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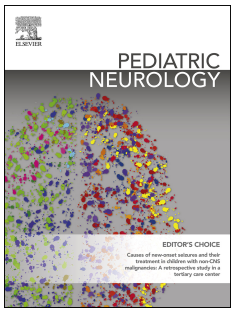

Use of Stiripentol in Dravet Syndrome: A Guide for Clinicians

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Use of Stiripentol in Dravet Syndrome: A Guide for Clinicians

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Abstract

Dravet Syndrome is a developmental and epileptic encephalopathy characterized by frequent, prolonged convulsive seizures and status epilepticus. Symptoms usually appear in the first year of life, and in addition to ongoing severe and intractable epilepsy, children with Dravet Syndrome experience neurodevelopmental, behavioral, and motor impairments, along with high rates of mortality, especially in the first 12 years of life. Prompt diagnosis and initiation of treatment with broad-spectrum anti-seizure medications are recommended to reduce seizure frequency and status epilepticus, and to potentially minimize the comorbidities associated with the epileptic encephalopathy. Stiripentol is an anti-seizure medication approved for adjunctive use in Dravet Syndrome in patients as young as 6 months of age. Data from randomized clinical trials and real-world studies demonstrate that stiripentol added to first-line therapy with clobazam and/or valproate is associated with high rates of seizure control, including freedom from status epilepticus, for extended periods of time including into adulthood. Stiripentol has multiple mechanisms of action and also inhibits several metabolic drug metabolizing enzymes that can enhance the efficacy of co-administered anti-seizure medications. Stiripentol is well-tolerated and treatment-emergent adverse events can often be managed by dose adjustments of comedications. This review updates the use of stiripentol in the modern era.

Keywords: anti-seizure medication; Dravet Syndrome; stiripentol

INTRODUCTION

Dravet Syndrome (DS; formerly designated Severe Myoclonic Epilepsy in Infancy) is a rare treatment-refractory and severe form of epileptic encephalopathy with an incidence of approximately 2.5-6.5 per 100,000 live births.[1-3] DS typically presents in children between 1 and 18 months of age as recurrent, prolonged, tonic-clonic or hemiconvulsive seizures often associated with hyperthermia, although other seizure types, including myoclonic, focal, and atypical absence seizures, may also occur.[4,5] Status epilepticus (SE) is common in DS[6] and SE lasting 30 minutes or more is associated with serious long-term consequences such as neuronal injury, neuronal death, and functional deficits.[7] Patients with DS invariably experience persistent developmental delays, behavioral issues, and cognitive dysfunction.[8-10] Distressingly, these and other comorbidities are also accompanied by high rates of mortality, especially during the first 12 years of life.[11] The risk of all-cause mortality in DS has been estimated to be approximately 15% over the first 10 years after diagnosis, with up to 81% of those deaths attributable to sudden unexplained death in epilepsy (SUDEP) and SE.[12,13]

Box 1

Dravet Syndrome

- Dravet Syndrome is an early onset, developmental and epileptic encephalopathy associated with prolonged drug-resistant seizures, status epilepticus, and multiple comorbidities, including developmental delay, cognitive dysfunction, and behavioral issues
- Patients with Dravet Syndrome are at increased of risk of mortality, especially before the age of 12 years, primarily from status epilepticus and sudden unexpected death in epilepsy (SUDEP)
- Prompt diagnosis of Dravet Syndrome and early initiation of treatment with effective anti-seizure medications is recommended to reduce the severity and frequency of convulsive seizures, reduce the incidence of SUDEP and status epilepticus, and minimize the comorbidities associated with epileptic encephalopathy

DIAGNOSIS OF AND TREATMENT OF DRAVET SYNDROME

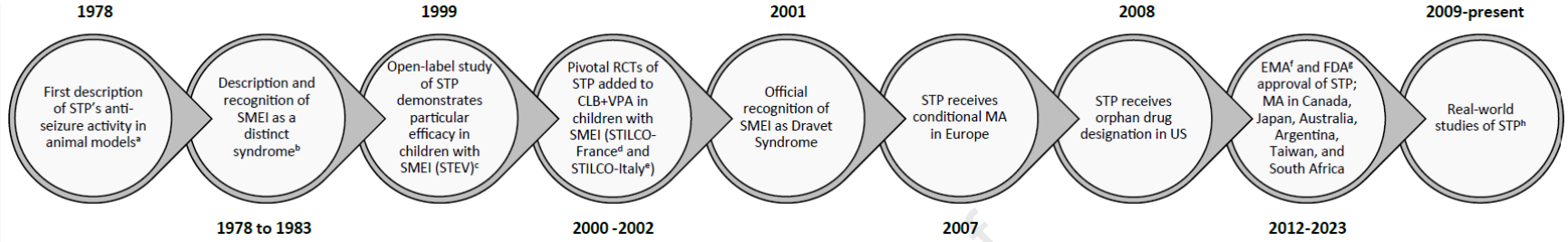
Criteria and consensus guidelines for diagnosis of DS have been published.[4,5,14] For patients meeting the clinical criteria for DS, it is recommended that a diagnosis be confirmed by genetic testing for inherited or de novo mutations in the voltage-gated sodium channel 1a gene (*SCN1A*).[4,5] *SCN1A* mutations are observed in 80%-85% of patients with DS,[4,5] but it should be noted that *SCN1A* mutations are also observed in persons with other epilepsy syndromes as well as healthy individuals,[15] and the lack of a positive genetic test for an *SCN1A* gene variant should not preclude a diagnosis of DS.[5] Therefore, the correlation between clinical presentation and results of genetic testing should be carefully considered.[16] The early accurate diagnosis of DS is important as it allows prompt initiation of treatment with an effective anti-seizure medication (ASM) regimen and avoids harmful outcomes associated with the use of contraindicated medications (eg, sodium channel blockers).[17] A recently developed DS prediction model based on age at febrile seizure onset and *SCN1A* genetic score has been shown to have improved power to discriminate between cases of DS and generalized epilepsy with febrile seizures plus (GEFS+) compared with earlier prediction models.[18] These readily accessible biomarkers (age at febrile seizure onset and *SCN1A* genetic features) can be entered into a web portal to obtain a model-predicted probability of DS.[19]

The goal of DS treatment is to control convulsive seizures (especially seizure clusters and SE), reduce overall seizure frequency, and minimize treatment side effects in order to maximize patient quality of life and reduce the risk of mortality due to SE and SUDEP.[4] Guidelines for treatment of patients with DS have been published, including US and European consensus recommendations.[4,14,20,21] North American and international consensus currently recommend a treatment tier consisting of valproic acid/sodium valproate (VPA) or clobazam (CLB) as first-line therapy, stiripentol or fenfluramine (FFA) as first- or second-line therapy, cannabidiol (CBD) as third-line therapy, and topiramate (TPM) and/or ketogenic diet as fourth-line therapy.[4] Levetiracetam, zonisamide, and clonazepam may be considered as later treatment options.[4,14]

It has been suggested that initiation of ASM treatment at the time of seizure onset (ie, typically within the first year of life) in order to prevent prolonged repeated seizures might also reduce progression to epileptic encephalopathy.[15] Among the recommended treatments for DS, stiripentol is the only one approved for use in children as young as 6 months of age.[22] Since 2007, stiripentol has been prescribed to patients in 55 countries, representing over 51,000 patient-years of exposure (**Figure 1**).[22-36]

The purpose of this review is to provide clinicians, especially those in the US, with practical information, based on nearly 50 years of clinical experience, on the use of stiripentol in patients as young as 6 months of age with DS. It is hoped that a wider appreciation of stiripentol's role in the therapeutic landscape may benefit patients with DS, their families, and care partners.

Figure 1. Timeline of key events in the development of stiripentol for Dravet Syndrome



CLB, clobazam; EMA, European Medicines Agency; FDA, Food and Drug Administration; MA, marketing authorization; RCT, randomized clinical trial; SMEI, severe myoclonic epilepsy in infants; STP, stiripentol; VPA, valproate.

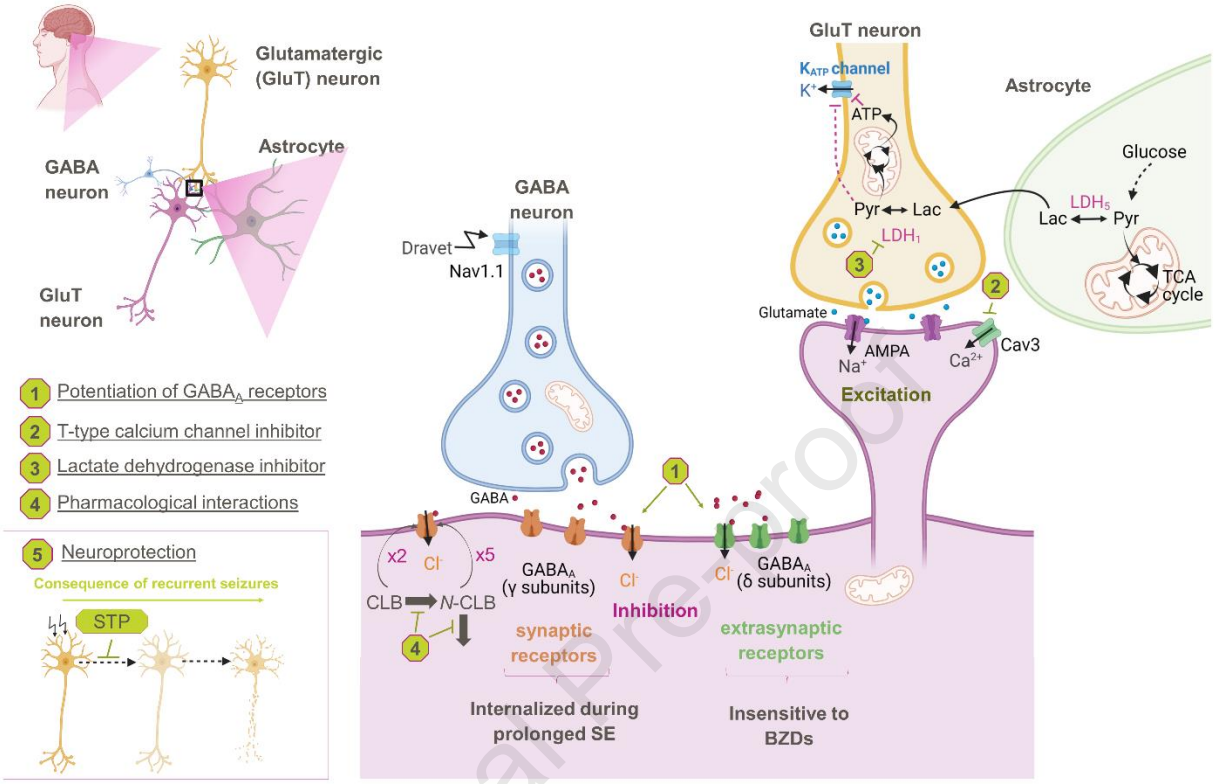
[a]Astoin et al. 1978.[23] [b]Dravet 1973.[24] [c]Perez et al. 1999.[25] [d]Chiron et al. 2000.[26] [e]Guerrini et al. 2002.[27] [f]DIACOMIT® [summary of product characteristics] 2021.[22] [g]DIACOMIT® [prescribing information] 2022.[28] [h]Inoue et al. 2009;[29] Wirrell et al. 2013;[30] Inoue et al. 2015;[31] Kim et al. 2016;[32] Myers et al. 2018;[33] Yildiz et al. 2019;[34] Yamada et al. 2021;[35] Chiron et al. 2023.[36]

STIRIPENTOL'S MECHANISM OF ACTION

Stiripentol is a broad-spectrum ASM with particular efficacy in DS. Anti-seizure medications in general act on multiple molecular targets, and stiripentol is no exception. It is therefore worth considering stiripentol's multiple modes of action in the context of its therapeutic action (**Figure 2**).[37]

Stiripentol is a positive allosteric modulator of ligand-gated γ-aminobutyric acid type A ($GABA_A$) receptors.[38] GABA is the main inhibitory cortical neurotransmitter and dysregulation of GABAergic signaling is associated with epileptic seizures.[39] Specifically, stiripentol binding to the $GABA_A$ receptor prolongs the open duration of the channel, thereby potentiating inhibitory signaling in the presence of GABA.[40] Stiripentol's positive modulation of $GABA_A$ receptors is most effective at receptors containing α3 or δ subunits.[38] mRNA encoding the α3 subunit is highly expressed in embryonic and early postnatal rat brain but is substantially decreased in the same regions in adults,[41] providing a plausible explanation for stiripentol's observed efficacy in childhood-onset epilepsies, including DS (see Efficacy of stiripentol, below). This explanation is consistent with evidence from rat models of SE[42,43] and from a mouse model of DS,[44] all of which demonstrated greater efficacy of stiripentol in immature compared with mature brains.

Figure 2. Mechanisms of action of stiripentol in Dravet Syndrome[37]



Summary of the different mechanisms of action of stiripentol (STP) in Dravet syndrome (DS). DS is characterized, in a majority of cases, by a deficit in the Nav1.1 sodium channel leading to decreased GABA transmission. (1) STP is a positive allosteric modulator of $GABA_A$ receptors, targeting both synaptic and extra-synaptic receptors. (2) STP inhibits ion channels, such as post-synaptic T-type calcium channels Cav3.1, 3.2, and 3.3. (3) STP can alter brain energy metabolism in neurons and astrocytes by inhibiting lactate dehydrogenase (LDH_1, LDH_5), involved in Lactate (Lac)-Pyruvate (Pyr) shuttle. (4) STP has pharmacokinetic interactions with concomitant antiseizure medications, such as clobazam (CLB) by inhibiting several cytochromes-450. (5) STP has an overall neuroprotective effect in neurotoxic conditions, such as during prolonged seizures.

ATP: adenosine triphosphate; BZDs, benzodiazepines; K_{ATP} channel, ATP-sensitive potassium channel; SE, status epilepticus; TCA: tricarboxylic acid.

Adapted from Bacq A, et al. *Adv Ther.* 2024;41(4):1351-71 and reproduced with permission from Springer Nature.

Stiripentol binds to $GABA_A$ receptors containing a γ subunit at a different site than benzodiazepines as well as to receptors containing a δ subunit, which are insensitive to benzodiazepines such as CLB.[38] Both of these characteristics lead to an additive effect of stiripentol and benzodiazepines.[38,40,43,45] Stiripentol further potentiates GABA inhibitory transmission by increasing brain GABA levels, possibly by inhibition of GABA re-uptake and/or by inhibition of GABA breakdown via GABA transaminase.[46]

Apart from its potentiation of GABAergic neurotransmission, stiripentol was recently shown to inhibit T-type voltage-gated calcium channels.[47] Interestingly, induction of SE in a mouse pilocarpine model of epilepsy is associated with long-term upregulation and functional alteration of T-type channels,[48,49] and their inhibition by stiripentol could account for some of stirpentol's protective effect against SE. Moreover, T-type calcium channels contribute to thalamocortical oscillations, which are altered in absence seizures.[50] Inhibition of T-type channels by stiripentol has been shown to produce a reduction in absence seizures in two rat models,[47] and may also help explain the therapeutic effect of stiripentol on atypical absence seizures seen in patients with DS.[35,51]

Stiripentol has additional pharmacological properties that may contribute to its efficacy in DS. For example, stiripentol is an inhibitor of lactate dehydrogenase (LDH).[52] In the context of seizure control, LDH inhibition reduces ATP production, decreases ATP-sensitive potassium (K_{ATP}) channel activation, hyperpolarizes neurons, and decreases neuronal excitability. Importantly, LDH inhibition has been shown to suppress seizure activity in mouse models of both acute and chronic seizures.[52] It is also interesting to note that LDH inhibition is one of the potential mechanisms for the efficacy of the ketogenic diet. Stiripentol is the only currently available ASM that possesses this mechanism of LDH inhibition.

Stiripentol also has important pharmacokinetic interactions with drug metabolizing cytochrome P450 (CYP) enzymes that can affect the plasma concentrations of other ASMs. This may result in synergistic drug combinations, further improving its efficacy. For instance, co-administration of stiripentol with CLB

results in increased serum concentration of CLB and its active metabolite, *N*-desmethylclobazam (norclobazam, *N*-CLB).[53] This drug-drug interaction increases the efficacy of CLB but also the potential for CLB-mediated side effects such as somnolence, anorexia, and asthenia.[54,55] The potential drug-drug interactions of stiripentol and their clinical significance are discussed further in the subsequent section, "Combination therapy with stiripentol."

Finally, stiripentol has been shown to have neuroprotective properties in preclinical models of neuronal injury and SE. Stiripentol administration reduced injury caused by oxygen-glucose deprivation and by glutamate excess in cultured neuronal-astroglial cells, possibly via voltage-dependent sodium and calcium channels.[56] In a lithium-pilocarpine rat model of SE, stiripentol significantly reduced cell injury in the polymorphic layer of the dentate gyrus in immature, but not mature, rats.[42] This neuroprotective effect is probably better viewed not as an independent mechanism of action but instead due to stiripentol's other pharmacodynamic effects. Similarly, stiripentol's overall efficacy in DS should be considered as the combined result of its multiple effects on neuronal signaling and metabolic activity, rather than as the product of a single mechanism.

EFFICACY OF STIRIPENTOL

Stiripentol is an α-ethylene alcohol structurally unrelated to other ASMs.[57] Stiripentol's anticonvulsant activity was first demonstrated 45 years ago in preclinical rodent models of electrically and chemically induced seizures[23] and has since been confirmed in additional animal models, including in primates.[57]

The first human clinical study of stiripentol as an add-on therapy in children aged 1 month to 20.5 years with refractory epilepsies demonstrated unexpected efficacy in patients with DS.[25] Of the 20 patients with DS who completed the open-label portion of the study, 10 responded to adjunctive stiripentol coadministered with CLB, demonstrating a ≥50% reduction in seizure frequency after 3 months of

treatment, with 3 of those becoming seizure-free.[25] These initial clinical findings have since been confirmed in pediatric patients with DS in 19 clinical studies, including randomized clinical trials (RCTs),[26,27] as well as prospective[29,31,33] and retrospective[30,32,34-36] observational studies (**Table 1**).

Table 1. Clinical and real-world studies of stiripentol in pediatric patients with Dravet Syndrome

Authors, date	Study design	Patients and duration	Key efficacy outcomes	Adverse events[a]
Perez et al., 1999[25]	Prospective open-label	n=20 3-month treatment period	Response rate: 50% Seizure-free: 15%	Not reported for patients with DS
Chiron et al., 2000; Guerrini et al., 2002 (pooled analysis)[26,27,58]	RCT	STP: n=33; PBO: n=31 Age: 3-21 years 2-month treatment period	Response rate: 70% STP vs 6% PBO Seizure-free: 48%-39% vs 0% PBO	Somnolence: 67% vs 23% PBO Decreased appetite: 46% vs 10% PBO Agitation: 27% vs 16% PBO Weight decreased: 27% vs 6% PBO Hypotonia: 18% vs 13% PBO Nausea: 15% vs 3% PBO Tremor: 15% vs 10% PBO Dysarthria: 12% vs 0% PBO Insomnia: 12% vs 7% PBO
Inoue et al., 2009[29]	Prospective observational	N=23 Age: 1-22 years Duration, mean (range): 14.1 (6-34) months	Response rate: 61% during first 4 weeks; maintained by 48% after an average 14.1 months of treatment Seizure-free: 9% SE-free: 4%	Loss of appetite: 13%-70% Drowsiness: 0%-65% Ataxia: 4%-30% Hyperactivity/irritability: 0%-30% Nausea: 0%-13%
Wirrell et al., 2013[30]	Retrospective observational	N=82	Response rate: 29%-35%[b]	Sedation/somnolence: 18%

		Age, median (IQR): 6.9 (4.2, 10.4) years Duration, median (IQR): 22.3 (9.9, 43.2) months	SE-free: 80%-97%	
Inoue et al., 2015[31]	Prospective observational	N=24 Age: 1-24 years Duration: up to 56 weeks	Response rate: 54% Seizure freedom: 10%	Somnolence: 75% Loss of appetite: 42% Ataxia: 50%
Kim et al., 2016[32]	Retrospective observational	N=14 Age, median (min, max): 7.4 (1.1, 20) years Duration, median (min, max): 21 (2, 45) months	Response rate: 64%	Somnolence: 29% Ataxia: 14%
Myers et al., 2018[33]	Prospective observational	N=41 Age, mean (min, max): 5.6 (0.9, 22) years Duration, mean (min, max): 37 (2, 141) months	Response rate: 49% SE-free: 26%	Anorexia/weight loss: 49% Drowsiness/sedation: 34% Behavioral change: 22% Neutropenia: 12% Abdominal pain: 10% Insomnia: 10%
Yildiz et al., 2019[34]	Retrospective observational	N=21 Age, mean (min, max): 8.2 (5.4, 15) years Duration, mean: 34.4 months	Response rate: 57% Seizure-free: 10% SE-free: 73%	Sedation: 29% Ataxia: 14%
Yamada et al., 2021[35]	Retrospective observational	Efficacy: n=409 Safety: n=410	Response rate: 43%	Somnolence: 36% Loss of appetite: 24%

		Duration: 2 years		Ataxia: 14%
Chiron et al., 2023[36]	Retrospective observational; STP initiated prior to 2 years of age	N=82 Age, median (min-max): 12.6 (3.8-23.7) months Duration Median (IQR): 27.8 (17.8, 39.1) months Short-term: <6 months treatment (n=114) Long-term: (<7 years of age at last visit on stiripentol): n=106	Response rate Short term: 52% Long-term: 35% Seizure-free Short term: 31% Long-term: 14% SE-free Short term: 55% Long-term: 67%	Loss of appetite/weight: 21% Sleep disorders: 11% Somnolence: 11%

Response rates are based on patients achieving ≥50% reduction from baseline seizure frequency.

AEs, adverse events; DS, Dravet Syndrome; IQR, interquartile range; PBO, placebo; RCT, randomized clinical trial; SE, status epilepticus (seizure lasting ≥30 minutes); STP, stiripentol.

[a]AEs in ≥10% of patients (all studies) and ≥5% greater than placebo (RCTs only). [b]Defined as a decrease in seizure frequency by ≥2 levels (eg, from "daily or more" to "at least less than weekly").

The efficacy of stiripentol in children with DS (median [range] age of 8.7 [3.0, 20.7] years) treated concomitantly with CLB plus VPA that was observed in the pivotal French[26] and Italian RCTs[27] formed the basis of stiripentol's US approval.[58] In a pooled analysis of the pivotal trials, significantly more patients treated with stiripentol than placebo demonstrated ≥50% reduction in baseline seizure frequency (23/33 [70%] vs 2/31 [7%]; $P<0.0001$). The absolute reduction in baseline seizure frequency with stiripentol was 84% compared with 6% in the placebo group ($P<0.0001$). After 3 months of double-blind treatment, 13/33 (39%) of patients in the stiripentol group were free from generalized clonic or tonic-clonic seizures compared with no patients in the placebo group.

The recommended adjunctive treatments for DS have not been compared directly in head-to-head trials. However, an indirect comparison of 5 RCTs in 565 patients with DS determined that stiripentol was associated with a higher probability of a ≥50% reduction in baseline convulsive seizure frequency (odds ratio [OR] 47.5) than FFA (OR 17.4) or CBD (OR 2.36) compared with placebo.[59] Additionally, a greater proportion of patients treated with stiripentol achieved seizure freedom (43%) than those treated with FFA (11%) or CBD (5%).

Stiripentol's effectiveness in long-term seizure control has been confirmed in multiple real-world observational studies.[29-36] During real-world stiripentol treatment ranging from 1.2 to 8 years, the median percentage of responders achieving ≥50% reduction in baseline seizure frequency was 57% (range 35% to 80%). In all studies, discontinuation of stiripentol due to lack of efficacy was 3% (1/33) in the pivotal RCTs[26,27,58] and ranged between 0% and 16% during real-world studies.[29-31,34-36]

Initiation of safe and effective ASM therapy shortly after a diagnosis of DS is recommended in order to reduce prolonged convulsive seizures and SE.[4] Status epilepticus in DS is associated with severe, irreversible encephalopathy and a significant future risk of cortical atrophy, neurologic regression, and

imminent (time-linked) death.[60] Status epilepticus in DS also carries a risk of later SUDEP, one mechanism of which may be a reduction in heart rate variability following an episode of SE.[61] The efficacy of stiripentol in reducing episodes of SE was not assessed in the pivotal RCTs; however, this has been looked at in multiple real-world studies.[29-36,62-66] Importantly, during up to 18 years of adjunctive stiripentol treatment, 77% (range 4% to 100%) of patients were free of SE.

Evidence for the efficacy of early use of stiripentol was provided by a retrospective analysis of 131 children with DS who initiated stiripentol by their second birthday.[36] Short-term (<6 months) and long-term (<7 years of age at last visit on stiripentol) treatment was associated with responder rates of 52% and 35%, respectively. In addition, freedom from SE was achieved by 55% of children during short-term treatment and by 67% of patients during long-term treatment.

Importantly for long-term patient management, the benefits of stiripentol treatment initiated in childhood appear to be maintained well into adulthood.[65] Forty patients who initiated stiripentol treatment early (before age 15 years) or late (after age 18 years) were followed for an a median of 18.1 years. At the last visit in adulthood, early treatment initiation was associated with lower seizure frequency, fewer patients with severe neurological and intellectual impairment, and fewer patients who were completely dependent compared with late treatment initiation. Also, at the last visit in adulthood, 25% and 13% of patients who began treatment before the age of 18 years had been seizure free for >1 year and for >2 years, respectively.[65]

SIDE EFFECT PROFILE AND TOLERABILITY

In the RCTs, the most common adverse events (AEs; >10% of patients and ≥5% greater than placebo) with stiripentol treatment were somnolence (67% vs 23% with placebo), decreased appetite (46% vs 10%), agitation (27% vs 16%), weight decreased (27% vs 6%), hypotonia (18% vs 13%), nausea

(15% vs 3%), tremor (15% vs 10%), dysarthria (12% vs 0%), and insomnia (12% vs 7%) (**Table 1**).[22] Adverse events reported during real-world observational studies of stiripentol were consistent with those seen in the pivotal RCTs, and no new safety signals were seen (**Table 1**).[29-36] Of note, AEs observed in patients who initiated stiripentol before the age of 2 were similar to those in older children.[36] Importantly for patient management, the incidences of AEs associated with adjunctive stiripentol such as somnolence, loss of appetite, agitation, irritability, and ataxia can be improved by reducing the dose of stiripentol or of VPA or CLB co-medications.[26,31,35,36]

During double-blind treatment in the pivotal RCTs, 2 patients (6%) discontinued stiripentol due to AEs, one due to somnolence and impaired balance and one due to an AE of SE.[22] During real-world treatment with stiripentol, discontinuation due to AEs ranged between 0% and 12% of patients,[29-32,34-36] with somnolence, appetite/weight loss, ataxia/vertigo, and behavioral changes among the most commonly cited reasons. During up to 8 years of real-world treatment, stiripentol retention rates ranged from 75% to 97%.[29,30,33-36,63]

PRESCRIBING AND DOSING CONSIDERATIONS

Once the decision to prescribe stiripentol has been made, the drug can be obtained by prescription or from a national specialty pharmacy.[67] Formulations of stiripentol available in the US are listed in **Table 2**. The packet and capsule formulations are bioequivalent in terms of time to peak serum concentration (T_{max}) and area under the plasma drug concentration-time curve (AUC) but not in terms of the maximum serum concentration (C_{max}).[28] The C_{max} of the packet formulation is slightly (23%) greater compared with the capsule, and clinical supervision is recommended if switching between the stiripentol capsule and powder for oral suspension. The absorption of both formulations is enhanced by taking them with a meal or immediately after eating. Note that for children following a ketogenic diet, the carbohydrate content of the 2 formulations is different and should be taken into account.

Table 2. Stiripentol formulation and dosing forms

	Packet		Capsule	
Dosage form	**250 mg**	**500 mg**	**250 mg**	**500 mg**
Formulation	Povidone K29/32 Sodium starch glycolate type A Glucose liquid, spray dried Titanium dioxide (E171) Aspartame (E951) Fruit flavor (contains sorbitol) Carmellose sodium Hydroxyethyl cellulose		Povidone K29/32 Sodium starch glycolate type A Erythrosine (E127) (250 mg capsule only) Titanium dioxide (E171) Indigotine (E132) (250 mg capsule only) Magnesium stearate (E470b)	
Excipient with known effect	Aspartame 2.5 mg Glucose liquid spray 500 mg Sorbitol 2.4 mg Sodium 0.11 mg Carbohydrate 500 mg	Aspartame 5 mg Glucose liquid spray 1000 mg Sorbitol 4.8 mg Sodium 0.22 mg Carbohydrate 1000 mg	Sodium 0.16mg Carbohydrate 3 mg	Sodium 0.32 mg Carbohydrate 6 mg
Capsule core	NA	NA	Povidone K29/32 Sodium starch glycolate type A Magnesium stearate 11	
Capsule shell	NA	NA	Gelatin Titanium dioxide (E171) Erythrosine (E127) Indigotine (E132)	Gelatin Titanium dioxide (E171)
Shelf life	3 years	3 years	3 years	3 years
Pharmaceutical form	Pale pink crystalline powder in packets for oral suspension		Size 2 pink capsule imprinted with “Diacomit” and “250 mg”	Size 2 pink capsule imprinted with “Diacomit” and “500 mg”
Packaging	Cartons of 60 packets		Bottles of 60 capsules	

See reference [22].

For patients between 6 months and 12 years of age, the recommended oral dosage of stiripentol is 50 mg/kg/day, administered in 2 or 3 divided doses (ie, 16.67 mg/kg three times daily or 25 mg/kg twice daily), depending on the patient's age and body weight, with a maximum total dosage of 3000 mg/day.[22] The powder (typically the 250 mg packet) can be mixed in 10 ml of water giving a concentration of 25 mg/ml and providing a convenient dosing volume for infants and young children (**Figure 3**). Stiripentol should be given shortly after a meal since it is rapidly degraded in the acidic environment of an empty stomach.[28] In children under the age of 12, stiripentol should be started at a dose of 20 mg/kg/day, and gradually escalated to reach the recommended dose.[28] In children older than 12 years, smaller dose increments are recommended during titration, and the final dose should be individually determined based on clinical judgement,[28] due to the fact that 50 mg/kg/day administered as twice-daily dosing may lead to excessive stiripentol exposure in adolescents, possibly due to age-related changes in metabolism and clearance.[68] A suggested algorithm[21,28,68] for dose escalation in children aged 6 months to >12 years is shown in **Figure 4**.

Figure 3. Preparation and administration of stiripentol powder for infants and young children

Step 1.
Measure 10 mL of water and pour into the provided drinking cup.

Step 2.
Tap a 250 mg packet of stiripentol for oral suspension to settle the powder to the bottom of the packet.

Step 3.
Using a clean pair of scissors, cut off the top of the packet and make sure the packet is fully open.

Step 4.
Empty the packet into the small drinking cup. Ensure that there is no medication left in the packet.

Repeat steps 2 though 4 for each packet of stiripentol needed for the total prescribed dose

Step 5.
Use the provided spoon to gently mix the medicine and the water until dissolved.

IMMEDIATELY AFTER MIXING:

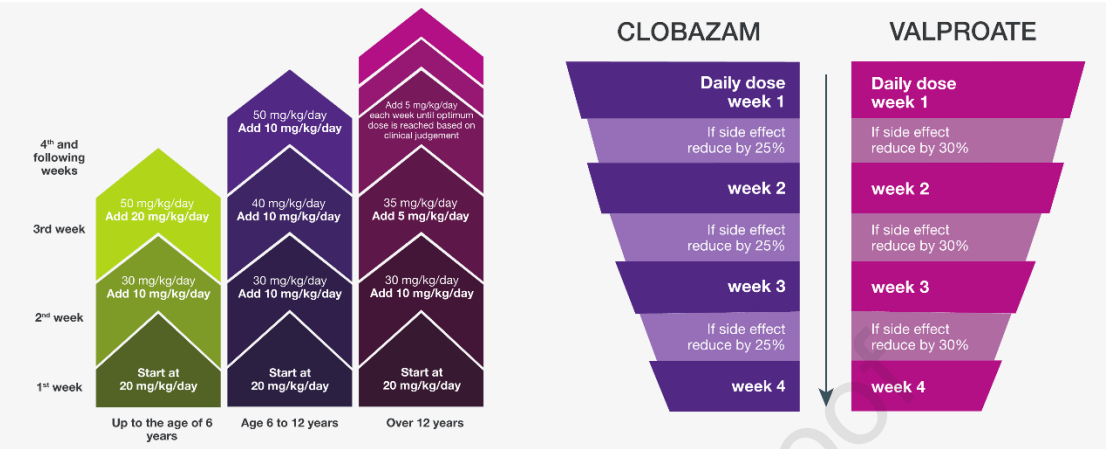
Have your child drink all of the mixture in the cup

Rinse the cup by adding an additional 10 mL of water and mixing

Have your child drink the mixture

STIRIPENTOL SHOULD ALWAYS BE TAKEN WITH FOOD

Figure 4 Titration of stiripentol and adjustment of co-medications



Stiripentol dose titration according to patients age (left) and dose adjustment of clobazam and valproate comedications by week (right).

COMBINATION THERAPY WITH STIRIPENTOL

Before 2018, there were no approved medications in the US for treatment of children with DS. However, even with the approval of stiripentol, CBD (2018), and FFA (2020), DS remains highly treatment resistant and optimal seizure control usually requires use of multiple ASMs (polypharmacy).[69] Therefore, the potential benefit of combination therapy, the pharmacokinetic properties of co-administered ASMs, and the potential for clinically relevant drug-drug interactions should be considered and carefully balanced. The pharmacokinetic properties of stiripentol and other ASMs commonly used in DS are shown in **Table 3**.[22,28,55,58,68,70-78]

Table 3. Pharmacokinetic parameters of adjunctive ASMs for Dravet Syndrome

	STP[22,28,58,68,70]	**FFA**[a][71,72]	**CBD**[55,70,73,74,78]	**TPM**[75-77]
Formulation and Dosing	Oral capsules or suspension (Can prepare 250 mg/100 ml); 2 or 3 divided doses	Oral solution, 2.2 mg/mL; 2 divided doses	Oral solution, 100 mg/mL; 2 divided doses	Liquid, oral tablets, or sprinkle capsules; 2 divided doses
Maintenance Dose	50 mg/kg/day (3000 mg/day max)	0.7 mg/kg/day max (26 mg/day max) With STP: 0.4 mg/kg/day max (17 mg/day max)	10 mg/kg/day (20 mg/kg/day max)	11-25 mg/kg/day max (400 mg/day max)
Food Effect	**Take with food**: degrades rapidly in acidic environment of an empty stomach	Absorption not affected by food vs fasting	**Take with food**: increased absorption with food (especially high-fat foods)	Absorption not affected by food vs fasting
Bioavailability	Well absorbed; majority of dose excreted in urine[b]	68% to 74%	~6% fasting ~24% with high-fat meal	80% (relative bioavailability)
Serum Protein Binding	~99%	50%	>94%	15% to 41%
T_{max}	2 to 3 hours	3 to 5 hours	2.5 to 5 hours	2 hours
C_{max}	14 to 33 mg/L as body weight increases from 10 to 70 kg	68 ng/L	1.6 mg/L (fed state)	6.8 mg/L
AUC	90 to 281 mg*h/L[c] as body weight increases from 10 to 70 kg	1390 ng*h/mL[d]	8.7 mg*h/L[e]	58.6 mg*h/L[e]

V_d	32 to 192 L (apparent V_d; V_{ss}) as body weight increases from 10 to 60 kg	11.9 L/kg (geometric mean apparent V_d, V_z/F)	20963 L to 42849 L	0.6 to 0.8 L/kg
Clearance	2.6 to 5.7 L/h as body weight increases from 10 to 60 kg	24.8 L/h (geometric mean)	67 to 74 L/h	20 to 30 mL/min
$t_{1/2}$	4.5 to 13 hours (adults) 8.5 hours to 23.5 hours (children, by body weight from 10 to 60 kg)	20 hours	21.6 to 33.5 hours	21 hours
Primary Metabolism	Hepatic CYP1A2 CYP2C19 CYP3A4	Hepatic Primary: CYP1A2 CYP2B6 CYP2D6 Additional: CYP2C9 CYP2C19 CYP3A4/5	Hepatic CYP2C19 CYP3A4 UGT1A7 UGT1A9 UGT2B7	Renal (70% unchanged)

[a]FFA is rapidly metabolized to nFFA; both compounds are pharmacologically active. [b]No IV formulation available to evaluate absolute bioavailability. [c]AUC over the 12-hour dosing interval at steady-state. [d]AUC from time 0 to 24 hours; [e]AUC from time 0 to infinity.

AUC, area under the plasma drug concentration-time curve; CBD, cannabidiol; CLB, clobazam; C_{max}, maximum concentration; CYP, cytochrome P450; DDI, drug-drug interaction; FFA, fenfluramine; IV, intravenous; nFFA, norfenfluramine; $t_{1/2}$, elimination half-life; STP, stiripentol; TPM, topiramate; T_{max}, time to peak concentration; UGT, UDP-glucuronosyltransferase; V_d, volume of distribution; VPA, valproate; V_{ss}, volume of distribution at steady state; V_z/F, apparent volume of distribution.

At therapeutic concentrations in vitro and in vivo, stiripentol has been shown to inhibit several cytochrome P450 iso-enzymes (CYPs), including CYP1A2, CYP2C9, CYP2C19, and CYP3A4,[79] leading to possible interactions with other ASMs prescribed for DS (**Table 4**). Stiripentol is primarily metabolized by CYP1A2, CYP2C19, and CYP3A4. Therefore, co-administration of stiripentol with other drugs that inhibit or induce these enzymes should be carefully considered. In addition, co-administration of strong CYP1A2, CYP2C19, and CYP3A4 inducers, such as rifampin, primidone, phenytoin, phenobarbital, and carbamazepine, results in a lower serum concentration for stiripentol due to increased metabolism.[80]

Table 4. Drug-drug interactions and side effects of stiripentol co-administration with other adjunctive ASMs for Dravet Syndrome

Effect of stiripentol on CYP isoenzyme metabolism	**Effect of stiripentol co-administration on co-administered ASMs[a]**				
	CLB	**VPA**	**FFA**	**CBD**	**TPM**
↓CYP2C19	↑CLB, ↑↑*N*-CLB[b] ↑Risk of somnolence	↑VPA (potential)[c] ↑Risk of appetite loss ↑Moderate risk of weight loss		↑*N*-CBD[d] ↑Risk of somnolence ↑STP (slight)[e] ↑Slight risk of somnolence	Potential (slight) for metabolic competition with STP and other CYP2C19 substrates[f]
↓CYP3A4	↑CLB[b]	↑VPA (potential)[c] ↑Risk of appetite loss ↑Moderate risk of weight loss			
↓CYP1A2		↑VPA (potential)[c] ↑Risk of appetite loss ↑Moderate risk of weight loss	↑FFA[g] ↓nFFA[h]		

[a]Additional documented and/or potential DDIs with other ASMs: STP may increase plasma concentrations of coadministered, primidone, ethosuximide, tiagabine, and diazepam; metabolic interactions are not expected with levetiracetam;[28] use of sodium channel blockers including carbamazepine, phenytoin, phenobarbital with STP is contraindicated,[28] although phenytoin may be considered as rescue medication.[4]

[b]Co-administration of STP with CLB increases the serum concentration of CLB by ~2-fold and of *N*-CLB (clobazam active metabolite associated with sedation[53]) by ~5-fold. If necessary, reduce CLB dose (See **Figure 4**) to 0.2-0.3 mg/Kg/day, to prevent excessive somnolence.

[c]The potential for metabolic interaction is considered to be modest and adjustment in valproate dosage is generally not necessary. In cases of anorexia or weight loss, valproate daily dose can be decreased by ~30% per week.[28]

[d]Co-administration of CBD and CLB results in increased *N*-CLB exposure and increased risk of excessive somnolence/sedation.[81] In combination therapy regimens with CLB, STP, and CBD, a reduction in CBD dose is recommended.[70]

[e]Patients receiving concomintant STP and CBD should be monitored for adverse reactions; reduce STP if necessary.[82]

[f]Metabolic competition not expected at therapeutic concentrations of TPM.[28]

[g]For clinical safety, a reduction in FFA may be necessary.[70]

[h]nFFA (norfenfluramine) is an active metabolite of FFA and is associated with the valvular heart disease liability of FFA.[83]

ASM, anti-seizure medication; CBD, cannabidiol; CLB, clobazam; DDI, drug-drug interaction; FFA, fenfluramine; *N*-CLB, *N*-desmethylclobazam; nFFA, norfenfluramine; STP, stiripentol; TPM, topiramate, VPA, valproate.

Combination therapy with clobazam and/or valproate

While stiripentol possesses anti-seizure activity when administered as monotherapy,[30] its efficacy when added to CLB is also the result of a combination of pharmacodynamic and pharmacokinetic interactions. Stiripentol and CLB are both potentiators of GABAergic neurotransmission via interactions at the $GABA_A$ receptor, and pharmacodynamic effects of these two ASMs leads to a combined activation and therapeutic effect that is greater than either can achieve on its own.[30,45] Stiripentol is a potent inhibitor of CYP3A4 and CYP2C19, which results in a 2- to 3-fold increase in the plasma concentration of CLB and a 5- to 7-fold increase in the concentration of *N*-CLB, an active metabolite of CLB (**Table 4**).[53] Clobazam, a benzodiazepine, is associated with benzodiazepine-like AEs, notably somnolence and sedation.[84] Population pharmacokinetic modeling suggests that the increased concentration of *N*-CLB would have the combined effect of increasing both the efficacy and side effect liability of CLB.[54] In light of the potential for sedating side effects, patients currently being treated with CLB should be monitored after starting adjunctive stiripentol therapy, and a 25% reduction in weekly CLB dosage to 0.2-0.3 mg/kg/day should be considered.[70,85]

Valproate is recommended as a first-line therapy in children with DS,[4] and the efficacy of VPA in DS is most likely related to its ability to increase GABA levels and inhibit of several ligand-and voltage gated ion channels.[86] Valproate treatment is associated with AEs, some serious, including a risk of hepatoxicity in children under the age of 2 years.[87,88] The potential for clinically meaningful metabolic interactions between stiripentol and VPA is considered modest, and modification of VPA dosage is generally not needed except for reasons of clinical safety.[28] In the pivotal studies of stiripentol, a VPA dose reduction of 10 mg/kg/day was permitted in the event of gastrointestinal adverse reactions such as anorexia and weight loss. Adverse events of anorexia and weight loss occurred in 46% of patients in the stiripentol cohort (**Table 1**) resulting in VPA dosage reduction in 21% (7/33).[58]

Combination therapy with fenfluramine, cannabidiol, or topiramate

Like stiripentol, FFA is recommended as an initial therapy or as a second-line therapy in patients with on-going seizure activity despite treatment with CLB and VPA,[4,14] and FFA is an effective add-on therapy in patients receiving combination ASM regimens containing stiripentol. An RCT of FFA added to stiripentol-containing regimens in patients with DS showed that coadministration of FFA was associated with significantly greater response rate (≥50% reduction in baseline seizure frequency) and with significantly more consecutive seizure-free days compared with placebo.[89] The most common AEs (decreased appetite, fatigue, diarrhea, and pyrexia) were similar to those observed in an earlier RCT of add-on FFA in the absence of stiripentol.[90] Three (7%, 3/43) patients who received add-on FFA discontinued treatment due to AEs.[89] In a phase 1 study of FFA in healthy volunteers, co-administration of FFA with a combination regimen consisting of stiripentol, CLB, and VPA resulted in a 1.2- to 1.7-fold increase in FFA exposure and a concomitant 1.7-fold decrease in norfenfluramine exposure compared with the combination regimen alone, most likely mediated by stiripentol's inhibition of CYP1A2.[91] Side effects related to FFA in regimens containing stiripentol should be managed by FFA dose reductions.[70] Norfenfluramine is a principle, active metabolite of FFA and is associated with development of valvular heart disease in overweight adult patients.[92] It should be noted, however, that valvular heart disease has not been observed in studies of FFA treatment in pediatric patients with DS.[93] However, as many patients with DS survive to adulthood, the combination of stiripentol and FFA may have benefits, with respect to increased therapeutic efficacy and a possible reduction in the risk of serious side effects, throughout the disease course.

Cannabidiol is currently recommended as a third-line treatment in patients with on-going seizure activity that is inadequately controlled by first- and second-line therapy.[4] Drug-drug interactions between stiripentol and CBD have been assessed in healthy volunteers[94] and in patients with epilepsy.[82] In both studies, co-administration of stiripentol and CBD resulted in a slight increase in stiripentol plasma concentration compared with administration of stiripentol alone, while CBD exposure was unaffected by

stiripentol.[94] The increase in stiripentol concentration in the presence of CBD may result from CBD inhibition of CYP2C19,[94] one of the enzymes involved in stiripentol metabolism (**Table 3**). It should be noted that a drug-drug interaction between CBD and *N*-CLB, resulting in a 2- to 3-fold increase in *N*-CLB exposure, as well in an increased incidence of excessive somnolence/sedation, has been described.[81] Accordingly, in CDB combination therapy regimens with CLB and stiripentol, a reduction in CLB dose may be necessary to avoid excess sedation/somnolence.[70,85]

Topiramate is currently recommended as a fourth-line treatment option for drug-resistant seizures in patients with DS.[4,14] Data regarding combination therapy including stiripentol and TPM are limited. A retrospective analysis of >1200 plasma samples obtained from patients undergoing ASM treatment demonstrated an increase in the concentration-to-dose ratio of TPM in patients receiving concomitant stiripentol.[95] Stiripentol and TPM are both metabolized by CYP2C19, although metabolic competition is not expected at therapeutic concentrations of TPM.[28] Based on clinical observations in patients with DS treated with concomitant stiripentol and TPM, dose adjustments for either medication should not be necessary.[28]

CONCLUSIONS

Dravet syndrome is a rare and severe treatment-refractory developmental and epileptic encephalopathy. Patients with DS are at risk of debilitating developmental, cognitive, and behavioral comorbidities, and have a mortality rate of 15.8 per 1000-person-years,[12] with approximately 80% of deaths due to SUDEP and SE. Initiation of ASM treatment as soon as possible after a diagnosis of DS is recommended to reduce the severity and frequency of convulsive seizures, reduce the incidence of SUDEP and SE, and minimize the comorbidities associated with epileptic encephalopathy.

Stiripentol is the only ASM approved in the US for use in patients with DS as young as 6 months of age. In a long-term study, patients who initiated stiripentol before the age of 2 years achieved high rates of

≥50% reduction in seizure frequency and of freedom from prolonged seizures and SE, lasting up to 7 years of age.[36] This suggests that there may a time-sensitive developmental window during which the brain is more responsive to the effect of stiripentol, possibly based on age-dependent $GABA_A$ receptor expression or on the reduction of neuronal changes that occur following uncontrolled seizures or SE. Studies of the long-term benefits of early stiripentol initiation over longer times would provide important additional information. In addition, improvements in earlier diagnosis of DS and paradigms for early initiation of treatment would help determine whether early use of stiripentol can produce benefits in cognitive and behavioral outcomes in addition to its already demonstrated benefit in seizure control.

Due to the treatment-refractory nature of DS, patients are invariably treated by therapeutic regimens consisting of 2 or more ASMs.[69] Stiripentol is well-tolerated during combination therapy with the first-line therapies CLB and VPA, and with the newly approved ASMs FFA, CBD, and TPM, and AEs stemming from drug-drug interactions can be effectively managed by decreasing the dosage of co-administered ASMs. Of the second- than third-line ASMs that have been studied to date, FFA when added to stiripentol-containing regimens seems to provide additional benefit in seizure control and an acceptable risk profile, suggesting that early treatment with stiripentol combined with FFA as first- or second-line therapy could be considered to maximize seizure control and treatment outcomes. It would be of interest to additionally assess the long-term benefit-risk profile of early initiation of concomitant stiripentol plus FFA in seizure and disability outcomes in adult patients with DS.

Box 2

Key Takeaways

- Stiripentol is an effective add-on treatment for patients with Dravet syndrome based on randomized clinical trials and real-world studies; most adverse events can be managed by reducing the dosage of concomitantly administered anti-seizure medications
- Initiation of stiripentol in patients before the age of 2 years produces a prolonged reduction in seizure frequency and sustained freedom from status epilepticus, and stiripentol initiation prior to age 12 years is associated with fewer patients with severe neurological and intellectual impairment in adulthood
- Early use of stiripentol combined with FFA as second-line therapy could be considered to maximize seizure control and treatment outcomes, and to reduce possible risks of the cardiovascular side effects associated with FFA metabolism

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