



# Dravet Syndrome as an Example of Precision Medicine in Epilepsy

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## Abstract

Dravet syndrome (DS) is a drug-resistant, early-onset, developmental and epileptic encephalopathy where there have been many recently approved therapies with many more in development. With the availability of more syndrome specific treatment options coupled with an earlier diagnosis, DS is well-positioned to be an example of how a precise syndromic diagnosis can guide treatment choices and improve overall outcomes and also allow for the development of potential disease modifying therapies to address more than just seizures. In this review we summarize the current state of DS approved therapies and those that are in various stages of development.

## Keywords

Dravet, precision medicine, developmental epileptic encephalopathy, anti seizure medication, disease modifying therapy, epilepsy syndrome

## Overview

Dravet syndrome (DS) is a drug-resistant, early-onset, developmental and epileptic encephalopathy that typically presents in the first year of life with prolonged febrile and afebrile, focal (usually hemiclonic) and generalized tonic-clonic seizures.<sup>1</sup> Development is normal at onset but then slows and global delays are usually evident by 2-3 years of age. Other significant comorbidities emerge with time including crouch gait, parkinsonian features, autistic features, attention deficit disorder, growth delay and feeding problems, dysautonomia and sleep problems.<sup>2</sup> The risk of sudden unexpected death in epilepsy (SUDEP) is significantly increased with a reported rate of 9.32 per 1000 person years.<sup>3</sup>

Over 85% of cases are found to have , mostly *de novo*, pathogenic, loss-of-function *SCN1A* variants which result in

haploinsufficiency of Na<sub>v</sub>1.1, the alpha-1 subunit of the sodium channel.<sup>1</sup> Both the underlying channelopathy and the recurrent severe seizures contribute to the presence and severity of comorbidities. In a prospective study of 67 children with DS, 15 of whom were studied longitudinally, Nabbout et al<sup>4</sup> found no correlation between epilepsy variables and developmental/intelligence quotient at last evaluation, but noted that those with a documented *SCN1A* variant exhibited greater delays than those without variants. This work suggests that the *SCN1A* variant significantly contributes to the encephalopathy. Conversely, other studies have reported that earlier use of appropriate therapies, or avoidance of therapies that exacerbate seizures may improve outcomes.<sup>5-8</sup> Since 2018, there have been 3 new antiseizure medications approved for seizures associated with Dravet syndrome.



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## Novel Pharmacological Agents Which do not Specifically Target *SCN1A*

### Pharmaceutical Grade Cannabidiol

Pharmaceutical-grade cannabidiol was approved by the FDA in June 2018 for the treatment of seizures associated with DS. Its exact mechanism of action is unknown – it does not significantly activate CB1 or 2 receptors, but rather may enhance neuronal inhibition (through GABAergic channels), modulate intracellular calcium (TRPV, GPR-55 or VDACC) and have an antiinflammatory effect (adenosine).<sup>5,9</sup>

Two randomized, double-blind, placebo-controlled studies have demonstrated efficacy of this compound in DS. In the first, 120 patients, aged 2-18 years who were having 4 or more convulsive seizures in the 4-week baseline period, despite current antiseizure medication (ASM) (median number of current ASMs 3.0, median number of previously failed ASMs 4.0) were randomized to receive either cannabidiol 20 mg/kg/d or placebo for a 14-week treatment period.<sup>10</sup> Median monthly convulsive seizure frequency decreased from 12.4 to 5.9 with cannabidiol vs 14.9 to 14.1 with placebo ( $P = .01$ ). A 50% or greater reduction in convulsive seizure frequency was achieved in 43% with cannabidiol vs 27% with placebo. There was also greater improvement seen on the Caregiver Global Impression of Change scale with cannabidiol, with 62% reporting improvement of at least one category compare to only 34% of the placebo-treated group ( $P = .02$ ).<sup>10</sup>

In the second study, 198 patients aged 2-18 years who had at least 4 convulsive seizures during the 4-week baseline period were randomized 1:1:1 to receive either 10 or 20 mg/kg/day of cannabidiol or placebo for 14 weeks.<sup>11</sup> Those treated with cannabidiol had significantly greater reduction in convulsive seizure frequency compared to placebo however there was no significant differences between the 2 doses of cannabidiol (percentage reduction from baseline of 48.7% for 10 mg/kg/day cannabidiol, 45.7% for 20 mg/kg/day cannabidiol and 26.9% for placebo) ( $P = .01-.03$ ).<sup>11</sup>

A subsequent open-label extension trial which included 95% of patients enrolled in the original randomized trials followed patients through a median treatment duration of 274 days and documented that the impact on seizure control was sustained over time.<sup>12</sup> The median reduction in convulsive seizure frequency was 38% over weeks 1-12 and 44% over weeks 37-48.<sup>12</sup>

Cannabidiol was well tolerated with the most common side effects including diarrhea, vomiting, decreased appetite, fatigue and somnolence, and in the open label extension study, only 6.4% discontinued due to adverse effects.<sup>10-12</sup> In most cases, these side effects resolve within approximately 14 weeks.<sup>13</sup> Up to 19.7% experienced a 3-fold or greater elevation in transaminases, and this is much more commonly seen with concomitant valproic acid.<sup>10,12</sup> However other evidence of liver dysfunction was not seen and, in all cases, transaminases returned to normal levels, often without withdrawal of cannabidiol.<sup>14</sup>

Despite improvements in convulsive seizure frequency, no significant benefits were seen on the Quality of Life in Childhood Epilepsy or Vineland Adaptive Behavior Scales comparing cannabidiol and placebo.<sup>10</sup>

### Stiripentol

In 2000, stiripentol was the first medication to be specifically studied in a small cohort of DS patients where 71% of patients receiving stiripentol had a 50% or greater reduction in generalized tonic-clonic or clonic seizures compared to only 5% of those who received placebo. Impressively, 9 of the 21 who received stiripentol were seizure free during the 2-month treatment period compared to no patients who received placebo.<sup>15</sup> All patients in this study were also on concomitant valproate and clobazam. There are several potential mechanisms of action including direct enhancement of inhibitory GABAergic neurotransmission in addition to inhibiting the *CYP1A2*, *3A4* and *2C19* metabolism of concomitant anti-seizure medications.<sup>16</sup> Limited follow-up studies followed and FDA approval was not granted until 2018 despite many US physicians being able to obtain stiripentol for their patients through Investigational New Drug (IND) compassionate use programs. In a retrospective study of 82 children who received stiripentol alone or in combination with clobazam and/or valproate under these INDs, reduction in seizures was noted in all groups though was more favorable in the most commonly used combinations of stiripentol with clobazam OR stiripentol with clobazam and valproate.<sup>17</sup> The mechanism of action is multifactorial. STP is known to inhibit a variety of hepatic P450 enzymes most notably *CYP1A2*, *CYP3A4* and *CYP2C19* resulting in increased concentration of commonly used concomitant ASMs and their metabolites but also enhances GABAergic transmission acting as a positive allosteric modulator of the GABA<sub>A</sub> receptor.<sup>16</sup>

### Fenfluramine

In 2015, a double-blind, placebo-controlled study of fenfluramine began enrolling and met its primary endpoint with the higher dose showing a 62.3% greater reduction in mean convulsive seizures compared to placebo. All the key secondary endpoints were also met; most notably 50% of patients in the high dose group and 23% of patients in the low dose group experienced a 75% or greater reduction compared to only 2% in the placebo group.<sup>18</sup> Near seizure freedom, defined as 0 or 1 seizures during the entire 14-week treatment period, was achieved in 25% of the high dose group and 12.8% in the low dose group. The treatment was well tolerated with the most common side effects being decreased appetite, diarrhea, fatigue and decreased weight. Despite the historical concerns regarding cardiac risk and fenfluramine exposure, there were no instances of cardiac valvulopathy or pulmonary hypertension in any subject at any time.<sup>17</sup> In 2020, based on these findings together with another study with concomitant stiripentol the FDA approved fenfluramine for seizures associated with DS.<sup>18</sup> Fenfluramine likely has multiple mechanisms of action, acting as both a potent serotonin releaser and a direct serotonin receptor agonist particularly at the 5HT<sub>2A</sub>, 5HT<sub>2B</sub> and 5HT<sub>2C</sub>, but also as a positive modulator of the sigma-1 receptor.<sup>19</sup> The contribution and importance of each of these mechanisms for the anti-seizure effects continues to be under investigation.

A subsequent open-label extension (OLE) trial of fenfluramine included 232 patients who were enrolled in one of the original



randomized trials and reported on seizure reduction after a median of 256 days (range 46–634).<sup>20</sup> Over the entire OLE, the median reduction in convulsive seizure frequency was –66.8% with similar adverse events as noted in the randomized trials.<sup>20</sup>

A post-hoc analysis of patients who enrolled in the various fenfluramine trials and received at least 1-year of treatment in the open-label extension study was done to evaluate for clinically meaningful changes on the Behavior Rating Inventory of Executive Function. In the 58 children included in this analysis, 45 (78%) achieved a greater than 50% reduction in seizures and there was clinically meaningful improvement both the emotional regulation index and the cognitive regulation index.<sup>8</sup> These findings support the notion that non-seizure outcomes can improve in this patient population and allows for redefining our treatment goals as we strive to treat all aspects of the syndrome.

### Other Agents in Clinical Trials

Additional mechanisms are also being explored with various agents in different stages of clinical trials including soticlestat (a cholesterol 24-hydroxylase inhibitor), as well as clemizole and lorcaserin both of which like fenfluramine, act via the serotonin pathway.<sup>21</sup>

## Potential Disease-Modifying Therapies

### Antisense Oligonucleotide Therapy

The *SCN1A* gene contains a nonsense-mediated decay exon that is used to regulate the *SCN1A* transcript and Na<sub>v</sub>1.1 protein production. If the mRNA transcript contains this exon, it degrades and thus protein is not produced. Targeted augmentation of nuclear gene output (TANGO) technology can target these nonproductive alternative splicing events to decrease nonproductive mRNA and thus boost protein production.<sup>22</sup> As this therapy targets the underlying pathogenesis, it carries the potential benefit to not only reduce seizures, but also attenuate or prevent comorbidities including SUDEP.

STK-001 is an antisense oligonucleotide (ASO), currently in clinical trials, which utilizes TANGO technology to boost Na<sub>v</sub>1.1 protein expression. Utilizing the *SCN1A* mouse model (*SCN1A* knockout/+), an animal model that leads to spontaneous seizures with significant mortality due to SUDEP by 30 postnatal days, intracerebroventricular administration of ASO-22 on postnatal day 2 or 14 markedly reduced the incidence of electrographic seizures and resulted in a marked reduction in mortality.<sup>23</sup> Furthermore in ASO-treated mice, Na<sub>v</sub>1.1 levels in mouse brains increased to amounts similar to wild type animals. In wild type animals treated with ASO, Na<sub>v</sub>1.1 also increased but this increase did not lead to clinical symptoms or increased mortality.<sup>22</sup>

Clinical trials are underway in humans. The Phase 1/2a MONARCH study is recruiting persons with DS aged 2–18 years with ongoing convulsive seizures. Preliminary data on the lower dose cohorts was recently reported at the 2021 American Epilepsy Society meeting. Single doses of STK-001 of 10–30 mg, and multiple doses of 20 mg given every 4 weeks ×

3 doses appear safe and well-tolerated.<sup>24</sup> A reduction from baseline convulsive seizure frequency was noted in 70.6% of patients and across all dosing cohorts, median reductions of 17–37% were seen.<sup>23</sup>

A population pharmacokinetic model in non-human primates suggests that more than 95% of human patients are predicted to have pharmacologically active STK-001 brain levels following 3 doses of 30 mg administered 1 month apart.<sup>25</sup>

This MONARCH study is continuing, with a similar open label study in the UK (ADMIRAL). These trials will continue to examine the safety and tolerability of multiple doses of STK-001 and examine pharmacokinetics in humans. Additionally, patients completing the Monarch study are eligible to continue treatment in SWALLOWTAIL, an open-label extension study to evaluate long-term safety and efficacy and evaluate potential impact on reduction of comorbidities (NCT04740476).

### AAV-9 Based Gene Therapy

Another novel, potential one-time disease-modifying approach to address the underlying Nav1.1 haploinsufficiency is being developed by Encoded Therapeutics. ETX-101 is an AAV-9 delivered gene therapy that expresses an engineered transcription factor under the control of a GABA-ergic cell-selective regulatory element which is designed to promote increased transcription and therefore translation of the *SCN1A* gene in inhibitory interneurons. This has also been studied in an *SCN1A* DS mouse model reducing frequency and severity of seizures at post-natal day 26–28 and reduced mortality up to 470 days post-dosing.<sup>26</sup> This interventional study is planning to enroll the first patient in late 2022.

## Conclusion

Making an accurate diagnosis of an epilepsy syndrome such as Dravet syndrome has allowed for the study of novel compounds and data to inform syndrome specific treatments. While this may not necessarily be a true precision medicine approach as some of the ASMs that have been approved for the treatment of seizures associated with Dravet syndrome have also demonstrated efficacy in other epilepsy syndromes, having efficacy and safety data does allow for a more systematic treatment approach for these patients.<sup>27</sup> Having the precise understanding of the underlying genetic etiology of Dravet syndrome has paved the way for development of true precision medicine approaches. If effective, these could change the overall natural history of the syndrome as we know it and lead to improvement in domains beyond just seizures, thereby further improving the overall outcomes and quality of lives for these patients and their families.

### Declaration of Conflicting Interests

Dr. Wirrell has participated in clinical trials for Zogenix, Jazz and Stoke and has received research funding from Biocodex. She has received consulting fees from Encoded. She serves on the Medical Advisory Board for the Dravet Syndrome Foundation. The author(s) declared no


potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Dr. Sullivan has participated in clinical trials for Zogenix, Stoke Encoded and Takeda. He has received consulting fees from Stoke, Encoded and Epygenix and holds restricted stock units in Epygenix. He serves on the Medical Advisory Board and Board of Directors for the Dravet Syndrome Foundation.

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