negative, or an epilepsy gene panel	Strong
		Child 12-35 months with >1 febrile seizures (all brief) before age 18 months and myoclonic and/or atypical absence seizures refractory to one or more antiepileptic drugs	Moderate
		Genetic testing should be pursued for a teen or adult without congenital dysmorphism, with pharmacoresistant focal and/or generalized seizures, with a nonfocal examination in whom an early-life history is not available. Testing should utilize an epilepsy gene panel rather than specific *SCN1A* analysis	Strong
		Genetic testing is not indicated for a child aged <12 months with single prolonged (>15 minute) focal or generalized febrile convulsion	Strong
Counseling and education			
	IV[35]	Genetic counseling must be provided to the family by any provider (genetic counselor, geneticist, epileptologist, or neurologist) with adequate knowledge about Dravet syndrome, ideally within 2 to 4 weeks of diagnosis	Strong
		Areas rated as *very important* to address include:	
		Risk of epilepsy in current/future siblings	Strong
		Mode of inheritance and causal or modifying genes	Strong
		Areas rated as *somewhat to very important* to address include:	
		How the *SCN1A* mutation results in clinical disease	Strong
		Risk of epilepsy in second degree relatives	Strong
Family education	II[7,8,19,20,36]	Topics that should be covered with families at the first visit include:	
		Risk and management of prolonged seizures/status epilepticus: Families must be provided a rescue medication, be instructed on its administration, and have an emergency treatment plan if home rescue therapy is unsuccessful	Strong
		Expected seizure control: Families should be counseled that complete seizure control is typically not achievable and the goals of therapy discussed	Strong
		Topics that should be addressed within 4 weeks of initial diagnosis include:	
		Risk of death from seizure (SUDEP, accidental, status epilepticus)	Strong
		Developmental outcome: Families should understand that while development is normal initially, all patients develop intellectual disability over time	Strong

Abbreviations:
AAN = American Academy of Neurology
EEG = Electroencephalography
MRI = Magnetic resonance imaging
SUDEP = Sudden unexpected death in epilepsy

Class II: A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most (>80%) patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patient's clinical presentations.

Class III: A selected, referral-clinic-based sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

Class IV: Expert opinion, case reports, or any study not meeting criteria for classes I-III.

* Class I: A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patient's clinical presentations.

† Indicates question posed solely to the physician group.

TABLE 3.
Treatment of Seizures: Summary of Expert Panel

	AAN Class of Evidence	Finding	Strength of Agreement
Priorities for seizure control			
Usual degree of seizure control	II[7,8,19,20]	Complete seizure control is typically not achievable	Strong
		Elimination or significant reduction of prolonged convulsive seizures and status epilepticus should represent the highest priority in treatment	Strong
		Most patients require, on average, three antiepileptic therapies taken consecutively to achieve optimal seizure control	Strong
Impact of specific seizure types on development	III[10,37-39]	Both the frequency and duration of convulsive status epilepticus have a *large* impact on developmental outcome	Strong
		Both the frequency and duration of prolonged convulsive seizures (5 to 29 minutes) have a *moderate to large* impact on developmental outcome	Strong
		Both the frequency and duration of obtundation status epilepticus have a *moderate to large* impact on developmental outcome	Strong
Strategies to reduce seizure triggers			
Effective measures	IV[40]	There was *no consensus* that any particular strategy was effective at preventing seizures in the *majority* of patients	No consensus
		The following strategies are effective in at least a *modest* number of patients:	
		Allowing the child to nap if tired	Strong
		Avoidance of overexertion	Strong
		Avoidance of high ambient temperature	Strong
		Prophylactic antipyretics with vaccination	Strong
		Prophylactic antipyretics with illness	Strong
		Prophylactic benzodiazepines with febrile illness	Strong
		The following strategies are effective in at least a *minority* of patients:	
		Avoidance of flashing lights	Strong
		Cooling vests	Strong
		Sunglasses	Strong
		Avoidance of placing the patient in a bath	Strong
		The following strategies are *not recommended* in patients with Dravet syndrome:	
		Avoiding immunization or selective immunization	Strong
		Routine use of antibiotics for febrile illnesses	Strong
Prophylactic antiepileptic medications			
First-line agents	III[41,42]	Clobazam and valproic acid are the optimal first-line medications in Dravet syndrome. Treatment should be initiated with one of these agents and the other added if control remains suboptimal	Strong
Second-line agents	I, stiripentol[13,42-45] III, topiramate[41,46-48]	Stiripentol and topiramate are the optimal second-line medications. One of these should be used if seizure control remains poor after use of both first-line therapies	Strong
		Stiripentol should be used in combination with valproate and clobazam, and there is no evidence to support its use as monotherapy	Strong
Later therapeutic options	III, levetiracetam[41,49] IV, bromides,[45,50-52] rufinamide[53] NA, others	In patients with suboptimal response to first- and second-line therapies:	
		Clonazepam, levetiracetam, and zonisamide are moderately effective	Strong
		Ethosuximide (for atypical absences) and phenobarbital may be effective	Moderate
		No consensus regarding efficacy of rufinamide, acetazolamide, or bromides	No consensus

(*continued on next page*)

TABLE 3. (*continued*)

	AAN Class of Evidence	Finding	Strength of Agreement
Exacerbating therapies	II[14,18,54-56]	Carbamazepine, oxcarbazepine, lamotrigine, phenytoin, and vigabatrin often exacerbate seizures and should be avoided	Strong
Dietary therapies			
Efficacy and impact on development	II[41,57-60]	The ketogenic diet is moderately effective for seizure control and could be considered second line in patients with suboptimal response to clobazam and valproic acid	Strong
		Dietary therapies have a positive impact on cognition and behavior in most patients	Moderate
Diet variations	NA	The traditional ketogenic diet*:	
		Is the best dietary option for young children aged less than six years	Moderate
		Is a good option for children aged 7-12 years	Moderate
		While the traditional diet could also be used in teens and adults, other diet options may be preferable	Strong
		Modified Atkins diet*:	
		Is the best dietary option for teens and adults and a reasonable option for children aged 2-12 years	Moderate
		Low-glycemic-index diet	
		No consensus regarding the use of a low-glycemic-index diet in Dravet syndrome	No consensus
Surgical therapies			
Efficacy versus risk	NA	Before considering any surgery, including vagus nerve stimulation, patients must be evaluated at a comprehensive epilepsy center with extensive expertise in Dravet syndrome to ensure other therapies have been maximized	Strong
Vagus nerve stimulation	III[41,57,61-66]	Vagus nerve stimulation can be considered but only after failure of both first- (clobazam and valproic acid) and second-line (stiripentol, topiramate, and ketogenic diet) treatments	Moderate
		Vagus nerve stimulation has a minimal to moderate impact on seizure reduction but is generally less efficacious than the ketogenic diet	Strong
		No consensus was reached regarding the efficacy of the magnet to prevent prolonged seizures	No consensus
		Vagus nerve stimulation does not significantly benefit development or behavior in most patients	Moderate
Temporal lobectomy	NA	Resective epilepsy surgery, including temporal lobectomy, should not be performed in patients with Dravet syndrome	Strong
Corpus callosotomy	III[66]	Callosotomy may be considered in a patient with intractable drop seizures but only after failure of clobazam, valproate, stiripentol, topiramate, levetiracetam, and the ketogenic diet	Moderate
		The benefit of corpus callosotomy in Dravet syndrome is unclear, and the potential risk/benefit ratio must be carefully considered, disclosed to and discussed with the family before surgery	Strong
Rescue medication for home use			
Need for home rescue medication	II[36]	All patients need both a home rescue medication and seizure protocol, which can be carried out at their local hospital	Strong
Optimal rescue therapies for age	NA	For children ≤6 years*:	
		Rectal diazepam	Strong
		Buccal/nasal midazolam	Strong
		For children aged 7-12 years and teens/adults*:	
		Buccal/nasal midazolam	Strong

TABLE 3. (*continued*)

	AAN Class of Evidence	Finding	Strength of Agreement
Parameters for administration of rescue medication	NA	At a minimum, rescue medication should be given within 3 to 5 minutes of onset of a convulsive seizure in all age groups*	Strong
		However, in those with a recent history of convulsive seizures that are typically prolonged, rescue medication should be given at the time of convulsive seizure onset	Strong
		A second full dose of rescue medication should be given 5 to 10 minutes after the initial dose in patients of all ages who continue to convulse*	Strong
		For brief convulsive seizures that are clustering, rescue medications should be administered*	Strong
		For clusters of nonconvulsive seizures, no consensus was reached regarding use of rescue medication	No consensus
Management of status epilepticus			
Recommended first-line agents	III[50]	Intravenous benzodiazepines should be the first medication administered if a patient presents to hospital with an ongoing seizure, and a second dose of benzodiazepine should be given if the seizure persists, particularly if the patient did not receive a home dose of rescue medication*	Strong
Recommended therapies if convulsive seizure persists after intravenous benzodiazepine	III[50]	If the patient continues to convulse despite intravenous benzodiazepine, a valproic acid load is an appropriate next option	Strong
		There was no consensus regarding other abortive therapies in the management of convulsive status epilepticus	No consensus
Use of alternative therapies			
Medical marijuana	III[67-69] (class I study in progress)	Medical marijuana is moderately effective for Dravet syndrome†	Strong
		There was no consensus regarding the specific type of medical marijuana recommended	No consensus
Selective serotonin reuptake inhibitors, verapamil, steroids, or intravenous immunoglobulin	IV[70,71]	Efficacy	No consensus was reached for these therapies

Abbreviations:
AAN = American Academy of Neurology
NA = Not available
* Standard of care for all persons with epilepsy, not unique to Dravet syndrome.
† Based on only nine respondents—the remainder indicated they had insufficient experience using this agent for Dravet syndrome to comment on efficacy.

Antiepileptic therapy

A summary of the expert panel regarding antiepileptic therapy is given in Table 3.

Priorities for seizure control

There was strong consensus that elimination or significant reduction of prolonged convulsive seizures and status epilepticus should represent the highest priority in treatment, as both the frequency and duration of convulsive status epilepticus have a large impact on developmental outcome. In addition, prevention and prompt treatment of obtundation status is a priority.

Strategies to reduce seizure triggers

Although there was no consensus that any particular strategy is effective at preventing seizures in most patients, consensus was reached regarding strategies that were effective in some patients. There was also strong consensus for the administration of routine immunizations and against routine use of antibiotics for febrile illnesses.

Maintenance antiepileptic medications and dietary therapy

There was strong consensus regarding recommended first- and second-line maintenance antiepileptic agents, including use of the ketogenic diet as a possible second-line therapy. Consensus was less strong for later therapeutic options. In addition, there was strong consensus that certain medications often exacerbate seizures and should be avoided. Figure 3 outlines the recommendations regarding maintenance antiepileptic therapy in Dravet syndrome.

Surgical therapies

Vagus nerve stimulation. There was moderate consensus for the use of vagus nerve stimulation if first- and second-line therapies have failed.

Resective surgery or corpus callosotomy. Panelists knew of 16 patients who had undergone either temporal lobectomy or corpus callosotomy, 13 (81%) of whom had undergone surgery before a diagnosis of Dravet syndrome was established. Only three (19%) had more than a 50% reduction in seizures,

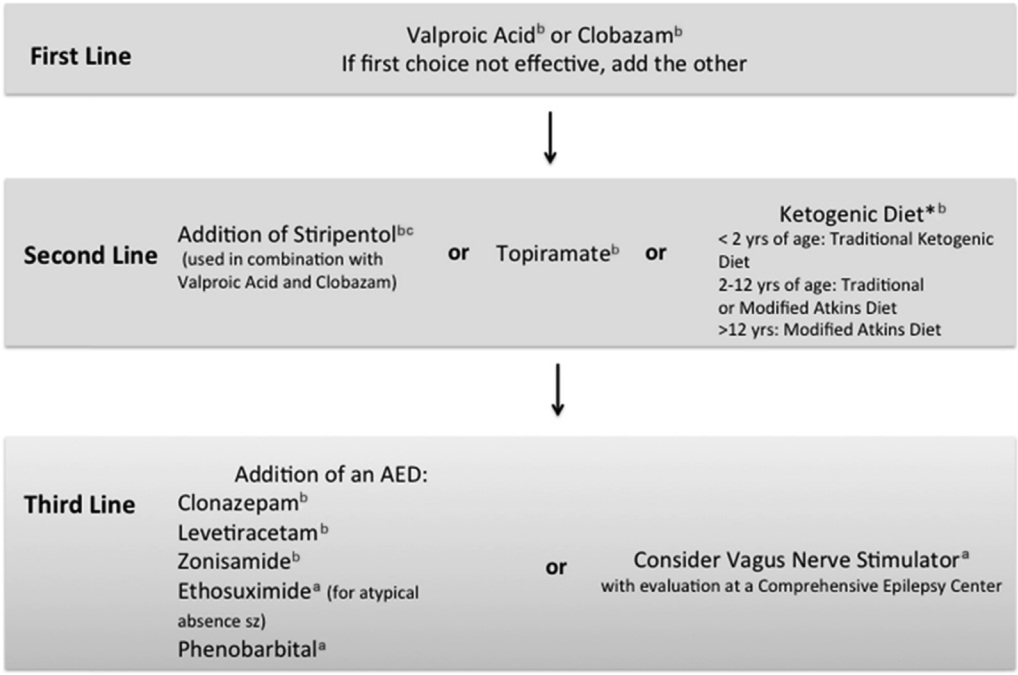

FIGURE 3.
Treatment algorithm for Dravet syndrome. *Ketogenic diet is not suitable for all patients; its use is not required before moving to third-line therapies. [a]Agreed upon by moderate consensus. [b]Agreed upon by strong consensus. [c]Stiripentol not approved for use in all jurisdictions. sz, seizures.

and none were seizure-free. There was strong consensus that there was no role for resective surgery, including temporal lobectomy, in patients with Dravet syndrome. Although there was moderate consensus that corpus callosotomy could be considered in a patient with drug-resistant drop seizures after failure of first- and second-line agents, the benefits of this procedure were unclear.

Use of alternative therapies

Medical marijuana/cannabidiol. Twelve of 18 (67%) panelists had experience with the use of medical marijuana in Dravet syndrome and nine had adequate experience to comment on perceived efficacy. Although these individuals felt that medical marijuana was moderately efficacious, no consensus could be reached regarding which concentration of cannabidiol/tetrahydrocannabinol should be used.

Selective serotonin reuptake inhibitors, verapamil, steroids, or intravenous immunoglobulin. Among the participants, experience with these therapies was too limited to provide any recommendations.

Rescue medication for home use

There was consensus regarding the need for both home rescue medication and a seizure protocol that can be carried out at the local hospital, as well as specific types of recommended rescue therapies and parameters for use for convulsive seizures. No consensus was reached regarding the recommendations for rescue therapy use for clusters of nonconvulsive seizures.

In-hospital management of status epilepticus

There was consensus that benzodiazepines should be administered first line for in-hospital management of status epilepticus. There was little consensus regarding the next best option if benzodiazepines were ineffective. Only valproic acid was recommended as a preferred next option. No consensus could be reached on the use of fosphenytoin or phenytoin for the treatment of convulsive status epilepticus, with these agents rated as preferred choices by seven of 13 physicians and one of five parents and as non-preferred choices by four of 13 physicians and four of five parents. The remainder of respondents indicated they were unsure or neutral about their use. Levetiracetam was considered a preferred option by nine of 13 physicians and one of five parents, with the remainder of parents indicating that they were unsure or neutral regarding its use.

Comorbidities

A summary of consensus of the expert panel on comorbidities is given in Table 4.

Development and gait

There was strong consensus regarding the need for a formal developmental assessment just before starting school. Children should also be screened periodically at clinic visits for gait disorders, starting in early childhood.

Although the group acknowledged that sleep problems, dysautonomia, constipation, and dysmotility may be seen in Dravet syndrome, the exact prevalence of these symptoms is not known, and referral is indicated only if there are clinical concerns.

Seizure detection devices and SUDEP risk reduction

Although the group acknowledged that seizure detection devices may help reduce the risk of SUDEP, rigorous

TABLE 4.
Comorbidities: Summary of Consensus of Expert Panel

	AAN Class of Evidence	Finding	Strength of Agreement
Developmental and behavioral concerns			
Screening	IV[9,11,23]	The neurologist/epileptologist should routinely survey development and behavior at clinic visits*	Strong
		Children should undergo formal developmental or cognitive assessment before starting school. Earlier referral may be indicated if there are clinical concerns about development	Strong
		Children should be assessed by speech, physiotherapy, and occupational therapy before school entry	Strong
Intervention	NA	Subspecialty referral to a behavior specialist or psychiatrist is only indicated if there are clinical concerns*	Strong
		Early enrichment is helpful for children with Dravet syndrome, even before delays are evident	Moderate
		Risperidone and/or stimulants may be helpful for behavior and attention problems but clear data for efficacy are lacking*	Moderate
Gait and orthopedic concerns			
Screening and intervention	III[11,72-74]	Ataxia and crouch gait are typically present by early adolescence and may appear earlier. Screening for gait disorders should be routinely performed at clinic visits starting in early childhood	Strong
		If gait abnormalities are detected, referral to physiotherapy should be made	Strong
Sleep concerns			
Screening and intervention	IV[11,75]	Sleep disorders are commonly reported in Dravet syndrome, and sleep should be routinely queried at clinic visits, starting in early childhood	Strong
		There was no consensus regarding which specific sleep disorders were most prevalent in Dravet syndrome	No consensus
		Formal assessment by a sleep medicine specialist and/or polysomnography is only indicated if there are identified sleep concerns*	Strong
		Melatonin is at least somewhat beneficial for insomnia or recurrent awakenings*	Strong
Gastrointestinal concerns			
Incidence	IV[11]	Constipation and dysmotility may be seen but the exact prevalence is not known	Strong
Endocrine concerns			
Incidence and management	NA	There was no consensus regarding the type(s) or prevalence of endocrine problems in Dravet syndrome	No consensus
		Although there was no consensus on how often women with Dravet syndrome experience catamenial provocation of seizures, oral contraceptives or progesterone implants/intrauterine devices may be considered in such cases*	Modest
Dysautonomia			
Incidence and management	IV[11]	Symptoms of dysautonomia, including dizziness, syncope, hypertension, abnormal flushing, and cool extremities, may be seen, but their incidence is not known	Strong
		There is no consensus regarding the role of further investigations or pharmacologic management for such symptoms	No consensus
Cardiac concerns			
Screening and management	NA	There is no consensus regarding the need for routine ECG screening in Dravet syndrome	No consensus
		Referral to cardiology is indicated only if there are clinical concerns*	Strong
SUDEP risk reduction and seizure detection			
Efficacy of devices	NA[76,77]	Although seizure detection devices may reduce the risk of SUDEP, rigorous scientific evidence for such a claim is lacking*	Strong
Recommended strategies for seizure detection	NA	The use of a baby monitor at night is recommended	Strong
		There was no consensus for recommendation of the following: Bedsharing† Room sharing† Seizure lattice pillows Seizure detection devices other than baby monitors† Oxygen saturation monitors†	No consensus
Benefits of seizure detection devices	IV[76,77]	Alerts caregivers to a seizure so rescue medication can be given*	Strong
		Improved sleep and quality of life for caregivers*	Moderate
Drawbacks of seizure detection devices	IV[76,78]	False-positive alarms resulting in sleep disruption*	Strong
		False negatives with failure to detect actual seizures*	Strong
		Cost to family, as insurance often does not cover these devices*	Strong
Home oxygen	NA	There was no consensus for the use of home oxygen	No consensus

(*continued on next page*)

TABLE 4. (*continued*)

	AAN Class of Evidence	Finding	Strength of Agreement
Home care and family support			
Indications for home care	IV[11,36,79,80]	Home care may be required for the following situations, although a caregiver other than a nurse can likely provide this service*:	
		Patients with inadequate parent or caregiver support	Strong
		Patients with gait problems at high risk of falls	Strong
		Patients with severe behavior and/or sleep problems	Strong
		Patients with frequent convulsive seizures	Moderate
Social work	II[11,36,79,80]	A social worker with expertise in children and/or adults with neurological disabilities should be available for consultation to families*	Strong
Family support groups	II[11,36,79,80]	Dravet syndrome-specific organizations and web sites (Dravet Syndrome Foundation, Dravet.ca) are excellent resources for families	Strong
Dravet clinic	NA	The following personnel are essential members of the Dravet Clinic Team:	Strong
		Epileptologist or neurologist with expertise in Dravet syndrome	
		Epilepsy nurse	
		Social worker	
		The following personnel should be readily accessible to the team:	Strong
		Geneticist or genetic counselor	
		Dietician with expertise in ketogenic diet	
		Sleep medicine physician	
		Pharmacist	
		Physiotherapist, occupational therapist, and speech therapist	
		Access to the following individuals is strongly recommended:	Strong
		Psychologist/psychiatrist	
		Developmental pediatrician	
		Cardiologist	
		Gastroenterologist	
		Endocrinologist	
		Orthopedic surgeon or physiatrist	

Abbreviations:
AAN = American Academy of Neurology
ECG = Electrocardiography
NA = Not available
SUDEP = Sudden unexpected death in epilepsy

* Standard of care for all persons with epilepsy, not unique to Dravet syndrome.
† When physician responses were excluded, *strong consensus* was obtained from families.

scientific evidence for such a claim is lacking. Consensus was reached for the use of baby monitors, as well as benefits and drawbacks of seizure detection devices.

Home care and family support

Consensus was reached regarding indications for home care, recommended resources for families, and essential and recommended components of the Dravet Clinic Team.

Discussion

Dravet syndrome is among the most challenging of epilepsy syndromes. The medically intractable seizures, recurrent status epilepticus, increased mortality rate, and multiple comorbidities, including intellectual disability and behavioral problems, profoundly affect the quality of life both for the affected child and his or her family.

There are limited data to guide diagnosis and management in the literature. In the absence of high-quality evidence, particularly for rare diseases such as Dravet syndrome, expert opinion is often relied upon. The Delphi approach is a systematic method for compiling experience-based opinion from a group of experts.[16] This process permits the identification of areas for which there is strong consensus, as well as areas for which consensus cannot be reached. Although the consensus opinions derived from such a process should ultimately be subject to rigorous study, these opinions can provide a basis to inform practice. Utilizing this process, we were able to identify specific areas for which panelists achieved consensus regarding the diagnosis, management of seizures, and assessment and management of comorbidities.

Diagnosis

Despite a fairly classic presentation, typically with recurrent, prolonged, hemiconvulsive seizures, a definitive diagnosis of Dravet syndrome is often delayed. A multicenter US study documented a median time from seizure onset until definitive diagnosis of Dravet syndrome of 4.8 years.[13] This delay may in part reflect that, although Dravet syndrome remains a useful clinical term, it can be difficult to use when discussing etiology and prognosis, particularly in young children. The etiology is challenging because *SCN1A* mutations cause 80% or more of the patients, with the cause in the remaining individuals having either other genetic abnormalities or no known defect.[3,81] Data on the clinical significance of *SCN1A* variants demonstrate that not all *SCN1A* changes impair function and not all children with a functionally significant *SCN1A* variant will necessarily have the severe features of Dravet syndrome.[82]

However, early diagnosis of Dravet syndrome is critically important to (1) choose the best available treatments and avoid exacerbating medications, (2) to eliminate the need

for further costly and invasive testing, and prevent attempts at futile therapies such as resective epilepsy surgery, and (3) to provide to the family a clear explanation for what has caused their loved one's serious medical condition and an understanding of what the future may hold.

This consensus process identified the characteristic clinical features that, when present in combination early in the course, are highly suggestive of Dravet syndrome. In addition, we identified features that should suggest this possible diagnosis in an older individual, who remains undiagnosed and for whom the characteristic early history is not available. We hope that elucidation of these features will reduce the rates of misdiagnoses of other early-life epilepsies and lesional focal epilepsy.

There was strong consensus that genetic testing should be performed for all individuals with suspected Dravet syndrome. Although either *SCN1A* specific testing or an epilepsy gene panel is appropriate for individuals with typical clinical findings, an epilepsy gene panel is preferred for individuals with atypical manifestations. The panel reached consensus that genetic testing should be done in developmentally normal infants who present with recurrent, prolonged febrile convulsions of unknown etiology, with the notable exception of individuals in which the seizures are consistently generalized, where no consensus was obtained. This is surprising, given a 2013 report from the Genetics Commission of the International League Against Epilepsy recommending that "*SCN1A* testing should be considered in people with possible Dravet syndrome where the typical initial presentation is of a developmentally normal infant presenting with recurrent, febrile or afebrile prolonged, hemiclonic seizures or generalized status epilepticus."[5] The expert panel in the current study also recommended genetic testing for a child aged 12-35 months with normal early development, no known seizure etiology, and myoclonic and/or atypical absence seizures refractory to one or more antiepileptic drugs, if they have a history of either one or more prolonged febrile seizures or recurrent brief febrile seizures before 18 months, and for nondysmorphic teens and adults with pharmacoresistant focal and/or generalized seizures of unknown cause, in whom an early-life history is not available. We note that genetic testing technologies are evolving rapidly, and the distinction between single gene and epilepsy panel testing may be moot in the near future. It is likely that genetic testing will become much more broadly used in the early evaluation of children with early-life epilepsies.

Treatment of seizures

Complete seizure control is typically not achievable in Dravet syndrome.[6] Panelists strongly endorsed that the highest priority should focus on avoiding prolonged convulsive seizures and obtundation status given their morbidity and impact on developmental outcome.[37] Seizure burden is highly variable, and optimal control should be individualized and is a balance between a reduction in seizure severity and frequency and minimizing treatment-related adverse effects. The ultimate goals are safety for the patient and maximizing developmental potential and quality of life. Certain triggers may exacerbate seizures in Dravet syndrome,[7,8] and although panelists strongly concurred that addressing known seizure triggers has benefit, there is no strategy that is effective at seizure prevention in most patients. Despite the somewhat limited evidence, our panel of experts reached strong consensus regarding first- and second-line prophylactic therapies, including the role of the ketogenic diet and medications that should be avoided because of high risk of seizure exacerbation.

The literature is much more limited on the role of surgical intervention for Dravet syndrome.[57,61-66,83,84] There was strong consensus that there is no role for resective surgery in Dravet syndrome. Palliative approaches, specifically stimulators and callosotomy, may have a minor role but only after all other options have been exhausted.

There has been much excitement in the lay press regarding the potential benefit of medical marijuana.[67,68] Half of our panelists had adequate expertise with the use of this product and noted moderate efficacy. The results from a randomized controlled trial of purified cannabidiol in children with Dravet syndrome have been published in abstract form.[85]

The literature clearly documents a high risk of recurrent, prolonged convulsive seizures, especially early in life.[18] Panelists strongly endorsed the need for home rescue medication and a clear seizure plan for all patients. Rescue medications recommended are similar to what is used in other types of epilepsy (rectal diazepam for very young children or buccal or nasal midazolam at any age).[86] However, given the risk of status epilepticus, panelists strongly endorsed that rescue medication be given at seizure onset, rather than after three to five minutes, in those with a history of convulsive seizures that are typically prolonged.

The literature on the in-hospital management of status epilepticus in Dravet syndrome is exceedingly sparse.[14,50] Our panelists strongly agreed on first-line (benzodiazepine) and second-line therapies (valproic acid), but no consensus was reached regarding other options. Phenytoin and fosphenytoin are generally used early in the course in convulsive status epilepticus; however, the benefit of these agents, specifically in patients with Dravet syndrome, is debated, given their action on sodium channels and thus potential worsening of seizures. Our panel did not reach consensus on this topic, and further prospective studies are required to clarify the optimal in-hospital management of convulsive status epilepticus in patients with Dravet syndrome.

Comorbidities

Within the Dravet community, concerns regarding sleep, dysautonomia, and gastrointestinal, cardiac, and endocrine concerns are common, a finding that was endorsed by our panel. However, no study has carefully assessed the exact nature and prevalence of such concerns, and further research in this area is warranted. As is the case for many patients with medically intractable epilepsy, comprehensive care of a patient with Dravet syndrome must involve screening for and managing comorbidities, as well as treatment of seizures. Routine questions regarding the development, behavior, and gait concerns should be a part of the functional inquiry, starting at diagnosis. More formal developmental assessment before school entry can help in documenting areas that may require additional services and therapies to maximize their educational experience.

Patients with Dravet syndrome have a high rate of SUDEP, noted at 9.32 per 1000 person-years in one study,[12] similar to rates seen in adults with drug-resistant epilepsy.[87] A seizure monitor device is used at night by many families, in the hopes that seizures may be detected earlier and SUDEP risk reduced. Although our panel acknowledged the benefit of such devices on early recognition of seizures and more timely administration of rescue medication, as well as improved sleep and quality of life for caregivers, they noted that rigorous scientific evidence of reduced SUDEP risk is lacking. Although there are many devices on the market, baby monitors were the only devices routinely endorsed by most of the panel.

The medical care of an individual with Dravet syndrome is a team effort, with core team members including an epileptologist or neurologist with particular expertise in Dravet syndrome, an epilepsy clinic nurse, and a social worker with expertise in children or adults with neurological disabilities. Access to other providers who can assist with diagnosis (geneticist or genetics counselor), treatment (pharmacist, dietician with ketogenic diet expertise), or diagnosis and management of comorbidities (psychologist or developmental pediatrician; physical, occupational, and speech therapists; sleep medicine physician; cardiologist; gastroenterologist; endocrinologist; and physiatrist) is highly recommended.

Given the high seizure burden and associated comorbidities, many patients with Dravet syndrome require 24 hour supervision, and thus additional family support and home care may be required, particularly in the presence of frequent convulsive seizures, gait problems with high risk of falls, and significant behavioral or sleep problems.

Furthermore, having a child with severe epilepsy, intellectual disability, and other comorbidities can result in tremendous anxiety, social isolation, and poor quality of life for families. Referral to lay organizations such as the Dravet Syndrome Foundation (http://dravetfoundation.org) and Dravet Canada (http://dravet.ca) allows families to connect to other parents facing similar struggles and provides both increased knowledge and support. Furthermore, such organizations enhance the development of partnerships between families and researchers to identify patient-centered goals, and conduct multicenter research, which is essential to make progress in the treatment of rare disorders.

This project is unique in that an expert panel including both epileptologists and parents or caregivers utilized a modified Delphi method to develop recommendations for early, accurate diagnosis, optimal treatment of seizures, and screening for and management of comorbidities. This method was used previously in West syndrome.[88] We were able to identify areas where there was strong consensus and other areas where consensus could not be reached and further research is needed. This type of effort provides useful information to guide practice where knowledge gaps in the medical literature exist. This technique may be useful in the future for other rare diseases for which traditional research methods require multicenter collaboration because of small numbers of children presenting at any single center.

This project has several limitations. First, these recommendations are developed by expert consensus, as evidence in the medical literature is often lacking. They provide an initial starting point based on considerable experience and a process designed to identify areas of clear consensus. The recommendations are not “evidence based” but can and should be evaluated in future studies to determine their accuracy and assess whether their use affords earlier diagnosis and improved outcome for patients with Dravet syndrome. Furthermore, areas lacking consensus could be evaluated in future research. Second, the expert panel included only providers and families from North America and therefore may not reflect the care and needs of children with Dravet syndrome living in other regions of the world.

It is our hope that these standards will (1) inform health care providers on the optimal diagnosis and management of patients with Dravet syndrome, (2) support reimbursement from insurance companies for genetic testing and Dravet syndrome-specific therapies, and (3) improve the quality of life for patients with Dravet syndrome and their families by avoidance of unnecessary testing and provision of an early accurate diagnosis allowing optimal selection of therapeutic strategies.

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*Article also included in literature review sent to panelists.

SUPPLEMENTARY TABLE 1.
Panelist Data

Panelist	Affiliation	Area of Expertise	ABPN[1] or RCPSC[2] Certification	Epilepsy Organization Advisory Board Member	Member of PERC[3] or CPEN[4]	Prior Publications on Dravet Syndrome
Core panel: physicians						
Elizabeth Donner, MD	Associate Professor of Pediatrics, University of Toronto	Pediatric Epileptologist, Director, Comprehensive Epilepsy Program, Hospital for Sick Children, Toronto	RCPSC	SUDEP Aware	CPEN	0
Kelly Knupp, MD	Associate Professor of Pediatrics and Neurology, University of Colorado	Pediatric Epileptologist and Director of Dravet Syndrome Program, Children's Hospital Colorado	ABPN	DSF Medical Advisory Board	PERC—cofounder and steering committee member	2
Linda Laux, MD	Assistant Professor of Pediatrics, Northwestern University Feinberg School of Medicine	Pediatric Epileptologist	ABPN	DSF Medical Advisory Board		8
Ian Miller, MD	Director of Neuroinformatics and Medical Director of the Comprehensive Epilepsy Program, Nicklaus Children's Hospital	Pediatric Epileptologist	ABPN	DSF Medical Advisory Board		2
Joseph Sullivan, MD	Associate Professor of Neurology and Pediatrics, University of California, San Francisco	Pediatric Epileptologist	ABPN	DSF Medical Advisory Board	PERC—steering committee member	3
Elaine Wirrell, MD	Professor of Neurology, Mayo Clinic	Pediatric Epileptologist and Director of Pediatric Epilepsy, Mayo Clinic	RCPSC	DSF Medical Advisory Board	PERC—cofounder	11
Core panel: family members/ caregivers						
Mary Anne Meskis	Executive Director of Dravet Syndrome Foundation	Parent of child with Dravet syndrome				0
Michelle Welborn, PharmD	President and Founder, Intractable Childhood Epilepsy Alliance	Parent of child with Dravet syndrome				0
Extended expert panel: physicians						
Danielle Andrade, MD	Associate Professor, University of Toronto	Adult Epileptologist, Medical Director of Epilepsy at Toronto Western Hospital, Director of Epilepsy Genetics Program and Epilepsy Transition Program	RCPSC	No	No	7
Peter Camfield, MD	Professor Emeritus, Dalhousie University	Pediatric Epileptologist, Former Chair of Pediatrics, IWK Health Centre and Dalhousie University	RCPSC	Advisory Board, Epilepsy Nova Scotia	CPEN	8
Mary Connolly, MD	Clinical Professor of Pediatrics, University of British Columbia	Pediatric Epileptologist, Chair of Pediatric Neurology and Director of Epilepsy, BC Children's Hospital	RCPSC	Advisory Board, BC Epilepsy Society	CPEN cochair	2
Dennis Dlugos, MD	Professor of Neurology and Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania	Pediatric Epileptologist and Director of Clinical Neurophysiology and Epilepsy, Children's Hospital of Pennsylvania	ABPN	Scientific Advisory Board member, Dravet Syndrome Foundation	PERC	2

(*continued on next page*)

SUPPLEMENTARY TABLE 1. (*continued*)

Panelist	Affiliation	Area of Expertise	ABPN[1] or RCPSC[2] Certification	Epilepsy Organization Advisory Board Member	Member of PERC[3] or CPEN[4]	Prior Publications on Dravet Syndrome
Anne Lortie, MD	Associate Clinical Professor of Neurology and Pediatrics, University of Montreal	Pediatric Epileptologist, CHU Sainte-Justine	RCPSC			0
Phillip Pearl, MD	William G Lennox Chair and Professor of Neurology, Harvard Medical School	Pediatric Epileptologist and Director of Epilepsy and Clinical Neurophysiology, Boston Children's Hospital	ABPN			2
Russ Saneto, DO, PhD	Professor of Neurology and Adjunct Professor of Pediatrics, Seattle Children's Hospital and University of Washington	Pediatric Epileptologist, Neurometabolic-Neurogenetics Disorders. Head of Mitochondrial Medicine, Seattle Children's Hospital	ABPN	Scientific Advisory Member, Northwest Epilepsy Foundation	PERC	3
Extended expert panel: family members/ caregivers						
Patti Bryant	Chair, Dravet.ca Former Director and Treasurer for Dravet.org Vice President Epilepsy Newfoundland and Labrador Director, Canadian Organization for Rare Disorders	Parent of child with Dravet syndrome				0
Karina Fischer	Research library coordinator for Dravet Syndrome Foundation	Parent of child with Dravet syndrome BA in Education and Education Management				2
Nicole Villas	Dravet Syndrome Foundation Board Member	Parent of child with Dravet syndrome MEd				0

SUPPLEMENTARY TABLE 2.
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