

Treatment of Dravet Syndrome

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ABSTRACT: Dravet syndrome is among the most challenging electroclinical syndromes. There is a high likelihood of recurrent *status epilepticus*; seizures are medically refractory; and patients have multiple co-morbidities, including intellectual disability, behaviour and sleep problems, and crouch gait. Additionally, they are at significant risk of sudden unexplained death. This review will focus predominantly on the prophylactic medical management of seizures, addressing both first-line therapies (valproate and clobazam) as well as second-line (stiripentol, topiramate, ketogenic diet) or later options (levetiracetam, bromides, vagus nerve stimulation). Sodium channel agents—including carbamazepine, oxcarbazepine, phenytoin and lamotrigine—should be avoided, as they typically exacerbate seizures. Several agents in development may show promise, specifically fenfluramine and cannabidiol, but they need further evaluation in randomized, controlled trials. In addition to prophylactic treatment, all patients need home-rescue medication and a *status epilepticus* protocol that can be carried out in their local hospital. Families must be counselled on non-pharmacologic strategies to reduce seizure risk, including avoidance of triggers that commonly induce seizures (including hyperthermia, flashing lights and patterns). In addition to addressing seizures, holistic care for a patient with Dravet syndrome must involve a multidisciplinary team that includes specialists in physical, occupational and speech therapy, neuropsychology, social work and physical medicine.

Keywords: Antiepileptic drug, Dravet syndrome, ketogenic diet, stiripentol

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Dravet syndrome (DS) is an intractable paediatric electroclinical syndrome beginning in the first 24 months of life, with generalized or hemi-convulsive seizures initiated by fever (often associated with vaccines) or hyperthermia, which are often prolonged. In early childhood, between 1 and 5 years of age, other seizure types emerge, including myoclonic, atypical absence and focal seizures, as well as periods of obtundation (non-convulsive) *status epilepticus*. This review will outline treatment goals and the first-, second-line and later therapies for seizures (pharmacologic and non-pharmacologic) and agents in development, as well as address management of *status epilepticus*.

TREATMENT GOALS

In managing patients with DS, the aim is to significantly reduce seizure frequency (particularly prolonged events) and limit antiepileptic drug toxicity. Complete seizure cessation is rarely achievable. Another therapeutic goal is to minimize co-morbidities, including intellectual disability, behavioural and psychiatric problems, seizure-related injury and sudden unexplained death in epilepsy (SUDEP). A greater degree of cognitive and behavioural impairment has been linked to both higher frequency of convulsive¹ and non-convulsive seizures.^{2,3}

The typical seizure pattern changes over time. *Status epilepticus* is most problematic during the first two years of life and reduces in frequency after five years of age. In early childhood, frequent non-convulsive seizures may negatively impact development. In the adolescent and adult years, frequent but brief nocturnal generalized convulsive seizures are most common and place the patient at risk of SUDEP.

Provocation of seizures by hyperthermia, and less frequently by photosensitivity or pattern sensitivity, is commonly noted. Antipyretics for fever, minimizing warm baths or exercise

on warm days, and avoiding photosensitivity triggers are recommended.

PROPHYLACTIC SEIZURE MANAGEMENT (SEE TABLE 1)

Treatment of DS should begin when this diagnosis is suspected, rather than waiting for genetic confirmation. Importantly, certain antiepileptic agents should be avoided, as they have been clearly shown to exacerbate seizures in DS. These include carbamazepine,⁴ oxcarbazepine, phenytoin, lamotrigine,⁵ vigabatrin,⁴ phenobarbital^{6,7} and rufinamide.⁸

There have been few evidence-based studies to evaluate the best therapies for DS, and recommendations for most first- and second-line therapies are based predominantly on expert opinion and a limited number of small, mostly retrospective, open-label studies. Only one agent, stiripentol, has published evidence of level 2 efficacy, based on placebo-controlled, randomized, double-blind studies.⁹ However, preliminary data from a randomized, placebo-controlled, double-blind study on cannabidiol also provide level 2 evidence of efficacy (gwpharma.com), although these data are not yet published. Open-label prospective studies have also been performed using topiramate^{10,11} and levetiracetam.¹² The Oxford Center for Evidence-Based Medicine has defined five levels of evidence to determine therapeutic benefit, ranging from the highest (level 1: evidence of efficacy based on a systemic review of randomized trials) to the lowest (level 5: evidence of efficacy based on mechanism-based reasoning only).¹³ For each

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Table 1: Second-line medications in Dravet Syndrome

Author	Study design	Level of evidence*	AED	Outcome
Stiripentol				
Chiron et al., 2000 ¹⁹	Randomized, placebo-controlled	2	STP (added to VPA/CLB)	France: 41 patients: (20 placebo, 21 STP) 9 on STP were seizure-free during 2nd month Overall 69% reduction in seizures from baseline compared to 7% increase on placebo Odds ratio of responding to STP compared to placebo 32 ($CI_{95\%} = 6.2, 161$)
Inoue et al., 2015 ¹⁵	Retrospective	4	STP	13/24 (54%) achieved a >50% reduction in GTCS; 2 were seizure-free
Wirrell et al., 2013 ²¹	Retrospective	4	STP	82 patients: most children experienced reduction in seizures independent of whether added to VPA or CLB
Kassai et al., 2008 ⁹	Meta-analysis of STP	1		64 children in 2 randomized control trials; odds ratio of responding to STP relative to placebo was 32 ($CI_{95\%} = 6.2, 161$), and stiripentol reduced seizures by 70% ($CI_{95\%} = 93\%, 47\%$)
Topiramate				
Coppola et al., 2002 ¹⁰	Prospective add-on Median follow-up: 12 months	3	TPM	18 patients: 3 seizure-free 10 had >50% reduction
Nieto-Barrera et al., 2000 ¹¹	Prospective add-on Median follow-up: 10 months	3	TPM	18 patients: 3 (16%) seizure-free 10 (55%) >50% reduction
Kroll-Seeger et al., 2006 ²³	Retrospective	4	TPM	36 patients: 78% had >50% reduction in GTCS 17% seizure-free for at least 4 months
Dressler et al., 2015 ¹⁴	Retrospective	4	TPM	35% responders
Bromides and zonisamide				
Oguni et al., 1994 ²⁷	Add-on Mean follow-up: 19 months	4	Bromide	22 patients: 8 (36%) >75% reduction 9 (41%) 50-75% reduction in GTCS at 3 months but only 8 responders at 12 months Less effective for focal or myoclonic/absence seizures
Tanabe et al., 2008 ²⁶	Retrospective questionnaire	4	Bromides, ZNS	42% on bromides and 13.5% on ZNS had no <i>status epilepticus</i>
Lotte et al., 2012 ²⁵	Retrospective review of 32 patients	4	Bromides	After 3 months, 81% had >50% reduction At 12 months, nearly half still had >50% reduction in seizure frequency
Levetiracetam				
Striano et al., 2007 ²⁴	Prospective, add-on, open-label, after 12-week "evaluation" period	3	LEV	28 patients: GTCS: 3 seizure-free and 15 with >50% reduction Myoclonic: 2 seizure-free and 7 >50% reduction Focal: 3 seizure-free and 3 >50% reduction Absence: 1 seizure-free and 3 >50% reduction
Fenfluramine				
Ceulemans et al., 2012 ²⁸	Retrospective, add-on Mean follow-up: 6 years	4	Fenfluramine	12 patients: 7 seizure-free for at least 1 year

STP = stiripentol; VPA = valproate; CLB = clobazam; TPM = topiramate; LEV = levetiracetam; ZNS = zonisamide; CI = confidence interval; GTCS = generalized tonic-clonic seizure.

*Based on Oxford Centre for Evidence-Based Medicine, 2011.¹³

therapeutic intervention, the level of evidence to support its use in DS will be provided.

FIRST-LINE MANAGEMENT: VALPROIC ACID AND CLOBAZAM

First-line management typically involves either valproic acid or clobazam. Valproic acid is a broad-spectrum agent with multiple possible mechanisms of action, including potentiation of GABAergic function, inhibition of voltage-sensitive sodium channels and antagonism of NMDA receptor-mediated neural excitation. There is minimal literature on its use in DS (level 4),

and in retrospective studies^{14,15} responder rates (>50% reduction in seizure frequency) were 22.2-48%.

Valproic acid has the potential for several severe adverse effects, including hepatotoxicity (particularly with underlying mitochondrial disease), hyperammonemia, pancreatitis and thrombocytopenia. Additionally, other adverse effects may include decreased or increased appetite, tremor (at higher doses), hair loss and sedation. It is typically 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 typically recommended, particularly in younger children.

Clobazam is a benzodiazepine that is felt to have a lower potential for sedation and acts on the GABA_A receptor, a pentameric structure with five subunits (2 α , 2 β , and one γ , δ , ϵ , θ or π) around a central pore, through which chloride ions pass, resulting in cellular hyperpolarization. Clobazam acts on the γ -containing GABA_A receptors, which are most prevalent, predominantly responsible for fast phasic inhibition and located within the synapse. Clobazam is typically started at doses of 0.2-0.3 mg/kg/d, with target doses of 0.5-2.0 mg/kg/d commonly reached in DS. The main adverse effects of clobazam include behavioural disinhibition, sedation, ataxia and increased salivation. Again, there is a limited amount of data on the efficacy of clobazam in DS (level 4), with a single retrospective study¹⁴ documenting responder rates of 28%.

Typically, if one first-line agent provides suboptimal control, the other is added on. However, the majority of children will require addition of a second-line agent.

SECOND-LINE THERAPIES

At present, most epileptologists consider stiripentol, topiramate or the ketogenic diet as the best second-line options for patients who continue to experience poor seizure control despite valproic acid and clobazam.

Stiripentol

Stiripentol is a positive allosteric modulator of the GABA_A receptor, acting on both the benzodiazepine-sensitive γ -containing GABA_A receptors as well as on the benzodiazepine-insensitive δ -containing GABA_A receptors, which are predominantly peri- and extrasynaptic in location and responsible for mediating tonic inhibition.¹⁶ Thus, the combination of stiripentol and benzodiazepines enhances GABAergic neurotransmission beyond the effect of each compound administered alone. Furthermore, in *status epilepticus*, stiripentol continues to be efficacious, both by maintaining phasic inhibition, due to its action on α 4-containing GABA_A receptors (which are not internalized), and tonic inhibition, by its action on δ -containing GABA_A receptors. In contrast, pharmacoresistance develops to benzodiazepines due to internalization of the GABA_A receptors containing the γ 2 subunit.¹⁷ Stiripentol has also been shown to have particular affinity for the α 3 subunit-containing GABA_A receptors, which are found at the highest levels in the immature brain.¹⁸

Stiripentol is approved by Health Canada as adjunctive therapy for refractory generalized tonic-clonic seizures in DS not adequately controlled with valproic acid and clobazam. It is the only agent that has been studied in a randomized, placebo-controlled, blinded manner (level 2).^{9,19} In the pivotal STICLO studies,¹⁹ children receiving stiripentol added on to clobazam and valproate achieved a 69% reduction in seizure frequency from baseline, compared to a 7% increase in those treated with placebo. Overall, the odds ratio of responding to stiripentol compared to placebo was 32 ($CI_{95\%} = 6.2, 161$). Other retrospective analyses^{4,14,15,20,21} have confirmed efficacy, with 57-89% having a >50% reduction in seizure frequency, 9-17% seizure-freedom, and significant reductions in seizure duration, frequency of *status epilepticus*, frequency of rescue medication use and ER visits.

Stiripentol inhibits CYP2C19, and thus, when used as a co-therapy with clobazam, results in approximately a twofold increase in clobazam levels and a three- to fivefold increase

in norclobazam levels. However, subsequent studies²² have suggested that the efficacy of stiripentol is independent of its pharmacokinetic interaction with clobazam.

Stiripentol should be combined with valproic acid and/or clobazam, as there are no clinical data to support its use as monotherapy. It is typically started at a dose of 10-15 mg/kg/d and titrated up to an initial target dose of approximately 50 mg/kg/d over 2-4 weeks. The dose can be further increased as needed to a maximum of 100 mg/kg/d in young children, although adolescents and adults require a lower dose (20-30 mg/kg/d). Because of the pharmacokinetic interaction, clobazam doses must be reduced, typically to approximately 0.2 mg/kg/d. The side effects of stiripentol are typically dose-dependent and include somnolence, fatigue, ataxia and decreased appetite.¹³ It is recommended that a complete blood count and liver enzymes be monitored at baseline and then every six months while on therapy.

Topiramate

Topiramate is a widely available broad-spectrum antiepileptic agent that acts through multiple mechanisms, including blockage of voltage-dependent sodium channels, carbonic anhydrase inhibition, AMPA/kainite receptor antagonism and enhancing GABA_A activity.

Four modest-sized, observational, open-label, prospective and retrospective studies^{10,11,14,23} assessing the efficacy of topiramate in patients with DS (levels 3 and 4) have shown responder rates of 35-78%, with 10-17% of patients becoming seizure-free at least in the short term.

Doses used in DS are similar to other epilepsy types, starting at 0.5-2 mg/kg/d and increasing to a target of 8-12 mg/kg/d. Adverse effects include somnolence, decreased appetite, slowing of verbal processing, metabolic acidosis and nephrolithiasis. While topiramate may reduce sweating, thus predisposing to hyperthermia, which is a known seizure trigger in DS, this concern is more theoretical than practical in DS.

Ketogenic Diet (Table 2)

The ketogenic diet is a well-recognized therapy for medically intractable epilepsy, and several open-label retrospective studies (level 4)^{14,28-31} have documented efficacy in DS. Overall, approximately two-thirds of patients are responders, with a minority achieving either freedom from seizure or a marked seizure reduction. In younger children, most centers utilize a traditional ketogenic diet, although the modified Atkins or low-glycemic index options may be more palatable and better tolerated in older children and teens. This diet requires strict adherence and careful supervision by a dietician. Side effects include nausea, vomiting, constipation, nephrolithiasis and hyperlipidemia.

LATER THERAPEUTIC OPTIONS

Although the data are limited, levetiracetam, bromides or vagal nerve stimulation appear less efficacious than stiripentol, topiramate or the ketogenic diet and should be considered only after failure of these second-line agents.

Levetiracetam

Levetiracetam, another broad-spectrum antiepileptic medication, whose exact mechanism of action is unknown but which

Table 2: Ketogenic diet in Dravet Syndrome

Study	Study design (n)	Details	Response
Caraballo ³⁵	Add-on (24)	Failed a mean of 6.5 AEDs Mean age at KD onset: 6 years	At 2 years, 16 (67%) remain on the diet: 2: seizure-free 10: 75-99% improved 4: 50-74% improved
Kang et al. ³⁶	Add-on (14)		10 responders (>50% reduction) 4 non-responders
Nabbout et al. ³⁷	Add-on (15)	Age at KD onset: 4-11 years 13/15 SCN1A-positive All had partial response to AEDs including stiripentol	At 1 month: 10/15 had >75% reduction 8/10 maintained response at 3 and 6 months 6/10 maintained response at 9 months All responders showed improved behaviour and attention
Laux et al. ³⁸	Add-on (20)	All SCN1A-positive Failed mean of 5.4 AEDs Mean age at KD onset: 2.9 years	13 (65%) had >50% reduction 6 (30%) had >90% reduction Responders showed improved alertness, cognition and behaviour

AED = antiepileptic drug; KD = ketogenic diet.

binds to the synaptic vesicle protein SV2A, was reported to have a responder rate of 64% in a single open-label prospective study of 28 patients (level 3).²⁴ However, other retrospective studies¹⁴ show significantly lower efficacy—closer to 11%.

It is generally a well-tolerated medication, and its major adverse effect is behavioural disinhibition. Dosing is typically 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. Routine blood monitoring is not required.

Vagus Nerve Stimulation (Table 3)

Several relatively small retrospective case series of vagal nerve stimulation in DS are reported, again providing level 4 evidence of efficacy.^{28,32-37} Responder rates are approximately 25-35% overall, which is lower than what is typically obtained with the ketogenic diet, but they vary significantly between studies.

Bromides

Bromides were initially used in the 19th century for epilepsy and are currently utilized mostly in veterinary practice. They are not available by prescription in North America. Bromides are given in the form of bromide salts, including potassium bromide, sodium bromide and ammonium bromide.

The exact mechanism of action is not known, but it is presumed that bromides act on the chloride channel of the GABA_A receptor, causing hyperpolarization. Bromides have shown level 4 efficacy in DS in retrospective studies,^{15,25-27} 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 colleagues²⁷ suggested that bromides were most effective for generalized tonic-clonic seizures and less effective for focal, absence or myoclonic seizures. The side effects of bromides are typically minor and include rash, somnolence and decreased appetite.

Table 3: Vagus nerve stimulation in Dravet syndrome

Study	Number of patients	Patient details	Response
Zamponi et al. ³⁹	8	Failed a mean of 3.2 AEDs Implanted at mean of 10.3 years (<i>SD</i> = 6.6)	At 12 months: 5/8 had reduction in seizures of 50-61% 3/8 had no benefit But all still having monthly seizures
Rossignol et al. ⁴⁰	2		1 had >90% reduction 1 no benefit
Shahwan et al. ⁴¹	2		1 had reduction by >50% 1 no benefit
Caraballo ³⁵	3	Implanted at 13-16 years	Followed for 21-29 months 2/3 50-74% reduction 1/3 no benefit
Spatola et al. ⁴²	1	Implanted at age 19 years	At 3 months, 1/1 had >90% reduction
Bremer et al. ⁴³	13		1/13 responder (>50% reduction) 12/13 non-responders
Orosz et al. ⁴⁴	20		Responder rates (>50% reduction in seizures) 6 months, 2/16 (12.5%); at 12 months, 5/20 (25%) 24 months, 5/13 (38.5%)

AED = antiepileptic drug; *SD* = standard deviation.

AGENTS IN DEVELOPMENT

Fenfluramine

Fenfluramine, an agent that releases serotonin by disrupting vesicular storage and reversing serotonin transporter function, has been reported in a single level 4 study²⁸ of 12 patients to have remarkable efficacy in DS. Patients were treated for a mean of 11.4 years. Ten (83%) continued on fenfluramine at follow-up and seven (58%) were seizure-free for longer than a year. Fenfluramine combined with phentermine (Fen-Phen) was previously used as an anti-obesity treatment and was pulled off the market due to cardiac valvulopathy. However, in a Belgian study of DS,²⁸ mild heart valve thickening was seen in only two cases and was not progressive. A randomized placebo-controlled phase 3 study followed by a long-term open-label extension study of fenfluramine in DS is presently underway.

Cannabidiol

Despite much media attention, there are few reports in the literature that evaluate the efficacy of cannabinoids in DS. In a retrospective chart review²⁹ of 13 children with DS in a single center in Colorado who trialed various strains of oral cannabis extract, only 3 (23%) were responders. Somewhat more encouraging results were obtained in a multicenter open-label study of 25 patients³⁰ with DS who received >99% pure oil-based cannabidiol extract. After three months of treatment, the overall seizure frequency was reduced by 63% and 16% were seizure-free. A randomized placebo-controlled study of plant-based cannabidiol has just been completed, with early results showing it to be more efficacious than placebo. Overall, patients randomized to cannabidiol experienced a 39% reduction in monthly convulsive seizures compared to only 16% in the placebo group ($p=0.01$) (gwpharma.com), although the results are not yet published.

MANAGEMENT OF STATUS EPILEPTICUS

All patients with Dravet syndrome are at risk of *status epilepticus* and should be provided with a home-rescue medication (diazepam, midazolam or lorazepam). In addition, each patient with DS should also have an individualized *status epilepticus* protocol, which can be carried out at their local emergency room. Based on a survey of 99 patients with DS from Japan,²⁶ efficacy for termination of ongoing *status epilepticus* was best with intravenous barbiturates (75-100%), modest with intravenous benzodiazepines (54.3-68.8%) and relatively low with intravenous lidocaine or phenytoin (15.4-21.4%).

TREATMENT OF OTHER CO-MORBIDITIES

Seizures in DS are clearly problematic, but they represent only one aspect of this disorder. While children are typically developmentally normal at seizure onset, nearly all develop intellectual disability over time.² Additionally, behavioural, sleep and psychological issues are problematic.^{31,32} By adolescence, many develop a typical “crouch gait.”^{33,34} Multidisciplinary team involvement—including neuropsychology, physical, occupational and speech therapy, and social work—is essential to maximize the quality of life and well-being for the patient with DS and their family.

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