Dravet syndrome: Treatment Options & Management of Prolonged Seizures

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Summary points

- An early accurate diagnosis is key to optimal treatment in Dravet syndrome
- Prompt rescue treatment with personalised protocols for prolonged seizures is key, as well as avoidance of precipitants of seizures
- Clobazam, stiripentol, valproate and more recently cannabidiol appear effective treatments
- Fenfluramine is a promising agent demonstrating specific efficacy in trials to be considered for the future

Abstract:

Over time, with careful delineation of the syndrome, we have gained experience in treatments most likely to lead to improvement in seizures, as well as those that should be avoided. Sodium Valproate, Clobazam, stiripentol and topiramate are all medications that may lead to benefit, as well as the ketogenic diet. Bromides may be utilised in resistant cases. However equally important is outlining prompt rescue treatment for prolonged seizures, as well as avoidance of precipitants. Newer agents including cannabidiol and fenfluramine have been demonstrated to be of benefit in clinical trials. We propose an algorithm for management, although appreciate with time the positioning of the newer agents in such is yet to be established.

Introduction

Our understanding of the treatment of Dravet syndrome has evolved over the years since the original description. However review of long term outcomes show that despite our increased knowledge, the majority continue to have seizures in the long term with poor prognosis for cognitive and behaviour outcome[1,2]. In part this is related to a relatively late diagnosis[3]. In the first instance early diagnosis remains key; a history of a single prolonged lateralised clonic (hemiclonic) seizure in an infant less than 9 months, in the absence of a structural brain lesion, should prompt *SCN1A* genetic testing, and introduction of antiepileptic drugs/emergency rescue protocol considered where diagnosis is confirmed. However in a recent survey of Dravet families across Europe only 6.3% reported seizure freedom in the last 3 months[3]. Although traditionally labelled an epileptic encephalopathy in view of the early normal neurodevelopmental progress prior to the onset of the epilepsy, it is difficult to find evidence that seizures wholly impact on outcome – there is likely to be an underlying developmental contribution from the underlying genetics[4]. This aside, it appears appropriate to strive for optimal seizure control, in order to optimise neurodevelopmental outcome and quality of life.

As a well defined population, with careful delineation of the phenotype, and a need for newer agents, Dravet syndrome has been specifically included as a population on which to try novel therapies. Originally this resulted in the first RCT in a rare epilepsy – utilisation of stiripentol in addition to clobazam and sodium valproate vs placebo in children with convulsive seizures the result of Dravet syndrome[5]. With careful delineation of the phenotype, an RCT was able to define a significant benefit of stiripentol over placebo in reducing convulsive and prolonged seizures when added to clobazam and valproate. Maintained benefit was also seen in the longer term[6]. Other agents have been reported in open label cohort studies to be beneficial such as topiramate[7] and bromides[8], as well as the ketogenic diet[9] in the treatment of this group of children following failure

of optimised treatments. Bromides have specifically been reported to be effective in certain settings where standard treatments have failed[8] although of limited availability.

It appears likely that the avoidance of possible aggravating treatments may have an equal impact to utilisation of beneficial anti-epileptic drugs. Guerrini et al were the first to determine that sodium channel blockers eg carbamazepine, lamotrigine, may aggravate myoclonus in the Dravet population[10]. Their use in childhood might negatively impact the cognitive outcome[11]. It has since however been reported that some may be responsive to such medication, particularly lamotrigine – with aggravation of seizures seen on a wean of this medication[12] and therefore careful consideration needs to be given prior to an automatic wean if established without a definitive history of worsening of seizures.

However, despite progress in our understanding of the disease, the majority of individuals continue to have seizures in the long term. Further, little inroads have been made into improving neurodevelopmental outcomes. There remains a real need to evaluate newer treatments optimising early management and working towards improving outcomes. Much interest has been expressed in cannabis derived products, and more recently there have been impressive results reported with the repurposed agent fenfluramine.

Emergency treatments and protocols

A component of the phenotype to Dravet syndrome is prolonged convulsive seizures, often requiring emergency attendance at hospitals. In a survey of caregivers of patients with Dravet syndrome on experiences of management and health services, with responses from 584 caregivers of children (83%) and adults (17%), half of patients required at least one emergency admission and 46% at least one ambulance call in the past 12 months[3]. Younger rather than older patients were prone to emergency admission (94% and 76% vs 30% and 28% in infant and pre-school vs adolescents and

adults respectively). It is established that the earlier prompt treatment of seizures, will reduce the likelihood of status epilepticus and consequent admission to hospital. Although standard treatment of prolonged seizures is 5 minutes[13], in Dravet syndrome where many, particularly younger children, will be guaranteed to experience a prolonged motor seizure whenever such a seizure occurs, it is reasonable to indicate use of emergency rescue medication immediately rather than wait a customary period of time. It is therefore recommended that patients with Dravet syndrome have an individual care plan with regard to emergency treatment about which all individuals involved in their care are aware and that can be administered by the care givers. It is also prudent to try and avoid precipitants; hyperthermia is a significant trigger in nearly all young children and up to half of adults with Dravet [14,15]. Consequently it is recommended to avoid situations that may provoke this such as high ambient temperature, or immersion in hot baths, as well as recommend prompt treatment of fever and illness with utilisation of antipyretics.

With regard to what medication to use for emergency rescue, a benzodiazepine would be the first line, for home or hospital use (figure 1). This may be buccal midazolam in the community in most countries; rectal diazepam would be a substitute if buccal midazolam is not available. A clear indication of how many times this may be repeated in a home situation must be agreed and stated; a maximum of 2 doses of a benzodiazepine should be administered in total including out and in hospital administration in view of the risk of subsequent respiratory depression[16]. On arrival of mobile medical team or presentation to a hospital emergency department and if the seizure is still ongoing, lorazepam, midazolam or other intra venous benzodiazepine should be used. Subsequent second line medication may depend on previous response of an individual to such medication, as well as local protocols. Concern has been expressed about the possible poor response to standard second line agents, particularly phenytoin. Many at presentation will have been undiagnosed and consequently knowledge of response to such medications will be known. If phenytoin has been effective then there is no reason why this should not continue in the individualised protocol. Phenobarbitone has frequently been used as an alternative second line agent but there has been

reports of a possible negative effect of this medication[17]; Chipaux et al. reported on three children with DS who experienced convulsive status epilepticus of 2 to 12 hours in duration, who also experienced subsequent severe cognitive and motor deterioration, with hypoxic-ischaemic lesions on magnetic resonance imaging, despite no evidence of hemodynamic compromise. The only common finding in clinical care was the use of phenobarbitone, and they speculated that the medication may reduce local cerebral blood flow resulting in such MRI and clinical deterioration. However, fatal cerebral edema causing mass effect after fever-associated status epilepticus has since been reported in 5 children with Dravet syndrome, 3/5 of whom did not receive phenobarbitone in their management[18]. On the other hand, even the Stiripentol, considered efficacious in the reduction of the frequency of prolonged seizures and Status Epilepticus does not seem to be protective against the Acute Encephalopathy; in fact, of the 5 cases published by Myers one was on Stiripentol[187]. This consequently is likely to be unrelated to treatment, possibly triggered by high fever and ion channel dysfunction. The role of other second line agents such as iv sodium valproate or levetiracetam overall is yet to be determined, although such agents may be utilised in individual protocols[19] .

Evidence and update on stiripentol

Stiripentol (marketed as Diacomit®) was approved as adjunctive therapy for Dravet syndrome in Europe (2007), Canada (2012), Japan (2012) and USA (2018). The first attempt to use stiripentol in Dravet syndrome was performed in an open-label, prospective, add-on, exploratory short term study on a large population of children and adolescents with various types of refractory epilepsies[20]. In this study children with Dravet syndrome, who also received valproate and clobazam, were amongst those exhibiting the best responder rates compared to baseline. Based on these encouraging results, two controlled trials were performed in Dravet syndrome. A first randomized double-blind , randomized, placebo-controlled trial was performed in children aged above 3 years of age who had

not responded to valproate and clobazam[5]. Stiripentol 50 mg/kg/day for 2 months, or placebo, were randomly allocated as adjunctive therapy to valproate and clobazam for 2 months. The primary endpoint was the percentage of responders (> 50% reduction in the frequency of clonic or tonic–clonic seizures) during the second month of the double-blind period compared to baseline. Responders were 71% on the stiripentol arm and 5% on placebo (P<0.0001). The number of seizure free patients (9 vs none) and the changes in absolute numbers of seizures from baseline were more marked on stiripentol (-69%) than on placebo (+7%) (P<0.002). A second placebo-controlled trial with a similar design yielded similar results (67% of responders on stiripentol versus 9% on placebo – P=0.009)[21].

A meta-analysis performed on the intent-to treat patients with Dravet syndrome included in both controlled trials confirmed that responder rates were higher when stiripentol was added to clobazam and valproate compared to the addition of placebo to the same drugs[22]. A second meta-analysis, assessing the risk-ratio confirmed the superiority of stiripentol compared to placebo with respect to responder rate and seizure freedom[23] .

Subsequent observational long term studies in Dravet syndrome, retrospectively[6,24-26] or prospectively[24] assessing the long term efficacy of stiripentol, in combination with valproate and clobazam[6] or more variable drug regimens[24-26], reported rates of seizure reduction to be maintained within the 48 % to 63% range, in addition to a significant reduction of the number of patients experiencing status epilepticus, of the frequency of prolonged seizures, of hospitalizations, and of use of rescue medication. One study specifically reported that the beneficial effects were obtained with either clobazam or valproate comedication being present or not[25]. A very long term study, conducted on the historical Dravet syndrome cohort participating to the first randomised trial on stiripentol[5,27], confirmed the long term effectiveness and retention rate, with a progressive mean decrease of dosage from 39 to 25 mg/kg/d, whereas clobazam and valproate had remained stable.

Drug-related adverse effects were reported in 100% of patients on stiripentol versus only five 25% of those on placebo (P=0.0009) in the randomised initial randomised controlled trial[5] . The most frequently reported adverse events were drowsiness (19/21 patients) and loss of appetite (7/21 patients). Reduction of concomitant antiepileptic drugs, resolved the adverse events in 17 of the 21 patients. There were no dropouts due to side effects in the stiripentol arm. The observational studies[24,25] confirmed the adverse event profile reported in the first controlled trial; drowsiness, reduced appetite, irritability and ataxia, were the most commonly reported but dosage adjustments were usually effective in attenuating or reversing them and the number of patients discontinuing stiripentol for adverse effects did not exceed 5%[25]. Asymptomatic neutropenia (<1,000/mm3) has been reported in 1%–10% of patients and was also reversed by dosage reduction[27] .

It is hypothesised that the antiepileptic effects observed in Dravet syndrome with stiripentol administration derive from the sum of two mechanisms of action[28], one indirect, i.e its well documented interactions with clobazam and the consequent increase in concentration of its active metabolites, and one indirect, i.e. an enhancement of GABergic transmission linked to a site of action on the post synaptic GABA receptor which is different from that of benzodiazepines[29,30] .

Studies conducted in adult volunteers demonstrate that stiripentol is rapidly absorbed (tmax around 1.5 hours), heavily bound to plasma proteins, mainly metabolized by the microsomal CYP450 complex (CYP1A2, CYP2C19, and CYP3A4), and exhibits a nonlinear, dose-dependent pharmacokinetics[31,32]. There are no sufficient data to figure out the relationships between oral dosage, plasma concentration, efficacy, and safety of stiripentol[27]. However, preliminary results of a pharmacokinetic study in children aged 1–17 years, receiving a median dosage of 45 mg/kg/day, in addition to valproate and CLB, revealed that apparent volume of distribution, apparent oral clearance, and elimination half-life of stiripentol increased as body weight increased from 10 to 60 kg: from 32 to 192 L, 2.6 to 5.7 L/hour, and 8.5 to 23.5 hours[33]. A therapeutic drug monitoring study on 75 patients with different types of epilepsy[34] found plasma concentrations of stiripentol to be

40% lower in children 6–12 years old and 57.5% lower in children <6 years than in those > 12 years. Stiripentol plasma concentrations were not affected by valproate co-medication but CLB determined a 25% increase, while phenobarbital and phenytoin determined 63% reduction.

In vitro and in vivo studies indicate that stiripentol acts as a powerful inhibitor of several CYP enzymes, particularly CYP2C19 and CYP3A4[35,36] Consequently, plasma concentrations of other antiepileptic drugs metabolized by the same enzymes increase when they are co-administered with stiripentol. Valproate concentrations are not significantly increased by stiripentol co-medication[5] but clobazam levels are almost doubled and those of norclobazam (NCLB), an active metabolite, increase five to seven times[5]. Dose adjustment of these co-medications used with stiripentol help to decrease adverse effects. In particular, controlled studies have shown that somnolence was considerably higher in patients on stiripentol than in those on placebo and was mainly attributed to an increased concentration of clobazam metabolites. Although no fixed conduct has been set on how to optimize clobazam doses when stiripentol is added, a suggested strategy could be of reducing clobazam by 25% if somnolence appears or becomes pronounced when stiripentol target doses have been reached. If somnolence persists, further 25% reduction should be considered as should adjustment of dosage of any other concomitant drug with sedative potential, always counterbalancing improved tolerability and seizure control.

Ketogenic diet

The ketogenic diet (KD), a high-fat, low-carbohydrate, adequate-protein diet, and its more flexible variants -the medium chain triglyceride diet, the low-glycemic-index diet, and the Atkins diet- are currently considered safe and effective non-pharmacological treatment options for patients with difficult-to-treat epilepsy[37]. An additional advantage of the KD is that it has less neurotoxic side effects (lethargy, cognitive, behavioral) than the pharmacological treatments[38]. Increasing evidence suggests that the diet may be particularly effective for seizure control in specific epilepsy syndromes.

In Dravet syndrome (DS), complete seizure control with pharmacological treatment is often not achieved[39]. Currently, the KD is considered to be a good treatment option after three or four antiepileptic drugs have failed.

Since 1990 then until May 31, 2017, of 89 patients who met diagnostic criteria for DS in a single centre, 42 were placed on the KD and were followed up for a minimum of 2 years. Part of this series was published in 2005[40] and updated in 2011[41]. Thirty (71%.4) of 42 patients remained on the diet. Three patients (10%) became seizure free, 15 children (50%) had a 75-99% decrease in seizures, five (16.6%) had a 50-74% decrease in seizures and the remaining seven children (23.3%) had a 25-50 % decrease in seizures. Fourteen patients have been off the diet for more than 2 years; one of them is seizure free, nine have sporadic seizures, and four, who abandoned the diet after 3.5 years of adhering to it, relapsed. Overall, 75% of children who remained on the diet had a significant reduction in the number of seizures. The adverse effects were transient and could be controlled without withdrawing the patient from the KD. Even in patients in whom seizure reduction was not dramatic, an improvement in quality of life was seen, and in all of them the number of AEDs was reduced to one or two. One of these patients did not show any further mental deterioration.

A further four studies report on utilisation of the ketogenic diet in Dravet syndrome. Nabbout et al. reported on 15 DS patients over 3 years of age with a partial response to AEDs including stiripentol who had been prospectively placed on the KD[9]. At 1 month, 10/15 (66%) had a 75% decrease in seizure frequency. Efficacy was maintained in eight responders at 3 and 6 months, and in six responders at 9 months. Five patients (33%) remained on the KD over 12 months, and one became seizure free. They reported that the KD also improved behavior disturbances including hyperactivity even in a few nonresponders. None of the patients had to discontinue the KD because of side effects. Dressler et al. (2015) retrospectively analyzed 32 children with DS treated with the KD[42]. To evaluate efficacy and safety, the authors compared the effects on seizure frequency with that of different AED regimens and vagus nerve stimulation. Response to the KD was 70% at 3 months, and

60% at 12 months. None of the patients had status epilepticus (SE) and a reduction in prolonged generalized and myoclonic seizures was observed. Further, none of the patients had side effects severe enough to require withdrawal of the diet. The authors found that noncompliance was more frequent in solid-fed older children compared with infants treated with the liquid KD formula.

Laux et al. (2013) retrospectively evaluated 20 children with DS trialled on the KD, 13 experienced a greater than 50% reduction in seizure frequency[38]. All patients had a pathogenic variant of SCN1A. A greater than 50% reduction in seizure frequency was seen in 13/20 (65%) patients and in six (30%) patients, a greater than 90% seizure reduction was noted. Improved cognition and behavior was also observed by the parents in 75% of the patients. Finally, in a prospective study, Yan et al (2018) placed 20 Dravet patients on the KD[43]. Genetic testing revealed SCN1A mutations in all patients. Before KD initiation, 15 patients had SE, and 20 patients had generalized seizures of ≥5 min duration. A greater than 50% reduction in seizure frequency was seen 17 patients after 3 and 6 months on the KD. None of the patients exhibited SE or prolonged general seizures. In 80% of the patients an improvement in cognition was note.

These clinical findings are supported by a mouse model of DS where the efficacy of the KD was studied in the treatment of SCN1A-derived epilepsy[44]. Scn1a mutant mice were placed on a 6:1 KD or a standard diet for two weeks and thresholds to seizures measured as induced by the chemiconvulsant flurothyl after 2 weeks. Seizure thresholds were found to be elevated in Scn1a mutant mice confirming that the KD may be effective in the treatment of refractory seizures in patients with pathogenic variants of SCN1A [44]. It would appear prudent to consider utilisation of the ketogenic diet early in the clinical course, when initial resistance to standard AEDs has been demonstrated.

Cannabidiol

There has long been interest in the possible role of the cannabinoids in the treatment of the epilepsies, brought specifically to media attention recently by families seeing particular response[45] The two major neuroactive components in cannabis are the psychoactive compound D9-tetrahydrocannabinol (THC) and the non-psychoactive cannabidiol. Whereas the latter has been demonstrated to be anticonvulsant in vitro, there has been concern about THC not only with regard to longer lasting effects on a child brain but also it has been shown to be proconvulsant in some in vitro studies[46,47].

Epidiolex, an oil liquid formulation of pure plant-derived cannabidiol, or CBD, <0.1% THC (GW Pharma) is produced in a consistent quality assured way to pharmaceutical standard, so there is a reliability to the content and stability. It is registered as a pharmaceutical, to be assessed in appropriate clinical trials; efficacy has specifically been evaluated in Dravet syndrome, and it has recently been approved by the FDA for use. In the primary study conducted by GW Pharma in 23 centres across the USA and Europe, a total of 177 children age 2-18 years were screened with ultimately 120 randomised to either cannabidiol (up to 20mg/kg/day) or placebo having experienced at least 4 convulsive seizures over the four week baseline period[48]. The mean age in the CBD group (9.7 years) was not different from the placebo group (9.8 years). The median number of anti-epileptic drugs trialled was 4, and the patients were taking a median of 3 (range 1-5), most commonly clobazam (65%), valproate (59%), stiripentol (42%), levetiracetam (28%) and topiramate (26%). In the cannabidiol group the primary end-point of convulsive seizure frequency at the end of the treatment period decreased by a median -38.9% from baseline. This was significantly greater than in the placebo group (-13.3%, p=0.01)). The responder rate (>50% reduction in seizures) was 43% in the CBD group vs 27% placebo; this did not reach significance (p=0.08). The placebo rate was relatively high, as has been noted previously with predominantly paediatric studies[49]. Adverse events during the treatment period were reported in 93% CBD vs 75% placebo; 89% adverse events were

mild or moderate. In both groups the first occurrence of an adverse event was most commonly reported during the 14 days dose escalation. Common adverse events (>10% frequency) in the cannabidiol group were vomiting, fatigue, pyrexia, upper respiratory tract infection, decreased appetite, convulsion, lethargy, somnolence, and diarrhoea. In the cannabidiol group, 8 patients withdrew from the trial owing to adverse events, as compared with 1 in the placebo group.

It became clear from an early stage that the norclobazam metabolite of clobazam was dramatically increased when patients were on concomitant treatment through an effect on cytochrome p450 system in the liver[50]. In the Dravet syndrome RCT 65% of children were taking clobazam as concomitant medication. Some of the side effects eg somnolence could well be attributed to this active metabolite increase. Some may question therefore whether any of the effect of CBD on seizures is the result of such an interaction, or a direct effect of the medication itself. A pharmacokinetic dose finding study was performed prior to the RCT but only published subsequently[51]. Thirty four children with Dravet syndrome age 4-10 years were randomised 4:1 to CBD (5, 10 or 20mg/kg/day) or placebo taken twice a day; 32 completed treatment. The double blind trial comprised 4 week baseline, 3 week treatment, 10 day taper and 4 week follow-up. Pharmacokinetic sampling for measurement of CBD, metabolites and antiepileptic drug levels were performed on the first day of dosing and at the end of treatment. CBD did not affect concomitant AED levels except norclobazam; levels increased on all doses of CBD, but not placebo, and not if there was concomitant stiripentol. Although numbers were small with only four patients taking both clobazam and stiripentol, this suggests that stiripentol maximally inhibits CYP2C19. Where stiripentol was taken concomitantly, clobazam metabolites were unlikely to have risen further and the efficacy of CBD was at least partly independent of the interaction with CLB.

The effect of CBD on seizures is not restricted to Dravet syndrome; it is unlikely to be a specific effect but a more general anti-epileptic effect.Significant effect over placebo has also been demonstrated in two RCT of epidiolex as add on therapy vs placebo in Lennox Gastaut syndrome[52,53] . There also

remains the question as to whether additional benefit may be gained with inclusion of some THC; there is much professional concern about the lack of knowledge about ongoing safety of inclusion of THC and therefore there would be an advantage as to the knowledge of whether additional benefit could be gained or whether CBD alone gives maximal benefit. There is a single report of an open label study utilising CBD with 2% THC from Canada in 20 children with Dravet syndrome[54]. The dose ranged from 2 to 16 mg/kg/day of CBD and 0.04 to 0.32 mg/kg/day of THC. Nineteen patients completed 20 weeks intervention; one child who died of SUDEP was excluded from the analysis. As with the RCTs somnolence, anorexia, and diarrhoea were the most common adverse events seen, with abnormalities of liver transaminases and platelets observed with concomitant valproic acid therapy. 12/20 reported >50% reduction of seizures, not dissimilar figures to the RCT of CBD alone. There appears little evidence at present therefore that there is an advantage of CBD with THC over CBD alone.

Fenfluramine

Fenfluramine was previously used in combination with phentermin as an appetite suppressor, but because of cardiac side effects (valvular hypertrophy and pulmonary hypertension), when used in high dosages, it was banned as a therapeutic drug in 1997[55]. Fenfluramine has a high affinity for serotonin receptors in the brain (especially 5HT 2A and 2C), leading to a higher serotonin concentration, and also is a positive modulator of the sigma 1 receptor[56]. In the past, several case reports described that fenfluramine in low dosages could stop self-induced syncopes and intermittent light induced paroxysmal events in children with behavioural problems. Because it could also abolish photosensitivity on the EEG in some patients, it was hypothesized that fenfluramine should be tested as an anti-epileptic drug[57,58] . Boel and Casaer published in 1996 a first paper showing that low dose fenfluramine was highly beneficial in children with refractory epilepsy[59]. In this case series, all children had intellectual disability and early onset epilepsy with

drug resistant self-induced seizures which were classified as generalized seizures. The effect of fenfluramine was remarkable in that case series, with a long lasting seizure freedom in 7/11 children. Later it was realized that 5 children who did respond very well to fenfluramine, all had the typical symptoms of Dravet syndrome. This was later also confirmed with genetic testing. Despite the world wide prohibition, a Royal Decree in Belgium allowed for continued use of fenfluramine in a limited number of children with Dravet syndrome. This resulted in a retrospective analysis on the effect of fenfluramine in children and adolescents with Dravet syndrome[60,61]. This long term follow up confirmed previous findings with 7/10 patients seizure free for at least 1 year (mean 6 years and 7 months). An interesting finding in that study was also that in 7 children fenfluramine had to be stopped temporarily because of drug supply problems. This resulted in immediate return of the seizures. Restarting fenfluramine made these children seizure free again. Careful cardiac follow up in these children did not show any clinical cardiac side effects during the long follow up.

Now, data from 2 prospective, double blind, placebo controlled trials are available and they both confirm the efficacy and safety of low dose fenfluramine in Dravet syndrome (Lagae et al, Nabbout et al, 2017 and 2018, presentations at American Epilepsy Society meetings). In a first study, Dravet children who were refractory to standard-of-care treatment, but who were not taking stiripentol, were included. Two dosages (0,2 and 0,8 mg/kg/day) were tested against placebo. At both fenfluramine dosages, the effect was significantly higher than in the placebo group (see figure 2). The number of 50% responders in the 0,8 and 0,2 group was 70% and 41% respectively, whereas this was only 7,5% in the placebo group. In the 0,8 mg/kg/day group, 25 % of the children ware seizure free or only had 1 seizure during the 14 week trial. The drug was well tolerated with appetite problems in 37% of the children in the highest dosage group, although this resulted in weight decrease in only 5% of the children. More importantly, prospective cardiac follow up (clinical, ECG and ultrasound) did not show any cardiac problem. These findings were also seen in the second trial, now also including children who were on stiripentol at the time of inclusion. Because of the drug interaction with stiripentol, only 0,5 mg/kg/day was compared to placebo. All primary and secondary

end points were also met in this study, with fenfluramine being 54 % better than placebo. Here the number of 50% responders was 53,5% in the fenfluramine arm compared to 4,5% in the placebo arm. No new side effects were seen and there were also no cardiac side effects (poster AES?). Recently, the first data on the long term extension study of both core studies became available. Most patients who finished the 2 trials entered the extension phase. In that study, at inclusion, all patients were started at the lowest dose (0,2 mg/kg/day), regardless of their final dosage in the core trial. After 4 weeks, fenfluramine dosage could be increased following clinical needs. During the first 6 months in the extension phase, the concomitant anti-epileptic drugs remained unchanged. It is interesting to see that those children who were at a higher dosage at the end of the core trial, initially had an increase in seizure frequency. After 1 month, and with increasing dosages, they again had a significant seizure frequency reduction. Overall, in this extension phase, the efficacy remained stable over > 1 year follow up, with an average decrease of mean monthly convulsive seizure frequency of 66,8 % compared to their baseline in the core trial. 41,2 % had a seizure frequency reduction of > 75%. Cardiac safety was followed every 3 month and no signs was valvular heart disease or pulmonary hypertension was seen in any of the children.

These data on low dose fenfluramine in Dravet syndrome are very consistent, with a long lasting high efficacy and apparently no development of tolerance. In now more than 200 children exposed to fenfluramine for > 1 year, there was no cardiac safety problem.

Other treatments to be considered

In some parts of the world bromides have been utilised, and reported to show benefit where other medications have failed. Although a very old antiepileptic drug that went out of use with the development of perceived more useable medications, Oguni and colleagues reported benefit in a small series of children with severe myoclonic epilepsy of infancy, now recognised as Dravet syndrome, as well as children with what they described as borderline. Eight of 22 (36%) of patients

with generalized tonic-clonic seizures (GTCS) had >75% reduction in total seizure frequency or duration, and 9 (41%) had 50-75% reduction 3 months after introduction of bromide[62]. More recently a german series reported benefit using potassium bromide in a series of 32 patients with Dravet syndrome associated with *SCN1A* mutation; after 3 months of treatment, 26 patients (81%) showed a relevant improvement with a reduction of seizure frequency by >50% (>75%) in 18 (12) patients (56 and 37%, respectively), adverse events only leading to termination of treatment in 5[8]. Eighteen remained on treatment after a mean of 60 months; it was reported to be used in combination with almost all available anti seizure medications including stiripentol. Limitation of use however may remain through the availability and need for monitoring. It must also be considered however, in countries with limited availability of anti seizure medications, phenobarbitone may still remain useful.

Current practice

Current practice in management of Dravet syndrome remains with optimising anti-epileptic treatment for seizure control whilst minimising side effects. A North American Consensus panel has reviewed the evidence as it stands with currently available antiepileptic treatment and has set out an optimal flow chart of treatment options (Figure 2)[19]. This aside the availability of cannabidiol is a further option available to some, and fenfluramine holds great promise. Where these sit in the order of treatments to be utilised remains to be seen, although it appears likely such agents will rapidly become at least second line . We propose the plan as highlighted in figure 3, with utilisation of sodium valproate on diagnosis, with rapid addition of stiripentol with or without clobazam. If however efficacy and safety of fenfluramine is confirmed, it is likely this will be moved to second line, if not first in the longer term. Until then ketogenic diet should be an early consideration where eating behaviours allow. Throughout, an optimised emergency treatment plan should be developed

for the family to utilise and make available for all those involved in care of the child from an early stage.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

Disclosures

JHC has acted as an investigator for studies with GW Pharma, Zogenix, Vitaflo and Marinius. She has been a speaker and on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. Her work is supported by the NIHR Biomedical Research Centre at Great Ormond Street Hospital & University College London.

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FV has received grants from UCB, Shire, Eisai, Livanova; he acts on advisory boards for UCB, Shire, Eisai, Sanofi, GW Pharmaceutical, Zogenix. He has been a principal/secondary paid investigator for UCB, Eisai, Empatica, Zogenix.

RG has acted as an investigator for studies with Zogenix, Biocodex, Biomarin, UCB, and Eisai Inc.

He has been a speaker and on advisory boards for Zogenix, Biocodex, Novartis, Biomarin, GW Pharma and Biocodex

LL received speakers honoraria from and is participating at advisory boards of : Zogenix, Livanova, UCB, Eisai, Novartis, NEL and Epihunter

Figure legends

Figure 1: Proposed protocol for the treatment of prolonged seizures in association with Dravet Syndrome

Figure 2: Treatment algorithm for Dravet syndrome as outlined by the North American consensus panel. *Published with permission from Wirrell EC, Laux L, Donner E et al Ped Neurol (Elsevier) 2017: 68:18-34.e3*

*Ketogenic diet is not suitable for all patients; its use is not required before moving to third-line therapies. [a]Agreed upon by moderate consensus. [b]Agreed upon by strong consensus. [c]Stiripentol not approved for use in all jurisdictions. sz, seizures.,

Figure 3: Authors proposed protocol for the treatment of Dravet syndrome. *ASM: anti seizure medication*

References

1. Catarino CB, Liu JYW., Liagkouras I, et al. Dravet Syndrome as epileptic encephalopathy: evidence from very long-term course and neuropathology Brain 2011;134:2982-3010
2. Takayama R, Fujiwara T, Shigematsu H, et al Long-term course of Dravet syndrome: a study from an epilepsy center in Japan. Epilepsia 2014;55:528-538.
3. Lagae L, Brambilla I, Mingorance A, et al. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey Dev Med Child Neurol 2018;60: 63-72
4. Nabbout R, Chemaly N, Chipaux M, et al. Encephalopathy in children with Dravet syndrome is not a pure consequence of epilepsy. Orphanet J Rare Dis 2012;8:176-
5. Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet. 2000;356: 1638–1642.
6. Thanh TN, Chiron C, Dellatolas G, et al. [Long-term efficacy and toler- ance of stiripentol in severe myoclonic epilepsy of infancy (Dravet's syndrome)]. Arch Pediatr. 2002;9:1120–1127
7. Coppola G, Capovilla G, Montagnini A, et al. Topiramate as add-on in severe myoclonic epilepsy in infancy: an Italian multicentre open trial Epilepsy Res 2002; 49:45-48
8. Lotte J, Haberlandt E, Neubauer B, et al. Bromide in patients with SCN1A mutations manifesting as Dravet syndrome. Neuropediatrics. 2012;43:17-21.
9. Nabbout R, Copioli C, Chipaux M, et al. Ketogenic diet also benefits Dravet syndrome patients receiving stiripentol: a prospective pilot study. Epilepsia 2011;52:e54-7.
10. Guerrini R, Dravet C, Genton P, et al. Lamotrigine and seizure aggravation in severe myoclonic epilepsy Epilepsia 1996;39:508-512
11. de Lange IM, Gunning B, Sonsma ACM, et al. Influence of contraindicated medication use on cognitive outcome in Dravet syndrome and age at first afebrile

seizure as a clinical predictor in SCN1A-related seizure phenotypes. Epilepsia. 2018;59:1154-1165.

12. Dalic L, Mullen SA, Roulet Perez E, et al. Lamotrigine can be beneficial in patietns with Dravet Syndrome Dev Med Child Neurol 2015;57:200-2
13. Trinka E, Cock H, Hesdorffer D, et al A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus Epilepsia, 56:1515–1523, 2015
14. Akiyama M, Kobayashi K, Yoshinaga H, et al. A longterm follow-up study of Dravet syndrome up to adulthood. Epilepsia. 2010;51:1043–52.
15. Genton P, Velizarova R, Dravet C. Dravet syndrome: the longterm outcome. Epilepsia. 2011;52(Suppl 2):44–9.
16. Chin RF, Neville BG, Peckham C, et al. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. Lancet Neurol. 2008;7:696-703.
17. Chipaux M, Villeneuve N, Sabouraud P, et al Unusual consequences of status epilepticus in Dravet syndrome. Seizure. 2010;19:190–4.
18. Myers KA, McMahon JM, Mandelstam SA, et al. Fatal Cerebral Edema With Status Epilepticus in Children With Dravet Syndrome: Report of 5 Cases. Pediatrics. 2017;139. pii: e20161933
19. Wirrell EC, Laux L, Donner E, et al Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel. Pediatr Neurol. 2017;68:18-34.e3.
20. Chiron C, Musial C, et al. Stiripentol: efficacy and tolerability in children with epilepsy. Epilepsia. 1999;40:1618–1626.
21. Guerrini R, Tonnelier S, d'Athis P, et al. Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial. Epilepsia. 2002;43(Suppl 8):s155.

22. Kassaï B, Chiron C, Augier S, et al. Severe myoclonic epilepsy in infancy: a systematic review and a meta-analysis of individual patient data. Epilepsia. 2008;49:343–348.
23. Brigo F, Storti M. Antiepileptic drugs for the treatment of severe myoclonic epilepsy in infancy. Cochrane Database Syst Rev. 2013;19:CD010483.
24. Inoue Y, Ohtsuka Y, Oguni H, et al. Stiripentol open study in Japanese patients with Dravet syndrome. Epilepsia. 2009;50:2362–2368.
25. Wirrell EC, Laux L, Franz DN, et al. Stiripentol in Dravet syndrome: results of a retrospective US study. Epilepsia. 2013;54:1595–1604.
26. Myers KA, Lightfoot P, Patil SG, et al. Stiripentol efficacy and safety in Dravet syndrome: a 12-year observational study. Dev Med Child Neurol. 2018 ;60:574-578.
27. Chiron C, Helias M, Kaminska A, et al. Do children with Dravet syndrome continue to benefit from stiripentol for long through adulthood? Epilepsia. 2018;59:1705-1717.
28. Mott DD, Grosenbaugh DK, Fisher JL. Polytherapy with stiripentol: consider more than just metabolic interactions. Epilepsy Behav. 2013;29:585.
29. Quilichini PP, Chiron C, Ben-Ari Y, et al. Stiripentol, a putative antiepileptic drug, enhances the duration of opening of GABA-receptor channels. Epilepsia. 2006;47:704–716.
30. Fisher JL. The anti-convulsant stiripentol acts directly on the GABA(A) receptor as a positive allosteric modulator. Neuropharmacology. 2009;56:190–197.
31. Levy RH, Lin HS, Blehaut HM, et al. Pharmacokinetics of stiripentol in normal man: evidence of nonlinearity. J Clin Pharmacol. 1983;23:523–533.
32. Levy RH, Loiseau P, Guyot M, et al. Michaelis-Menten kinetics of stiripentol in normal humans. Epilepsia. 1984;25:486–491.
33. Diacomit: EPAR – Product Information 2013; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000664/WC500036519.

34. May TW, Boor R, Mayer T, et al. Concentrations of stiripentol in children and adults with epilepsy: the influence of dose, age, and comedication. Ther Drug Monit. 2012;34:390–397.
35. Giraud C, Treluyer JM, Rey E, et al. In vitro and in vivo inhibitory effect of stiripentol on clobazam metabolism. Drug Metab Dispos. 2006;34:608–611.
36. Tran A, Rey E, Pons G, et al. Influence of stiripentol on cytochrome P450-mediated metabolic pathways in humans: in vitro and in vivo comparison and calculation of in vivo inhibition constants. Clin Pharmacol Ther. 1997;62:490–504.
37. Kossoff EH, Zupec-Kania BA2, Auvin S, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018 ;3:175-192.
38. Laux L, Blackford R. The ketogenic diet in Dravet syndrome. J Child Neurol. 2013;28:1041-4
39. Knupp KG, Wirrell EC. Treatment Strategies for Dravet Syndrome. CNS Drugs 2018;32: 335–350.
40. Caraballo RH, Cersósimo RO, Sakr D, et al. Ketogenic diet in patients with Dravet syndrome. Epilepsia 2005;46:1539-44.
41. Caraballo RH. Nonpharmacologic treatments of Dravet syndrome: focus on the ketogenic diet. Epilepsia 2011;52 Suppl 2:79-82.
42. Dressler A, Trimmel-Schwahofer P, Reithofer E, et al. Efficacy and tolerability of the ketogenic diet in Dravet syndrome - Comparison with various standard antiepileptic drug regimen. Epilepsy Res. 2015;109:81-9.
43. Yan N, Xin-Hua W, Lin-Mei Z, et al. Prospective study of the efficacy of a ketogenic diet in 20 patients with Dravet syndrome. Seizure 2018 Aug;60:144-148.
44. Dutton SB, Sawyer NT, Kalume F, et al. Protective effect of the ketogenic diet in Scn1a mutant mice. Epilepsia. 2011;52: 2050-2056
45. Maa E, Figi P. The case for medical marijuana in epilepsy. Epilepsia 2014;55:783-6.

46. Thomsen K, Callesena MB,. Ewing SWF Recommendation to reconsider examining cannabis subtypes together due to opposing effects on brain, cognition and behavior Neuroscience Biobehav Rev 2017:80:156–158
47. Karler R, Turkanis SA. Cannabis and epilepsy. Adv Biosci 1978;22-23:619-41.
48. Devinsky O, Cross JH, Laux L et al. Trial of cannabidiol for drug resistant seizures in the Dravet syndrome. N Eng J Med 2017;376:2011-20.
49. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than adults: a systematic review and meta-analysis in drug resistant partial epilepsy PLOS Med 2008;5:e166
50. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia 2015;56:1246-51.
51. Devinsky O, Patel AD, Thiele EA et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. Neurology 2018;90:e1204-e1211.
52. Thiele EA, Marsh ED, French JA et al. Cannabidiol in patients with seizures associated with Lennox Gastaut syndrome (GWPCARE4): a randomised, double blind, placebo-controlled phase 3 trial. Lancet 2018; 391(10125):1085-1096
53. Devinsky O, Patel A, Cross JH et al. Effect of cannabidiol on drop seizures in the Lennox Gastaut Syndrome. N Eng J Med 2018;378:1888-97.
54. McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. Ann Clin Transl Neurol. 2018;5:1077-1088.
55. Schoonjans AS, Marchau F, Paelinck BP, et al. Cardiovascular safety of low-dose fenfluramine in Dravet syndrome: a review of its benefit-risk profile in a new patient population. Curr Med Res Opin. 2017;33:1773-1781.
56. Sourbron J, Smolders I, de Witte P, et al.. Pharmacological Analysis of the Anti-epileptic Mechanisms of Fenfluramine in scn1a Mutant Zebrafish. Front Pharmacol. 2017;8:191.

57. Gastaut H. Efficacy of fenfluramine for the treatment of compulsive behavior disorders in psychotic children. Presse Med. 1984 ;13:2024-5.
58. Aicardi J, Gastaut H. Treatment of self-induced photosensitive epilepsy with fenfluramine. N Engl J Med. 1985;313:1419.
59. Boel M, Casaer P. Add-on therapy of fenfluramine in intractable self-induced epilepsy. Neuropediatrics. 1996;27:171-3.
60. Ceulemans B, Boel M, Leyssens K, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia. 2012;53:1131-9
61. Ceulemans B, Schoonjans AS, Marchau F, et al. Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine. Epilepsia. 2016;57:129
62. Oguni, H, Hayashi, K, Oguni, M. Treatment of severe myoclonic epilepsy in infants with bromide and its borderline variant. Epilepsia. 1994;35:1140–1145.