

## Interdisciplinary Management

Dravet syndrome is considered one of the catastrophic pediatric epilepsy syndromes. It is highly resistant to treatment and seizures persist into adulthood. Poor cognitive development, global delays, behavior problems with hyperactivity, and autistic traits are common.<sup>3,4</sup> Psychosis has also been reported.

Developmental assessments should begin as early as possible and should be repeated regularly. Ideally, children with Dravet syndrome should be followed by a neurodevelopmental psychologist or pediatrician.

Early implementation of global therapies is essential to support optimal development. Children with Dravet syndrome should receive physical, occupational, speech, and social/play therapies and an enriched environment is encouraged.<sup>24</sup>

A number of co-morbid conditions appear to be commonly associated with Dravet syndrome and are currently under further investigation.<sup>25,26,27</sup> Preliminary data suggests that children with Dravet syndrome may be at increased risk for:

- Orthopedic conditions, including but not limited to, pes planus/pes valgus foot deformities, neurogenic scoliosis and crouch gait<sup>25,26</sup>
- Chronic upper respiratory infections and otitis media<sup>25</sup>
- Low humoral immunity
- Sensory integration disorders and other autism spectrum characteristics<sup>4,25</sup>
- Growth and nutrition issues
- Dysautonomia, including difficulty with temperature regulation, decreased sweating, intermittent tachycardia and slowed GI motility<sup>27</sup>

### Improve the Outcome

Implement early intervention therapies, enriched environment, and developmental assessments to help ensure patient reaches optimal potential.

Monitor for comorbid conditions.

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Dravet.org is the foremost global patient advocate organization for Dravet Spectrum Disorders, providing:

- Promotion and funding of medical research to find effective treatment and cure;
- medical updates and education enabling patients to get effective testing and treatments;
- patient advocacy and compliance assistance counseling;
- financial assistance for medication reimbursement;
- family networking, emotional support and hope; and
- resources to empower parents to provide a lifetime of care for their child.

Dravet.org recognized the mutual benefits of partnering with researchers, doctors, physician assistants, nurses, pharmaceutical companies, and the entire medical industry. It is our goal to further all understanding and treatment of Dravet Spectrum Disorders.

helping the **PATIENT**  
while finding the **CURE**



(formerly known as the IDEA League)

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Dravet Syndrome  
Improve the Outcome

an guide for physicians

## Introduction

Dravet syndrome, also referred to as Severe Myoclonic Epilepsy of Infancy (SMEI), is a catastrophic epileptic encephalopathy that begins in the first year of life in previously healthy children.<sup>1</sup> It was first described by Charlotte Dravet in 1978 and has been recognized as a syndrome by the International League Against Epilepsy since 1989.<sup>2</sup> Initial symptoms typically include prolonged, febrile, clonic or unilateral convulsions, which may progress to frequent status epilepticus.<sup>2,3,4</sup> Later on, seizures occur without fever. Between the ages of 12 and 48 months, other seizure types emerge, commonly myoclonic, partial and atypical absence.<sup>2,4,5</sup> Progressive slowing of psychomotor development, which may include regression of acquired skills, also becomes apparent during this timeframe.<sup>3</sup> Initial EEGs are usually normal, but generalized and multifocal spikes and spike-wave discharges later appear.<sup>2</sup> Photosensitivity is observed in about 42% of patients, though it is often transient.<sup>3</sup> Other neurologic signs, such as ataxia, may also appear.<sup>4,6</sup> The mortality rate is estimated at 16%<sup>2,6</sup> and is usually attributed to accident, complications of a seizure, or sudden unexplained death in epilepsy (SUDEP).<sup>6</sup>

## Epidemiology

Dravet syndrome is a rare disorder. Initial estimates from the 1990's place the incidence at one per 40,000<sup>7</sup> and one per 20,000<sup>8</sup>, representing 3% to 5% of all severe epilepsies beginning in the first year of life. However, given improved recognition of this disorder, new epidemiologic studies are needed to confirm these numbers.

## Genetics

SCN1A is currently the most clinically relevant gene known to cause epilepsy.<sup>5,9</sup> Mutations in the  $\alpha$ 1-subunit of this neuronal voltage-gated sodium channel gene are associated with a variety of phenotypes, including SMEI, SME Borderline (SMEB), Intractable Childhood Epilepsy with Generalized Tonic-clonic Seizures (ICEGTC) and Generalized Epilepsy with Febrile Seizures Plus (GEFS+).<sup>5,9,10,11</sup> Research continues to expand the phenotypic variability and it has been suggested that Dravet syndrome is the severe form of a broader clinical spectrum.<sup>5,11,12</sup> Mutations in SCN1A contribute to up to 80% of reported cases of Dravet syndrome,<sup>2,5,9</sup> according

to one large study, a higher rate than any other phenotype.<sup>5</sup> Of the many SCN1A mutations described in patients with Dravet syndrome, the majority arise de novo<sup>5,9,14</sup> and at least 50% are of a type (frameshift, nonsense, insertion, deletion) predicted to result in protein truncation with haploinsufficiency.<sup>1,5,15,16</sup> Relating genotype to phenotype has proven challenging. While truncating mutations occur almost exclusively in SMEI, missense mutations have been detected in both mild and severe phenotypes.<sup>10,12,13,16,17</sup> Microdeletions on chromosome 2q involving SCN1A are another cause of Dravet syndrome, and are easily missed by standard DNA sequencing techniques.<sup>14</sup> Modifying genes and environmental factors likely play an important role in clinical outcome.<sup>13,15,16,17</sup> Research is ongoing to identify additional factors that contribute to the severity of the Dravet syndrome phenotype.

## Differential Diagnosis

As the initial seizures are often associated with fever, distinction from benign febrile convulsions is important. In Dravet syndrome: (1) the seizure type is frequently clonic or hemi-clonic rather than generalized tonic-clonic; (2) the seizures are more prolonged and frequent, even when treated; and (3) hyperthermia is a triggering factor even when temperature is moderate.<sup>3,6</sup> The diagnosis is confirmed when other seizure types emerge. EEG, CT, MRI and metabolic studies are usually normal initially. EEG pattern, age of onset and initial seizure semiology distinguish SMEI from Lennox-Gastaut syndrome.<sup>3,6,18</sup> Myoclonic-Astatic Epilepsy (MAE) may be more difficult to distinguish early in the course of the disease.<sup>3,6</sup> The course of other sodium channelopathies such as GEFS+ and ICEGTC is similar to that of SMEI prior to the onset of multiple seizure types and developmental decline.<sup>8,10</sup> A majority of cases of Dravet syndrome will test positive for an SCN1A gene mutation, making testing a useful diagnostic tool. However, a negative test does not preclude the diagnosis, which should be made clinically.

## Improve the Outcome

*When an infant presents with more than one prolonged febrile seizure during the first year of life, ordering SCN1A gene testing will help confirm diagnosis of Dravet syndrome and aid in optimizing treatment.*

## Treatment

**Avoid** medications which may aggravate seizures in Dravet syndrome. These include:

**lamotrigine**<sup>6,19</sup> (Lamictal®)  
**phenytoin**\* (Dilantin®, Epanutin®)  
**fosphenytoin**\* (Cerebyx®, Prodilantin®)  
**carbamazepine**<sup>6,19</sup> (Tegretol®, Biston®, Calepsin®, Carbatrol®, Eptol®, Finlepsin®, Telesmin®, Timonil®)  
**oxcarbazepine** (Trileptal®)  
**vigabatrin** (Sabril®, Sabrilan®, Sabrilix®)

\*These drugs may be useful acutely in managing status episodes but are not generally helpful in chronic seizure management

**Refrain** from epilepsy surgery as SMEI is a diffuse epileptic process without identifiable focal abnormality.<sup>1</sup>

**Employ** treatments shown to be useful for chronic seizure management in Dravet syndrome based on scientific literature. These include:

**topiramate** (Topamax®)—decreases status episodes, partial and generalized seizures.<sup>1,6</sup>  
**divalproex sodium** and derivatives (Depakote®, Depakene®, Epilim®, Epival®, Micropakine®, Valcote®)—decreases status episodes, partial and generalized seizures, maybe absence.<sup>1,6</sup>  
**stiripentol** (Diacomit®)—decreases status episodes when used with valproic acid and clobazam or clonazepam; increases drug levels of several anti-epileptic drugs, which improves efficacy of these drugs.<sup>19,20</sup> *Important: Decreases in other AEDs of up to 50% may be required to avoid adverse effects.* Stiripentol is the only AED that is indicated for Dravet syndrome. It was approved in 2006 by the European Medical Association with the following indication: "Diacomit® is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate." Stiripentol has been designated as an Orphan Drug by the USFDA.  
**clonazepam** (Klonopin®, Rivotril®)—decreases myoclonic, generalized or partial seizures and possibly absence seizures.<sup>19</sup>  
**clobazam** (Frisium®, Urbanyl®)—decreases myoclonic, generalized or partial seizures as well as absence

seizures;<sup>19,20</sup> is less sedating and may have greater antiepileptic capacity than other benzodiazepines. Clobazam has been designated as an Orphan Drug by the USFDA.

**leviteracetam** (Keppra®)—decreases GTC, partial, myoclonic and absence seizures.<sup>21</sup>  
**bromides**—decreases GTC seizures.<sup>3,22</sup>  
**ketogenic diet**—improves overall seizure control.<sup>23</sup>

Please visit the IDEA League's online professional forum for dosing recommendations from our Professional Advisory Board as well information on importing these medications.

**Consider** treatments which may be helpful in Dravet syndrome, but which require further study. These include:

**vitamin B6 therapy**  
**IVIg therapy**  
**ethosuximide** (Zarontin®)  
**zonisamide** (Zonegran, Excegran®)  
**vagus nerve stimulation** (VNS)

**Implement** an aggressive acute seizure management protocol and encourage parents to adhere to it.<sup>1</sup> The protocol should include a fast-onset benzodiazepine (diazepam, midazolam, nasal versed, buccal lorazepam) or paraldehyde for any convulsive seizure lasting longer than five minutes, and instructions for when to call for emergency dispatch, as well as when to transport to a medical facility. Written hospital seizure protocols should also be determined and are beneficial for patients to have with them at all times.

**Instruct** parents to manage the syndrome on a day-to-day basis by avoiding seizure triggers. Common triggers in Dravet syndrome include mild to moderate hyperthermia (as from fever, exertion, environmental conditions, or warm baths), illness, stress, flickering lights, and patterns.<sup>8</sup> Prevent fevers as able; treat them immediately and appropriately as they occur.<sup>1</sup>

## Improve the Outcome

*Employ treatment regimens that have proven efficacy. Develop and implement seizure management protocols. Instruct parents to avoid seizure triggers and to manage the syndrome acutely.*