



What is Dravet syndrome?

Dravet syndrome is a distinctive epilepsy syndrome that presents in the first year of life with a reported incidence of 1:15,700[1]. Early clinical presentation of Dravet syndrome is unique, with onset of recurrent, convulsive seizures, which are often prolonged and triggered by fever, in a developmentally normal infant with normal MRI and nonspecific EEG findings.

In addition to refractory seizures, the few studies that assess long-term outcome also show emergence of other comorbidities including, but not limited to:

- Intellectual disability
- Motor defects and gait issues
- Language impairment
- Sleep disorders
- Dependence in adulthood [2,3]

Furthermore, persons with Dravet syndrome have significantly higher premature mortality due to status epilepticus, accidents, and sudden death in epilepsy (SUDEP), estimated at 15-20% [2,3,4,5,6].

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 seizures over 5 minutes as well as obtundation status are believed to have a significant impact on developmental outcome[6].

Physicians with questions can email info@dravetfoundation.org to be placed in contact with a member of DSF Medical Advisory Board.

After Diagnosis, Patients Should be Given Information on:

- Genetic counseling
- Risk & management of prolonged seizures
- Expected seizure control
- Risk of SUDEP & seizure-related accidents
- Developmental outcomes & expectations
- Social workers & other patient resources
- Dravet syndrome support groups
- Home care & family
- Support needs
- Reducing seizure triggers
- Reproductive implications

Best Practices:

- Let patient get adequate sleep
- Avoid high ambient temperatures; use cooling vest
- Avoid high temperature baths
- Use prophylactic antipyretics and/or benzodiazepines with vaccination and illness
- Use sunglasses and/or avoid flashing lights

Effective Multidisciplinary Teams include:

- Neurologist or epileptologist with expertise in Dravet syndrome
- Epilepsy nurse and a social worker with expertise in neurological disabilities
- Geneticist or genetic counselor
- Dietitian with ketogenic diet expertise
- Physiotherapist
- Occupational and Speech Therapist
- Sleep Medicine Specialist



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Could it be Dravet?

www.DravetFoundation.org



Mutations in the *SCN1A* gene are found in as many as 85% of patients clinically diagnosed with Dravet syndrome[7]. *SCN1A* mutations may also be found in less severe epilepsy types, such as generalized epilepsy with febrile seizures plus (GEFS+), and more severe forms of epilepsy such as migrating focal seizures[8], therefore careful clinical correlations are needed[9].

Genetic testing should be considered for all patients with a clinical picture suggestive of DS. While simple *SCN1A* sequencing is appropriate when all clinical criteria are met, an epilepsy gene panel may be preferable for infants, when clinical history is less distinct, or when atypical features are present.

Benefits of Early Diagnosis

Specialists experienced with Dravet syndrome believe that earlier diagnosis has the potential to improve long-term outcome for patients with improved seizure control and possible improved cognition. At the very least, earlier genetic testing and diagnosis helps avoid the negative consequences of treatment with contraindicated medications such as sodium channel blockers that exacerbate seizures, as well as unnecessary, costly and, at times, invasive testing. A recent multicenter study in the US documented that the diagnosis of Dravet syndrome is often made nearly 5 years after seizure onset[10].

Misdiagnosis

Common misdiagnoses include Myoclonic Atonic Epilepsy (Doose syndrome), Lennox-Gastaut syndrome, Myoclonic Epilepsy in Infancy, PCDH19-associated epilepsy, and generalized epilepsy with febrile seizures plus (GEFS+).

Initial presentation includes:

- Typical seizure onset between 1-18 months
- Recurrent generalized tonic-clonic or hemiclonic seizures which are mandatory for diagnosis. These are often prolonged, but may be shorter
- Myoclonic seizures may later emerge, typically by age 2. Obtundation status, focal dyscognitive seizures and atypical absences are also typical but usually occur after age 2 years. Typical absences and epileptic spasms are atypical
- Hyperthermia, which may be associated with vaccination or illness, triggers seizures in the *majority* of patients; other triggers may include flashing lights, visual patterns, bathing, changes in temperature, eating and overexertion
- Normal development and neurological examination at onset
- Normal MRI and nonspecific EEG findings at onset

Presentation in older children and adults:

In the absence of the early, characteristic history, the following features are characteristics of Dravet syndrome at any age

- Persisting seizures, which include focal and/or generalized convulsive seizures, and, in many cases, myoclonic, focal, atypical absence and tonic seizures. 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 may become less problematic in adolescence and adulthood
- Seizure exacerbation with the use of sodium channel agents
- Intellectual disability which is typically evident by 18-60 months of age
- Abnormalities on neurological examination which are typically evident by age 3-4 years and include crouched gait, hypotonia, incoordination and impaired dexterity
- An MRI which is typically normal, but may show mild generalized atrophy and/or hippocampal sclerosis

Maintenance Antiepileptic Medications

First Line	clobazam (Onfi, Frisium, Urbanyl) and valproic acid (Depakote, Depakene, Epilim, Epival)
Second Line	stiripentol [†] (Diacomit), topiramate (Topamax), ketogenic diet (positive effect on cognition)
Third Line	clonazepam (Klonopin, Rivotril), levetiracetam (Keppra), VNS zonisamide (Zonegran), ethosuximide (Zarontin-atypical absence)
 Contraindicated	carbamazepine (Tegretol, Celespin, Cargagen), oxcarbazepine (Trileptal), lamotrigine (Lamictal), phenytoin ^{††} (Dilantin, Epanutin), and vigabatrin (Sabril, Sabrilan, Sabrilex)

[†] In combination with valproic acid and clobazam. Stiripentol currently has Orphan Drug Status classification in the US, but not full FDA-approval, which can make insurance coverage difficult. Importation of stiripentol requires documentation of medical necessity. ^{††} Phenytoin and Fosphenytoin, while not recommended for daily use, are often used in emergency treatment of prolonged seizures with varying success in patients with Dravet syndrome. Caution is advised.

Emergency Medications

At Home: Rectal diazepam or buccal/nasal midazolam for young patients; buccal/nasal midazolam for older patients. To be administered within 3-5 minutes of seizure onset unless there is a recent history of prolonged convulsive seizures. In this case, medication should be given at seizure onset, with a second full dose 5-10 minutes after the initial dose.

In Hospital: Benzodiazepines as a first line therapy for a patient presenting at the hospital with an ongoing seizure. A second dose of benzodiazepine should be given if the seizure persists, particularly if the patient did not receive a dose of rescue medication at home. Valproic acid is a reasonable second line therapy, but specialists are not in agreement about subsequent treatment. Phenytoin and fosphenytoin, which are typically used in treating status epilepticus, are of debated usefulness due to their action on sodium channels.

