



# OVERVIEW OF DRAVET SYNDROME AND ITS RECENT TREATMENTS

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**Abstract:** In this paper brief introduction of Dravet Syndrome is Severe myoclonic epilepsy of infancy. It is early onset epilepsy syndrome. Dravet Syndrome show symptoms like severe developmental disabilities, Motor impairment, Speech impairment, Behavioral difficulties, Autism, Sleep abnormalities. Treatment of Dravet Syndrome in initial therapy clobazam, Valproic acid generally administered in combination. But some people who fails to react to this therapy the therapy one follow is of fenfuramide, tropiramide, Levetiracetam, bromides etc. as well as in conjugation with these the ketogenic diet also helps to manage the seizure. Some novel treatments include adjunctive therapy of Stiripentol and clobazam and Valproic acid etc. this paper discusses the in-vitro and in-vivo effect of Stiripentol and different aspects of the management of seizures.

**Keywords:** Dravet Syndrome (DS), Infants, Stiripentol, Ketogenic diet.

## Introduction and Background

Dravet Syndrome (Severe myoclonic epilepsy of infancy) discovered Charlotte Dravet in 1978 and then called as Dravet Syndrome in 1989 [1]. It's a rare form of early-onset epilepsy syndrome that manifests as intractable epilepsy and neurodevelopmental delays. It is a part of 8 epileptic encephalopathy syndromes, Reported by the International League through Epilepsy task force [1]. The 'Epileptic encephalopathy' is a term related to behavioral deterioration or regression together with cognitive decline due to epileptogenic activity during the brain maturation period [1]. The genetic basis of DS was coined in 2001 as a mutation in the alpha-1 subunit (SCN1A) gene on chromosome 2q24 [1].

DS evolves with age, neurodevelopmental delays leads to severe neurologic disability. During adulthood, it occurs as persistent motor and cognitive dysfunction [1]. There are many types of seizures are seen in Dravet syndrome includes convulsive, myoclonic, absence, focal, obtundation status and tonic seizures [1]. Motor system dysfunction occurs as ataxia, tremors, dysarthria, pyramidal, and extra pyramidal signs [1]. Most of the patients develop cognitive impairment, visual perception, and executive dysfunctions, along with language impairment [1]. Patients also seem to observe psychiatric disturbances such as aggressiveness, agitation, obsessiveness, and preservation [1]. Dravet syndrome patients have an increased mortality rate during infancy some them survive adulthood. Sudden unexpected death in epilepsy and status epilepticus is the common cause of death among DS patients.

Genetic alteration in SCN1A encodes the  $\alpha$ -subunit of the voltage-gated sodium channel [1]. While, DS is the primary phenotype in which a robust correlation with SCN1A defects has been confirmed [1]. 70–80% of the patients carry SCN1A abnormalities [1]. 700 mutations in the SCN1A gene that are associated with DS have so far been detected [1]. Most of them are de novo. Half of the patients with DS, appear to be associated with a more severe phenotype than missense mutations [1]. Micro chromosomal deletions consisting SCN1A or its promoter region are also determined in patients with DS [1]. Other genes potentially associated with DS or similar phenotypes include SCN1B, SCN2A and PCDH19. However, mutations in the former three occur rarely [1].

In Dravet syndrome, SCN1A mutations are caused in 70-80%. Haploinsufficiency is said to be the cause of the mechanism in most cases. Genetic modifiers and environmental factors probably contribute to the variable phenotype of patients with SCN1A mutations. Other genes involved in Dravet syndrome include SCN1B and GABRG2. PCDH19 and SCN2A mutations, and deletions involving the chromosome 2q SCN cluster have been reported in Dravet syndrome-like syndromes.[2]

### **Etiology**

The mutations were located on chromosome 2q24. De novo were more than 90% of these mutations while familial mutations like mis-sense in nature were located only in 5%-10% [3]. There are no identifiable mutations in SCN1A in about 20%-30% of patients with Dravet Syndrome. The different theory that has been stated in the pathophysiology of Dravet Syndrome is dysfunction of inhibitory neurons. SCN1A gene protein product has been the primary voltage-gated sodium channel of these inhibitory neurons [3].

### **Symptoms and Effects [4]**

- More than 90% of patients suffer from at least one non-seizure co morbidity, including:
  - Severe intellectual disabilities
  - Severe developmental disabilities
  - Motor impairment
  - Speech impairment
  - Behavioral difficulties
  - Autism
  - Sleep abnormalities

### **Effect of DS**

Dravet Syndrome developed during infancy and evolves with age, neurodevelopmental delays progress to severe neurologic disability. During adulthood, it manifests as persistent motor and cognitive dysfunction [5]. Various types of seizures have been seen in Dravet Syndrome which include convulsive, focal, absence, obtundation status, myoclonic, and tonic seizures [5]. Motor system dysfunction manifests as dysarthria, ataxia, pyramidal, tremors, and extrapyramidal signs [5]. Majority of the patients develop cognitive impairment, visual perception, and executive dysfunctions, along with language impairment [5]. Patients manifest psychiatric disturbances such as aggressiveness, agitation, obsessiveness, preservation, and hoarding behavior [5]. Dravet Syndrome patients have an increased mortality rate during infancy but some survive till sudden unexpected death in epilepsy and status epilepticus are the most common cause of death among Dravet Syndrome patients.

## Treatment of DS

### Initial Therapy

#### 1. Valproate

First-line management mainly involves either Valproic acid or clobazam. Valproic acid is a broad-spectrum agent with multiple possible mechanisms of action, including enhancement of GABAergic function, inhibition of voltage-sensitive sodium channels and antagonism of NMDA receptor-mediated neural excitation. There is very less literature is available on its use in DS treatment (level 4), and in retrospective studies<sup>14,15</sup> responder rates (>50% reduction in seizure frequency) were 22.2-48%. Valproic acid has the potential for some severe adverse effects, including hepatotoxicity, hyperammonemia, pancreatitis and thrombocytopenia. Other adverse effects such as decreased or increased appetite, hair loss and sedation. It is generally started at a dose of 10-15 mg/kg/d divided bid to tid, and increased to a target dose of 25-60 mg/kg/d, depending on achieved blood levels. Monitoring of platelet count and liver function is normally recommended, particularly in younger children.<sup>[6]</sup>

Valproate is a broad-spectrum AED with various mechanisms of action:

Increasing GABA neurotransmission, Inhibition of calcium channels, and reduction in glutamate synthesis. Experts examine valproate as a first-line AED for Dravet Syndrome. Valproate has not evaluated in any randomized studies in treatment of DS. Small retrospective studies showed a response rate of 22.4 to 48%.<sup>10,11</sup> Serious side effects such as hepatic failure are more common in children younger than 2 years, especially with polytherapy exposure<sup>[6]</sup>.

#### Clobazam [7]

Clobazam is also a benzodiazepine that has a lower potential for sedation and acts on the GABAA receptor, a pentameric structure with five subunits (2 $\alpha$ , 2 $\beta$ ) around a central pore, through which chloride ions pass, leading to cellular hyper polarization. Clobazam acts on GABA receptors responsible for fast phasic inhibition and located within the synapse. Clobazam doses stated at 0.2-0.3 mg/kg/d to 0.5-2.0 mg/kg/d commonly reached in DS. The most adverse effects of clobazam include sedation, ataxia and increased salivation. There's very minimum data on the efficacy of clobazam in DS (level 4), with a one retrospective study<sup>14</sup> documenting responder rates of 28%. Generally, if one first-line agent provides suboptimal control, another is added on. The majority of children need addition of a second-line agent [7].

### Patient who fails the therapy

#### Topiramate [7]

Topiramate is extensively available in broad-spectrum antiepileptic agent that acts through multiple mechanisms, these includes blockage of voltage-dependent sodium channels, carbonic anhydrase, AMPA/kainite receptor antagonism and increase GABAA activity. Four modest-sized, observational, prospective and retrospective studies<sup>10, 11,14, 23</sup> assessing the effectiveness of Topiramate in patients having a DS (levels 3, 4) shows good response of 35-78%, with 10-17% of patients becoming seizure-free for at least minimum period of time. Doses for Dravet Syndrome, starting at 0.5-2 mg/kg/d to 8-12 mg/kg/d. adverse effects of Topiramate includes decreased in appetite, slowing of verbal processing, metabolic acidosis and nephrolithiasis. While topiramate may decrease sweating, thus predisposing to hyperthermia, which also known seizure trigger in DS, this concern is more theoretical than practical in DS [7].

## Levetiracetam [7]

Levetiracetam, is a another broad-spectrum antiepileptic medicament, Exact mechanism of action is unknown but when binds to the synaptic vesicle protein SV2A, reported to have a responder rate of 64% in a single open-label prospective study of 28 patients (level 3). Other retrospective studies show significantly lower efficacy closer to 11%. It is generally well-tolerated medication, and major adverse effect is behavioral disinhibition. Dosing is generally started at 10-20 mg/kg/d divided bid to tid, and the dose may be increased to a maximum of 60-80 mg/kg/d. [7].

## Bromides [7]

Bromides used from 19th century for epilepsy and are recently used mostly in veterinary practice. Bromides are administered in the form of bromide salts, including potassium bromide, sodium bromide and ammonium bromide. The mechanism of action is not known, but it is assume that bromides act on the chloride channel of the GABAA receptor, causing hyper polarization. Bromides appear level 4 show efficacy in Dravet Syndrome in retrospective studies<sup>15,25-27</sup> with responder rates of 37-77% and seizure-free rates of 9%, although there is a suggestion that response rates taper off over time. Oguni and colleagues<sup>27</sup> proposed that bromides were most effective for generalized tonic-clonic seizures and less effective for focal, absence or myoclonic seizures. The adverse effects of bromides are very low and include rash, somnolence and decreased appetite.[7]

Bromides are rarely used and not readily available in many countries. Excellent short-term response rate was reported from numerous studies. Oguni et al reported that among 22 patients, 8 had >75% seizure reduction, and additional to that 9 had 50 to 75% seizure reduction after 3 months of treatment. five patients lost responsiveness during a 1-year follow-up. Tonic-clonic seizures responded greater than focal or myoclonic/absence seizures. 18 patient reported side effects like drowsiness, appetite loss, and skin rash. Lotte et al reported that 26 out of 32 patients had more than 50% seizure reduction after 3 months of bromide treatment and 15 patients had constant improvement (more than 50% reduction) after 12 months of treatment [8].

## Fenfluramine [9]

Fenfluramine was earlier used in combination with phentermin as an appetite suppressor, but when used in high dosages, it cause cardiac side effects and get banned as a therapeutic drug in 1997. Fenfluramine has affinity for serotonin receptors in the brain (especially 5HT<sub>2A</sub> and 2C), leads to a higher serotonin concentration, and also is a positive modulator of the sigma 1 receptor. Some case reports shows that fenfluramine in low dosages could stop self-induced syncopes and intermittent light-induced paroxysmal events in neonatal with behavioral problems. Because it could also affect photosensitivity on the electroencephalogram in patients, it was assumed that fenfluramine should be tested as an AED. In 1996, Boel and Casaer published the first paper shows low dose fenfluramine was very usefull in paediatrics with refractory epilepsy. In this case series, all children had intellectual inability and early onset seizures with drug-resistant self- induced seizures that were classified as generalized seizures. Then it is realized that 5 children gives good response to fenfluramine all children had the typical symptoms of DS. Later it confirmed with genetic testing. In spite the worldwide prohibition, a Royal Decree in Belgium allowed for continued use of fenfluramine in a limited number of children with DS. This resulted during a retrospective analysis on the effect of fenfluramine in children and adolescents with DS. This long-term follow-up confirmed previous findings, with seven of 10 patient's seizure-free for a minimum of 1 year.

These data on minimum dose of fenfluramine in DS are very constant, with high efficacy and no development of tolerance. In now >200 children exposed to fenfluramine for >1 year, there have been no heart safety problems [9].

## KETOGENIC DIET [10]

The KD is a high-fat with low-carbohydrate, adequate-protein diet and it is more flexible variants (the medium chain triglyceride diet, the low-glycemic-index diet, and the Atkins diet), are currently considered effective and safe nonpharmacological treatment options for patients with difficult-to-treat epilepsy. The main advantages of the ketogenic diet are that it has very less neurotoxin side effects (lethargy, cognitive, behavioral) than the pharmacological treatments. Increasing evidence shows that the diet may be effective for seizure control in specific epilepsy syndromes. In DS, complete seizure control with treatment is often not achieved. Currently, the KD is considered not great but a good treatment option after four AEDs have failed [10].

### Co-morbid conditions associated with Dravet syndrome can include: [10]

- Developmental delays and behavior issues
- Deficiency in social and learning skills
- Body movement and balance issues
- Growth of the body and nutrition issues
- Insomnia
- Upper respiratory infections
- Sensory integration disorders
- Disruptions of the autonomic nervous system (which regulates things such as body temperature, sweating, and toileting)

Dravet syndrome is a severe form of epilepsy distinguished by frequent, prolonged seizures often triggered by high body temperature, developmental delay, speech impairment, hypotonia, ataxia, sleep disturbances, and other health problems. The sodium ion channel is a gated pore-like structure in the cell membrane that controls the movement of sodium ions into and out of the cell, helping to propagate electrical signals through neurons. Sodium ion channels are critical part of any tissue need electrical signals including the brain and heart. More than 80% of patients with Dravet syndrome have a mutation in the SCN1A gene, but not all SCN1A mutations lead to Dravet syndrome. Dravet Syndrome is a disorder of the brain due to seizures. It also called “channelopathy” because the effects of the mutation on the sodium channel. Dravet Syndrome seems during the first year of life or else healthy infant, usually with a generalized tonic clonic or hemiclonic seizure which is often prolonged (>5 minutes). Status epilepticus lasting longer than 5 minutes and sometimes 30 minutes or more, is common, especially in the early years, and requires emergency medical interference.

Mortality is raised in DS above that found in the general population of epilepsy patients approximately 15% to 20% by adulthood. Sudden unexpected death in epilepsy is the most frequent cause of death and usually occurs during sleep. The second most common cause of death is status epilepticus (SE) [10].

### Novel Treatment

#### In-Vivo-In-Vitro effect of Stiripentol on CLB & VAL. [11]

It shows that the frequency of responders were higher on Stiripentol than that of placebo (5%, 95% confidence interval 0 –14.6) with a high significance. The mean daily dose of Stiripentol during the double-blind period was 492 mg/kg/day, resulting in a mean minimum plasma concentration at steady state of 10.0 3.6 mg/l. Mean normalized minimum plasma concentrations of CLB and NCLB increased significantly (p 0.001) from 0.39 to 0.84 (mg/l)/ (mg/kg) and from 3.6 to 11.6 (mg/l)/(mg/kg) respectively, whereas those of OH-NCLB decreased

significantly from 0.258 to 0.063 (mg/l)/(mg/kg). NCLB/CLB ratio of minimum plasma concentration was improved significantly by 269%, while OH-NCLB/NCLB decreased significantly by 86%. OH-CLB wasn't detected in the plasma of patients. There were no remarkable changes in plasma concentrations in the placebo group. The inhibition of clobazam demethylation by STP was best described by a noncompetitive inhibition model with apparent  $K_i$  1.6 M for the cDNA-expressed CYP3A4 and by a competitive inhibition model with  $K_i$  0.52 for the cDNA-expressed CYP2C19. Formation of OH-NCLB from NCLB by cDNA-expressed CYP2C19 was competitively inhibited by STP with a  $K_i$  0.14 M. Ketoconazole inhibited the demethylation of clobazam by the cDNA-expressed CYP3A4 with an  $IC_{50}$  almost 70 times lower than that of STP. Omeprazole inhibited the hydroxylation of NCLB by the cDNA-expressed CYP2C19 with an  $IC_{50}$  approximately 10 times higher than that of STP. [11]

### **Vagus nerve stimulation**

VNS consists of intermittent electrical stimulation of the left cervical Vagus nerve by an implanted helical electrode that is connected to a pulse generator [12]. Dibué-Adjei et al. performed analysis of 68 patients with DS; 52.9% of patients experienced a  $\geq 50\%$  reduction of seizures, and while the rate is different in between 0 and 100% across all 13 studies, they were same in almost all studies with more than 6 Dravet Syndrome patients (75%, 67%, 50%, 38%, 50%, 38%) [71]. Hoarseness was the most frequently reported side-effect. Overall, VNS appears to be beneficial in a proportion of patients with DS [12].

### **Pharmacokinetic data in children**

Data are still limited to establish a clear relationship between dosage, plasma concentration, efficacy, and safety of Stiripentol in DS. Pharmacokinetic data in children Data are still limited to establish a clear relationship between dosage, plasma concentration, efficacy, and safety of Stiripentol in Dravet syndrome [11].

### **Stiripentol Inhibits Metabolism of Other Anticonvulsant Drugs [13]**

STP has been tested for decades in combination with other antiepileptic drugs because of its inhibitory action on metabolic enzymes. Stiripentol inhibits a variety of hepatic cytochrome P450 enzymes, with high activity at human CYP1A2, CYP3A4, and CYP2C19. As it results into increases the peak concentrations and duration of action of several commonly used AEDs, including clobazam, carbamazepine, phenytoin, and Valproic acid. For the patients with Dravet syndrome, Stiripentol is commonly combined with clobazam and Valproic acid. Evidence suggests that much of the antiepileptic activity of clobazam is mediated through its active metabolite, nor-clobazam. Although co-administration with Stiripentol increases the concentration of both clobazam and nor-clobazam, it has a much higher impact on nor-clobazam levels. So, some of the improved efficacy is seen with the combination of STP and clobazam may be due to increased levels of nor-clobazam. In addition, its effects on drug metabolism, there is strong evidence that STP alone is directly antiepileptic. Stiripentol mono therapy decreases seizure severity in a variety of rodent models and in a primate model of focal seizure. This suggested that Stiripentol has additional effects on epileptic activity independent of alterations in drug metabolism. Subsequent studies have shown that STP acts directly on GABA<sub>A</sub> receptors (GABA<sub>A</sub> Receptor's) as a positive allosteric modulator [13].

### **Stiripentol Enhances GABAergic Neurotransmission [13]**

The GABA<sub>A</sub> Receptors are ligand-gated chloride channels responsible for fast inhibitory neurotransmission. They are targets for many commonly used anti-epileptics including benzodiazepines and barbiturates. Experimental evidence for the action of Stiripentol on the activity of GABA<sub>A</sub> Receptors was first proved by Quilichini et al. (2006). Utilizing neonatal rat brain slice preparation, they found that Stiripentol slowed the degradation of GABAergic miniature inhibitory post-synaptic currents (mIPSCs) in hippocampal CA3 pyramidal cells. STP increased both the frequency and the duration of postsynaptic events, suggesting both pre- and post-synaptic effects. A direct modulation of GABA<sub>A</sub> Receptors was finalized with single-channel recordings, which showed that STP increased the mean open time of GABA-activated channels [13].

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