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Guidance on Dravet Syndrome from Infant to Adult Care: Road Map for Treatment Planning in Europe

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Summary

Dravet syndrome (DS) is a severe, rare and complex developmental and epileptic encephalopathy affecting 1 in 16'000 live births and characterized by a drug resistant epilepsy, cognitive, psychomotor and language impairment, as well as behavioral disorders. Evidence suggests that optimal treatment of seizures in DS may improve outcomes, even though neurodevelopmental impairments are the likely result of both the underlying genetic variant and the epilepsy. We present an updated guideline for DS diagnosis and treatment, taking into consideration care of the adult patient and non-pharmaceutical therapeutic options for this disease. This up-to-date guideline, which is based on an extensive review of the literature and culminates with a new treatment algorithm for DS, is a European consensus developed through a survey involving 29 European clinical experts in DS. Theis guideline will serve professionals in their clinical practice and, as a consequence, will benefit DS patients and their families.

Key bullet points

- *SCN1A* genetic analysis should be requested when a diagnosis of DS is suspected.
- All children with a diagnosis of DS should have a personalised emergency protocol.
- VPA is the drug of choice as first line treatment in DS; Second line should be a combination of VPA, STP and CLB, with CBD and FFA as alternative second line drugs.
- Sodium channel blockers should be avoided in children, but their use in adults needs further exploration. RCTs of new DS medications should include adult patients.
- DS individuals should be managed by a multidisciplinary professional team, and supported by a dedicated group of patient advocates.

Keywords: genetic diagnosis, antiseizure medication, epilepsy, comorbidities, treatment algorithm

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Accepted Article

Introduction

Dravet Syndrome (DS) is a rare and severe infantile-onset developmental and epileptic encephalopathy (DEE) caused in more than 80% of patients by a pathogenic variant in *SCN1A*, a gene encoding the sodium voltage-gated channel alpha subunit 1 or NaV1.1 [1,2]. The first symptom of DS is a convulsive seizure appearing in the first year of life in a previously healthy child, usually accompanied by a normal interictal electroencephalogram (EEG). Typically, this first seizure is generalized tonic-clonic or focal clonic (sometimes hemiclonic) and in just over half of cases is febrile and therefore not easily distinguished from a self-limited febrile seizure, apart from an earlier age of onset in DS (Figure 1). Factors triggering seizures in DS are infection, environmental heat including hot baths, immunisation, sunlight, pattern stimulation, exercise or excitement.

Further febrile and afebrile seizures are often prolonged, sometimes evolving into status epilepticus (SE). During the latter part of the first year and second year of life, other seizure types (myoclonic, absence, focal, tonic seizures and obtundation status) appear, with an interictal EEG which may remain normal or demonstrate an abnormal EEG background activity in 50% of cases. In the second year, neurodevelopmental impairment becomes evident. Patients develop an unsteady gait and more general motor impairment, language delay is evident, and behavioral disturbances such as attention deficit, hyperactivity, autistic traits and social difficulties emerge. Other secondary conditions, such as sleep disturbances, growth and eating difficulties, and frequent respiratory tract infections, are shared by almost all DS patients. DS has a mortality rate of 15-20%, half of the cases due to sudden unexpected death in epilepsy (SUDEP) [3–7] (Figure 1).

The epilepsy in this syndrome is typically drug resistant and only a limited number of medications have been subject to randomised controlled trials (RCTs). Sodium-channel blockers such as lamotrigine, phenytoin, carbamazepine, oxcarbazepine, lacosamide and rufinamide are usually contraindicated as they can increase seizure frequency [8]. Whilst DS presents in childhood, symptoms evolve over time into adulthood. DS research however mainly focuses on children. Overall, seizures frequency is high in the first decade of the patient's life; myoclonic, atypical absences, focal seizures with impaired awareness and SE tend to decrease or even disappear in adulthood, when patients continue to present with behavior problems, associated with a lower health-related quality of life [9]. It has been claimed that early recognition and treatment for the mitigation of prolonged and repeated seizures in the first year of life of infants carrying a *SCN1A* mutation may limit the progression to epileptic encephalopathy [10].

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With the goal of proposing an updated guidelines for DS diagnosis and treatment which for the first time takes into consideration the adult patient and the therapeutic options for DS comorbidities, we have here performed an exhaustive revision of the literature, comparing it with our own clinical practice. Based on that critical review, and upon consultation of 29 European experts via a survey, we present a comprehensive guideline and a new treatment algorithm which can be used for the optimised management of DS in Europe.

Critical literature review

Genetic diagnosis

Currently, the diagnosis of DS is based on the electroclinical phenotype of the course of the disease. More than 80 percent of DS patients carry a *de novo* pathogenic variant of the *SCN1A* gene. Variants in other genes such as *GABRG2*, *GABRA1* or *STXBP1* have been linked to DS [11–13], however they are now considered to give rise not to atypical DS but to separately defined conditions [11]. It is important to distinguish these different entities, as they may require alternative treatment and patient care strategies.

Genotype-phenotype relationships are complex and are influenced by nature of the variant and for both missense and truncating variants which part of the gene and protein are affected. Broadly speaking, truncating variants are more likely to predict a severe phenotype however missense variants affecting functionally important parts of the gene can have as severe a phenotype [14]. Approximately 90 percent of mutations arise *de novo*, but it is important to notice that about 10% of the patients thought to have a *de novo* mutation have one parent with mosaicism for their variant [15]. When the pathogenic variant in *SCN1A* is inherited, family members harbouring the same mutation are usually asymptomatic or mildly affected. A family history of febrile seizures or other epilepsies may be seen in 30-50% of the cases, and may suggest the familial syndrome of genetic epilepsy with febrile seizures plus (GEFS+), another syndrome associated with variants in *SCN1A* [16].

As it remains an electroclinical syndrome, genetic analysis is not mandatory for diagnosis, but is an additional factor to take into consideration in the diagnosis of DS [17]. In clinical practice, if DS is suspected, the *SCN1A* gene should be sequenced. In addition, multiplex ligation-dependent probe amplification (MLPA), which detects intragenic deletions or duplications should also be performed [18]. Next generation sequencing (NGS) technologies, including gene panels, whole exome sequencing (WES) and whole genome sequencing (WGS) are now part of the diagnostic workup of rare diseases, including early

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childhood epilepsies. NGS techniques may have higher diagnostic yields than single gene-Sanger sequencing for the detection of *SCN1A* variants [13].

Performing a gene panel analysis to support a DS diagnosis is recommended in the early stage of the disease. Some investigators suggest requesting an epilepsy gene panel including the *SCN1A* gene in all infants experiencing a prolonged seizure before the age of 1 year, particularly if a patient is younger than 6 months and both brain magnetic resonance imaging (MRI) and EEG recordings are normal [19–21]. In addition, genetic analysis should be done in all patients, including adults, with a typical history of DS, although obtaining early history in adults may be challenging. The threshold for genetic analysis should, in our judgement, therefore be low. Importantly, the identification of pathogenic variants of the *SCN1A* gene may also be of interest both, for patients and clinicians, when gene therapy for DS becomes potentially available in the near future.

Seizure action plan and emergency protocols

A key component to the Dravet phenotype is the tendency to prolonged convulsive seizures [3]. These can result in regular admission to hospital, and often treatment in an intensive care unit (ICU) should first and second line of rescue medication not result in cessation of the seizure. The sooner a seizure is treated the more likely it is to stop; it is also clear that adherence to a protocol results in greater likelihood of response to treatment [22]. Benzodiazepines (BZD) are universally utilised as first line treatment where available. Studies have shown that age appropriate doses (0.3-0.5 mg/kg) of BZD prehospital (e.g., rectal diazepam, buccal or intranasal midazolam) lead to shortening of duration of SE, a greater likelihood of cessation of seizure prior to arrival at hospital and reduced likelihood of ICU admission [23–25]. Several preparations are now available that can be utilised in the community. This said no more than two age appropriate doses of BZD should be administered in total in view of the risk of subsequent respiratory depression [24]. It is advised to administer one adequate dose of BZD prehospital, with the second one given under medical supervision [26].

If a child with DS is still seizing on attendance at hospital, there should be clear advice as to what should be utilised as second line therapy. Concern is often raised about the use of phenytoin but whether acute use for termination of a prolonged seizure should be regarded in the same way as possible aggravation with regular use is unknown. Phenytoin may have been used as second line in a first episode of SE with previous standard protocols, and therefore knowledge provided as to whether it was effective. Increasingly levetiracetam or valproate (VPA) are being used as second line in the light of evidence from

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clinical trials and safety profiles [27–30]. Concern has been expressed with regard to the use of phenobarbitone with reports of a possible link in isolated cases to the development of hypoxic ischaemic lesions on MRI, despite no evidence of hemodynamic compromise with subsequent severe cognitive and motor deterioration [31]. However, fatal cerebral edema causing mass effect after fever-associated SE has since been reported in 5 children with DS, 3 of whom did not receive phenobarbitone in their management [32].

In the case of a child with DS it is important for there to be a clear advice for avoidance of triggers to a convulsive seizure where possible, e.g., avoiding hyperthermia, stress, excitement and emotional upset, intense exercise, direct sunlight or pattern stimulation, and administering regular antipyretics at times of illness. We also recommend a personalised protocol to be available with what to use and at what time point in the event of a convulsive seizure, how many doses of first line medication can be given and when, and at what point a request for medical assistance or attendance at hospital should be made. In some children immediate treatment is warranted rather than waiting for 5 minutes. Further, as highlighted above, how many doses of BZD should be given prior to second line treatment. Second line treatment with dose and timing should thereafter be listed, and the time waited before rapid induction anaesthesia should be undertaken. An example of a protocol with timings is given in Figure 2.

Initial treatment of seizures in infancy and childhood

DS is a difficult to treat epilepsy syndrome and a drug-resistant epilepsy. Evidence based treatment remains challenging as only few RCTs are available: at this moment RCTs are published only for stiripentol (STP), cannabidiol (CBD) and fenfluramine (FFA) [33–36]. Guidelines for treatment were published by a North American consensus panel and more recently by an European expert group [37,38].

In both published guidelines, VPA is drug of choice as a first line drug. Clobazam (CLB) monotherapy is an alternative option in the American guidelines, but very few European centers would follow this option. A common misunderstanding is that antiseizure medication (ASM) for focal seizures could be chosen, as the first seizures are frequently hemi-clonic (focal). But the choice of sodium channel blockers is contra-indicated as prolonged use of contraindicated drugs can increase the number of seizures, and is associated with a worse cognitive outcome [39]. The first line treatment with VPA can decrease the number of seizures and the severity (duration) of the subsequent seizures, but rarely the child will become seizure free. Following the guidelines, second line choices include STP in combination with VPA and CLB,

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topiramate (TPM), and ketogenic diet (KD). The more recent European guidelines now also include CBD (in combination with CLB in Europe) and FFA as possible second line treatment.

In 2000, Chiron and colleagues published the first RCT in DS: STP (in association with VPA and CLB) was compared to placebo in a small but adequately powered RCT [33]. There was a highly significant decrease of seizure frequency in the treated group. Interactions between STP and CLB are possible, because of the inhibiting effect of STP on CLB metabolism [40]. This can lead to more side-effects and especially drowsiness, requiring adjustments of the CLB dosage. Treatment with STP frequently reduces the number of long-lasting seizures/ SE [41]. Several studies reported beneficial effects of TPM, KD and bromide in DS although no RCTs are available [42–47] and bromides are of limited availability as they are not registered as ASMs in certain countries. In the study of Brunklaus *et al*. [48], the top five drugs that did yield a reduced seizure frequency in DS were VPA (51% of patients), CLB/clonazepam (34%), TPM (28%), levetiracetam (13%) and STP (13%). In that study, it was also reported that carbamazepine and lamotrigine increased seizure frequency in 60 and 43% respectively [48].

In recent years, 2 new anti-seizure medications have become available for the treatment of DS: CBD and FFA [34–36]. In an open label study with add-on CBD in children with drug resistant epilepsy, 32 children with DS were included [49]. In this subgroup, a significant reduction of all seizure types was observed, ranging from 47% for clonic seizures to 83% for non-motor focal seizures. The placebo controlled RCT confirmed a statistically significant decrease of seizures with add-on CBD in DS [34]. Median percentage reduction was 41%, compared to 16% decrease in the placebo group. A long term open label study confirmed a sustained effect in most patients [50]. More common side-effects are (reversible) liver toxicity and again the interaction with CLB, necessitating a reduction of the CLB dosage in many patients to avoid excessive drowsiness [51].

FFA is an old serotonergic drug which was frequently prescribed as an anti-obesity drug but withdrawn from the market in 1997 because of possible cardiac valvulopathy when used in high dosages and in combination with phentermine [52]. Older reports showed a positive effect in photosensitive epilepsy, one of the characteristics in early DS [53]. A retrospective study showed an unexpected high rate of long term seizure freedom in some DS patients [54]. Two RCTs confirm that FFA substantially reduces seizure frequency in DS [35,36]. In a first RCT [35], 70% of the included patients were 50% responders at the dose of 0,7 mg/kg/day, compared to 7,5% in the placebo group. In a second RCT [36], with STP as one of the concomitant medications, similar findings were obtained. At 0,5 mg/kg/day, 53,5% were responders, versus 6,8 % in the placebo group. In none of the FFA studies, valvular or other cardiac problems were

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observed. It is anticipated that both CBD and FFA, now collecting long term efficacy data, will very soon become second line treatments in the treatment flowchart of DS. However, further experience in clinical practice is needed to formally lift these ASMs up in the flowchart at the present time.

Approaching seizures in adults

There are no specific guidelines regarding treatment in adult patients with DS. According to the results of a survey of caregivers of patients with DS on experiences of management and health services, the use of VPA, CLB, and TPM persisted through childhood, adolescence and adult lives, whereas that of STP decreased with age (31% in adults) [6]. It has been reported that a small proportion of adult patients are treated with sodium channel blockers (many of them were exposed to this group of ASM in the past). In fact, it has been reported that some DS patients may be responsive to sodium channel blockers, particularly LTG, with aggravation of seizures observed upon medication weaning [55].

Most ASMs used in DS have been prescribed in adult patients (i.e., VPA, TPM, CLB…). However, the experience with the newest ASM is still limited in this age group. In the RCT with CBD, patients were predominantly included from the pediatric population, with only 5 adult patients who were 18 years old (1.6%) [34]. Therefore, limited efficacy and safety data have been obtained in the adult DS population, with most of the current information available reported in observational studies [56,57]. Similarly, the FFA RCT excluded patients older than 18 years [35] and only 6 adults were included in an Early Access Program reported from four Italian pediatric epilepsy centers [58]. Regarding STP, long-term data of patients aged older than 18 years has not been collected in a sufficient number to confirm maintenance of drug effect in this population [59]. A recent publication reported hyperammonemia in 77% of a cohort of 28 adult STP-naive patients who were on VPA and CLB, despite dose reduction of the latter drugs, claiming that treatment with carnitine could improve this condition [60]. Moreover, it must be considered that pharmacokinetics of ASM may be age-dependent, with this particularly relevant for STP. In a retrospective serum concentrations study, STP concentrations were decreased by 39.6% in children aged 6-12 years and by 57.5% in children younger than 6 years compared with patients older than 12 years [61].

The main differences in the treatment regarding age could be related with clinical variation in phenotypes. A long-term follow-up study of 31 DS patients in Japan, reported that convulsive SE had never occurred in any of the patients after age 10 [62] (Figure 1). In this series, of the 26 patients with persisting seizures, 19 (73%) were having mostly nocturnal seizures, whereas the remaining seven (27%) were having mostly diurnal seizures. Another cohort of 50 adult patients with DS reported similar

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outcomes, where seizures persisted in 80% of adults, but epilepsy severity progressively decreased with age [63]. A final series that included 14 adult patients reported generalized tonic-clonic seizures (often nocturnal) as the dominant seizure type in all patients, being less frequent than in childhood. Other seizure types were also less frequent or even remitted in this group of age [64], these findings could explain why older patients are less prone to emergency admissions and this could explain a less use of rescue medications and a need of lower number of concomitant ASM.

Finally, with respect to precipitant factors 10/31 patients of the Japanese series continued to have seizures provoked by fever, although no longer evolving into SE or clustering. Photosensitivity and pattern sensitivity also showed a tendency to disappear before the age of 20 although some retained light sensitivity [65]. Consequently, precipitating factors should also be minimised in older patients (Figure 1).

Other therapeutic options for seizure control

Regarding non pharmacological treatment, the use of the ketogenic diet (KD) seems to decrease with age (2% in adults) but, on the contrary, vagus nerve stimulation (VNS) is considered as a possible treatment option more often in older patients (17% in adults) [6].

The KD is a well-established treatment for drug resistant epilepsies [66]. Several studies have reported on the use of KD therapy for DS. Supplementary Table S1 depicts 3 prospective and 8 retrospectives studies reporting the efficacy of KD in a total of about 200 patients. One metanalysis comprising the 3 prospective studies and 4 of the retrospective studies is also included in Supplementary Table S1. One of the prospective studies in 15 patients who were treated with an ASM combination including STP showed that more than half of the patients responded after 3 months on the diet [67]. In addition, treatment with KD led to improvement in behavior disturbances and hyperactivity even in patients who did not experience any amelioration in seizure frequency [67]. To date, there is no evidence for any interaction between ASMs and KD [66].

Studies show that the KD is an effective treatment for convulsive seizures in DS, with a typical responder rate of 40-50%, defined by a >50% seizure frequency reduction compared to baseline. According to our experience, the side effect profile of the KD in DS patients is similar to that described for other epilepsy syndromes. Unfortunately, there is no RCT in DS specifically to further establish the efficacy of the KD.

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VNS has been reported to be beneficial for patients with DS, although there is limited published evidence supporting its use (Supplementary Table S2). In the 1 prospective and 5 retrospectives studies found, and shown in Supplementary Table S2, the responder rate (i.e., >50% seizure frequency reduction) ranged from 37.5% to 60%. Time to efficacy after surgery or special stimulation parameters for DS were not addressed in these studies. In absence of a dedicated study, VNS would be indicated as per criteria for other non-surgically remediable drug resistant epilepsies. The side effect profile of VNS in adults is similar to what has been described in the pediatric population (i.e., stimulation-induced symptoms such as hoarseness, cough, drooling, sleep apnea [needing investigation if suspected] and rarely dysphagia not requiring device removal, ipsilateral vocal cord paralysis, rare aspiration pneumonia, rare deep infection needing device removal, or possible device dysfunction due to lead fracture) [68,69]. A metanalysis conducted in 2017, and also included in Supplementary Table S2, summarized these findings [70].

Management of comorbidities

Although each affected person presents their own clinical picture, some secondary conditions, with different degrees of severity, are shared by almost all patients. Comorbidities in DS comprise growth and eating difficulties, dental problems, frequent respiratory tract infections, motor coordination and gait disturbances, speech and cognitive delay, autistic spectrum features, inattention and hyperactivity, sleep cycle disruptions, behavioural problems and deficiencies in social relations, etc. [71]

Whilst neurodevelopment appears normal in DS children at seizure onset, psychomotor developmental progression slows over time, and delays may become evident from 12 to 60 months of age [72] (Figure 1). In some patients, developmental regression can be seen following episodes of SE. However, in many cases the pattern corresponds to a developmental slowing and the consequent intellectual impairment, with most patients developing a disability ranging from severe (50%) to mild by 5 years of age [9].

Crouch gait develops in about half of the Dravet population, together with other gait abnormalities such as parkinsonian and cerebellar gait [73]. Children from 6 years of age can present with the beginning of a crouch gait (Figure 1), characterized by an increased hip and knee flexion and ankle dorsiflexion in the sagittal plane throughout the stance phase, and accompanied by bony malalignment in the transverse plane of medial femoral torsion, lateral tibial torsion, and planoabductovalgus of the feet, is characteristic of DS patients [74]. Walking disabilities can already occur between 4 and 7 years of age and, from adolescence, mobility ranges from independent walking to the need of using a wheelchair [5,74].

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Parkinsonian features are seen in patients from 19 years old, with a suggested progression of severity of the parkinsonian symptoms with age [9,75].

All patients, children and adults, show speech and language impairments. Speech may be intelligible in DS patients, and it is characterized by imprecise articulation, abnormal resonance, breathy voice, pitch and prosody errors, and language appears congruent with cognitive skills [76]. Sleep problems, mainly related to daytime sleepiness and night waking, are also typical in DS [77]. Sleep-wake transition disorders often affect children younger than 5, difficulty initiating and maintaining sleep is particularly common in patients older than 20 years, and sleep breathing disorders are frequent across all ages [78] (Figure 1).

The relative impact of the epileptic encephalopathy (seizures and abnormal EEG activity) and the developmental encephalopathy (impact of the *SCN1A* variant on other aspects of brain function) on the comorbidities seen in DS may be uncertain, but that both are implicated is clear. Age at onset seems to be a predictor of the rate of cognitive decline for patients with a missense mutation in *SCN1A* [10,14]. In addition, myoclonus, focal seizures and absences have been associated with a worse cognitive outcome, and a study from 584 patients showed that seizure burden is associated with increased comorbidities and lower quality of life in DS [6,79]. However, investigators fail to detect a robust correlation between severity of seizures and comorbidities [79,80], and they suggest a differential contribution of neurobiological and genetic factors on the neurodevelopmental quotient [81,82]. In agreement with the idea that mutations in *SCN1A* determine the severity of both epilepsy and comorbidity, experiments in mice show that convulsive seizures and some behavioral comorbidities are uncoupled [83].

Research on novel treatment options must not only focus on seizure reduction but also on the long-term effects of the disease, and DS comorbidities deserve an appropriate consideration by dedicated therapists who work in a collaborative manner to improve patients' quality of life. Early intervention programs involving active management of behavioral problems (e.g., medication such as methylphenidate can be used in some patients if hyperactivity is very prominent), speech and language therapy, physiotherapy, occupational therapy and, sometimes, social work may be important to ensure that patients' needs are met [84–87]. In fact, the ideal multidisciplinary team in charge of a DS patient shall be formed by a (child) neurologist, a nurse, a neuropsychologist, a physiotherapist, a speech therapist, a dental practitioner, and an occupational therapist, among others. In addition to this team, patient management should be supported by special education in regular or specialized centers, as well as by a dedicated group of patient advocates [85,88,89].

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Therapeutic perspectives for DS

Despite being a rare encephalopathy, research on DS is continuously advancing, and various novel drugs, such as clemizole, lorcaserin, trazodone, soticlestat and huperzine A, are currently in the pipeline. FFA, clemizole, lorcaserin and trazodone all act on serotonin signaling pathways. They have been found to be powerful suppressors of spontaneous convulsive behavior and electrographic seizures in zebrafish disease models for DS [90,91]. Clemizole exerts its antiepileptic action via serotonin and not through a histaminergic mechanism of action [91], and is being tested in patients aged 2 to 17 years in a phase 2 trial running in various US centers [92]. Locarserin is an agonist of the HT2C serotonin receptor with the potential of increasing GABA-mediated inhibition and reduce seizure frequency and/or severity in patients with DS [91]. It will be tested in patients from 2 years of age in a phase 3 trial in the US and Canada [93]. Trazodone, currently used as an anxiolytic and antidepressant, showed a positive effect in a 25-year-old Portuguese patient, who went from having several tonic-clonic seizures every day to an average of less than one per month during the 18-month study period, without any remarkable side effects [94]. At present, there are no studies announced with trazodone. Soticlestat is a highly-selective inhibitor of the cholesterol 24-hydroxylase (CH24H) that decreases NMDA receptor activation and glutamate production by reducing brain 24-hydroxycholesterol levels. In a recent phase 2 RCT in patients aged 2 to 17 years, a 33.8% reduction of convulsive seizure frequency was found during the 20-week treatment period, compared to a 7% increase in the placebo group [95–97]. Huperzine A is a potent acetylcholinesterase inhibitor believed to suppress DS seizures via triggering GABA release [98]. It is currently under early clinical development for the treatment of healthy adults and adults with refractory focal-onset seizures with impairment of awareness [99,100].

Other ASMs for DS, still in the preclinical phase, are, GNE-0723, GR-46611, PK11195, cannabis-based products others than CBD, verapamil, various NaV1.1 activators, and oxytocin. The experimental drug GNE-0723 is a positive allosteric modulator of GluN2A-subunit-containing NMDA receptors. It improves brain oscillations, synchrony and cognitive functions in mouse models of both Alzheimer's disease and DS [101]. GR-46611 is a 5-HT_{1D} receptor agonist shown to increase hyperthermia-induced seizure threshold, lower seizure severity and improve survival of DS mice [102]. PK11195, a translocator protein (TSPO) ligand and activator of the *pck1* gluconeogenesis gene, is capable of normalizing glucose levels and correcting metabolic deficits and electrographic seizures in a DS zebrafish model [103]. Consequent upon the antiepileptic efficacy of CBD, the effects on DS of other cannabinoids are being assessed. Cannabichromene (CBC) and its derivatives cannabichromenic acid (CBCA) and cannabichromevarinic acid

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(CBCVA) were reported to increase the temperature threshold at which Dravet mice had generalized tonic-clonic seizures [104]. Verapamil is a voltage-gated L-type calcium channel blocker and a specific inhibitor of the efflux transporter P-glycoprotein and the cytochrome P450 3A4 enzyme (CYP3A4). Able to cross the brain-blood barrier, verapamil is proposed to have an antiepileptic role via inhibition of the P-glycoprotein and the regulation of membrane depolarization induced by the abnormal function of sodium channels. Studies in patients aged 2 to 25 years with drug-resistant epilepsy, including DS, found a 50-99% reduction in seizures and an improvement in cognitive functions (reviewed in [105,106]). In addition, various drugs regulating sodium channel activity are also potential future medicines for DS. The NaV1.1 activator AA43279, and the NaV1.6 inhibitors MV1369 and MV1312, significantly reduced seizures and improved behavior in DS zebrafish [107], and AA43279 also had antiepileptic effects in a DS mouse model [108]. The dual activation of NaV1.1 in inhibitory neurons and inhibition of the *SCN8A*-encoded voltage-gated sodium channel NaV1.6 in excitatory neurons is thus proposed as a therapeutic option for DS. XPC-8770 is a highly selective enhancer of NaV1.1 shown to prevent seizures in DS mice [109]. The glucagon-like 1 peptide (GLP-1) analog liraglutide, used to treat diabetes, is claimed to increase expression of *SCN1A* and decrease seizures, epileptic neuronal death and cognitive dysfunction in mice [110]. Venom peptides from scorpion (Hj1a and Hj2a) and tarantula (Hm1a and Hm1b) also appear to activate NaV1.1 *in vitro* [111,112]. In fact, Hm1a was demonstrated to reduce seizures and premature death in DS mice receiving the toxin directly into the cerebrospinal fluid [113]. On the other hand, Hm1b seems to delay the rapid inactivation of NaV1.1 in cell cultures, and it inhibits NaV1.2, a sodium channel present in excitatory neurons. Thus, the combined action of Hm1b, activating Nav1.1 in inhibitory neurons and inactivating Nav1.2 in excitatory neurons, is proposed as a potential therapeutic option for DS [114]. Continuing on the therapeutic peptides, oxytocin, a hormone and neurotransmitter mediating certain aspects of social behavior, exhibiting neuroprotective and anti-inflammatory effects, and modulating neuronal excitability, has appeared as a promising treatment option for epilepsies caused by mutations in *SCN1A*, like DS. Nasal administration of nanoparticle encapsulated oxytocin (NP-OT) increased resistance to induced seizures, and restored social behavior in a mouse model of GEFS+ and DS [115]. Drugs in the pipeline for DS are summarized in Supplementary Figure S1.

Advanced therapies intended to modify the course of the DS disease, and not only seizures, are now in the spotlight of many investigators (Supplementary Figure S2). Because the *SCN1A* gene is large, typical vector-based full gene replacement therapies are difficult to develop for DS. However, promising genetic approaches are being evaluated. In fact, STK-001, a *SCN1A* antisense oligonucleotide (ASO), has the potential to become the first gene regulation therapy for DS. Now under phase 1/2a trials in US patients 2

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to 18 years old [116], STK-001 is designed to reduce seizures and SUDEP incidence in DS patients via the increase of productive *SCN1A* messenger RNA (mRNA) levels and thus, the elevation of NaV1.1 protein synthesis [117][118]. Another ASO-based strategy under study for DS, this time in preclinical research, is SCN1ANAT, a synthetic oligonucleotide-based compound claimed to increase *SCN1A* mRNA and NaV1.1 protein levels by displacing the expression-limiting natural antisense transcript (NAT) of *SCN1A* [119]. SCN1ANAT improved seizure phenotype in a mouse model of DS, and its administration was demonstrated to be safe for non-human primates [119].

There are other potential next generation therapies for DS currently in preclinical investigation. One example is ETX101, a GABAergic interneuron selective adeno-associated virus (AAV)-mediated gene regulation therapy which increases *SCN1A* expression, this time through gene transcription enhancement. ETX101 seems to reduce seizures and increase survival in a mouse model of DS [120], and is reported as safe and well tolerated in non-human primates [121]. ETX101 first clinical trial is anticipated to begin in 2022. Gene-replacement therapies employing helper-dependent adenovirus (HD-AdV) as vectors for the delivery of a healthy copy of *SCN1A* into the brain are being investigated [122]. Other examples of potential advanced therapies for Dravet are based on the CRISPR/Cas9 technology, which targets the *SCN1A* promoter to increase gene expression and thus, attenuates seizures and improves behavior in DS mice [123][124]. In addition, tRNA-based gene therapies, focused on *SCN1A* mRNA stabilization or nonsense codon suppression, are also proposed to treat DS [125]. To be noted, the tRNA-based codon suppression strategy, which inserts amino acids at premature stop codon sites generating wildtype functional proteins, differs from the ataluren compound which increases protein expression via promoting read-through of the premature stop codons. Unfortunately, a phase 1 trial evidenced no effect of ataluren in reducing seizure frequency and improving cognitive, motor or behavioral function in DS patients 2 to 12 years of age with nonsense mutations [126,127]. Last, other approaches search to prevent Dravet disease by genetically modifying factors that control epileptogenic processes. This is the case of tau, a protein that stabilizes neuronal cytoskeleton and whose reduction via gene deletion seems to suppress seizures and prevent autistic behavior in DS mice [128].

European consensus

Following the critical literature review, and before formally proposing an updated treatment algorithm for DS, we conducted a consultation with European based DS experts through a questionnaire. In order to select the experts, each author proposed 6 to 9 child and adult health professionals from diverse regions in Europe. A final list of 35 experts agreed by all authors was approached via e-mail. Names, roles and

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affiliations of the 32 European experts who accepted to participate in this consultation are listed in Supplementary Table S3.

The consultation consisted of a round of 18 statements agreed by the group of authors of this study, on genetic diagnosis, seizure action plan and emergency protocol, initial treatment of seizures in infancy and childhood, approaching seizures in adults, other therapeutic options for seizure control, and management of comorbidities (3 statements per topic reviewed in the literature). Participants were asked by individual e-mail to score all statements from the perspective of clinical practice and their personal experience. Within two weeks, 29/32 experts gave, in a complete anonymous manner and via an online survey form, their level of agreement with the 18 proposed statements using a 1 to 5 scoring system (1, strongly disagree; 2, somewhat disagree; 3, neither agree nor disagree; 4, somewhat agree; 5, strongly agree). In addition, some experts submitted explanations for their responses via e-mail to the authors. The statements proposed in the consultation and the scores given by the 29 responder experts are shown in Figure 3. The European survey was performed between May 6 and May 23, 2021. Taking these results and the expert's comments into consideration, and together with the critical literature review, we propose below a guideline for DS diagnosis and management.

Updated guidelines for DS diagnosis and management

Genetic testing including *SCN1A* sequencing and MLPA (Multiplex Ligation-dependent Probe Amplification, to detect gene copy number variations) should be requested when a diagnosis of DS is suspected. In particular, a panel analysis including genes in which variants may result in a phenotype similar to DS should be undertaken when possible. Apart from genetics, other factors such as repeated prolonged episodes of SE or the use of contraindicated medication (i.e., sodium channel blockers) might have an additional impact and thus, differentially contribute to the neurodevelopmental quotient in DS. Also, certain healthcare centers might have some restrictions to access genetic tests (e.g., costs, availability, delays to obtain the results, etc.). Therefore, *SCN1A* analysis could be considered after the occurrence of a prolonged seizure in an infant with normal MRI and normal EEG (see the intermediate level of agreement between the experts ([mean score of 3.62±1.08] with Statement 2 in Figure 3).

All children with a diagnosis of DS should have a personalised emergency protocol held by parents for the management of convulsive seizures. These seizures should be treated immediately with rescue medication when the infant has a history of prolonged seizures. Phenytoin is a sodium channel blocker and should be avoided as second line therapy in the acute treatment of prolonged seizures in DS.

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However, to date there is no data reporting the absence of efficacy nor the occurrence of side effects of this drug. This may explain the lower agreement score on phenytoin avoidance between the European experts (Figure 3, Statement 6, mean score of 3.72±1.22).

VPA is the drug of choice as first line treatment in DS. After failure of VPA, the second line treatment in these children should be a combination of VPA, STP and CLB, with CBD and FFA as alternative second line drugs (Figure 4). Treatment strategy in adults with DS should not be exactly the same as in children (Figure 3, Statement 10, mean expert agreement score of 3.55±1.12). Sodium channel blockers should be avoided in children. However, their use in adults is not clearly defined and needs further exploration (Figure 3, Statement 11, mean agreement score of 3.90±1.01, and Figure 4) [55]. The KD is an effective treatment of drug resistant seizure in patients with DS. However, the benefit-risk ratio and the feasibility of this diet for a person with DS should be discussed with a team experienced in delivering this therapy. The use of VNS for drug resistant seizures in DS patients still needs further investigation, as to date all reports have been from non-controlled studies. This may explain the hesitant level of agreement between the experts (Figure 3, Statement 15, mean agreement score of 3.28±1.16).

It is important to note the high level of agreement from all consulted experts (Figure 3, Statements 12 and 16) relating to the importance of investigating and treating both DS seizures and comorbidities (Figure 4). RCTs of new DS medications should include adult patients. For the optimal management of DS, individuals should be managed by a multidisciplinary team comprising a child or adult neurologist, a nurse, a neuropsychologist and a physiotherapist, among others, and supported by a dedicated group of patient advocates (Figure 3, Statement 18).

Conclusion

A treatment algorithm that includes the most recently approved medications and non-pharmacological therapeutic options is important to guide health professionals and carers of people with DS. Clinical research has mainly focused on children and neurologists treating adults with DS have had limited guidance on management a problem we hope this guideline will help to address.

The treatment algorithm (Figure 4) and the proposed guideline, developed from a European consensus panel of 29 DS experts, will serve professionals in their clinical practice and, as a consequence we hope will benefit patients suffering from the severe symptoms of this disease, improving their quality of life and that of their families.

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Disclosure of Conflicts of Interest

EC has no conflicts of interest to declare. SA has served as consultant or received honoraria for lectures from Advicenne Pharma, Biocodex, Eisai, GW Pharmaceuticals, Neuraxpharm, Nutricia, UCB Pharma, Xenon, Zogenix. He has been investigator for clinical trials for Eisai, UCB Pharma, GW Pharmaceuticals and Zogenix. VV has participated in advisory boards and symposium organised by Arvelle, Bial, Eisai Inc, Esteve, GSK, GW Pharma, Novartis, Pfizer, Sandoz, UCB Pharma and Zogenix. 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 research is supported by the National Institute of Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital. JHC holds grants from NIHR, EPSRC, GOSH Charity, ERUK, the Waterloo Foundation and the Great Ormond Street Hospital Biomedical Research Centre. SMZ has received research support from Epilepsy Research UK, Dravet Syndrome UK, Tenovus Foundation, Glasgow Children's Hospital Charity. His institution has undertaken / is undertaking commercial studies for GW Pharma, Zogenix, Stoke Therapeutics & Encoded Therapeutics. He has received honoraria for educational symposia, advisory boards and consultancy work from Encoded Therapeutics, Stoke Therapeutics, GW Pharma, Zogenix, Eisai, Bial & Veriton Pharma. LL received grants and is a consultant and/or speaker for Zogenix, LivaNova, UCB Pharma, Shire, Eisai, Novartis, Takeda/Ovid Therapeutics, NEL, Epihunter. He has a patent for ZX008 (FFA) for the treatment of DS and infantile epilepsies assigned to his institution and licensed to Zogenix. JAA, is president of Dravet Syndrome Foundation Spain (DSF). He and/or DSF have received grants and/or financial support from GW Pharma, Zogenix, Ovid Therapeutics, Encoded Therapeutics, Biocodex, Praxis and Stridebio to help carry out some of the DSF´s foundational activities or providing consulting services. JAA honoraria has always been directly or indirectly donated to DSF.

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.

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Figures and Tables

Figure 1. Clinical manifestations of DS and their relative incidence according to age. Schematic representation of clinical manifestations of DS and their relative incidence according to age, adapted from Gataullina & Dulac, 2017 [(129)] with updated information gathered in this review. FSz, complex febrile seizures; HS, hyperthermia sensitivity; MGOS, Motor generalized onset seizures; SE, convulsive status epilepticus; AE, acute encephalopathy; FOSIA: Focal onset seizure with impaired awareness; MSz, myoclonic seizures; DD, developmental delay; AA, atypical absences; ID, intellectual disability; BD, behavioural disturbances; OS, obtundation status; SD, sleep disturbances; CG, crouching gait; SUDEP, sudden unexpected death in epilepsy.

Figure 2. Example of an emergency protocol for DS patients. An emergency medical protocol specific for DS patients, like the example here proposed, should be filled, signed and stamped by the neurologist –adapted to each patient– and always accompany the patient to be given to the emergency staff in the event of a long-lasting severe seizure. To ease medicament recognition by the emergency staff, including commercial names of the ASMs mentioned in the protocol is recommended.

Figure 3. European consultation results. Level of agreement on 18 statements related to the diagnosis, treatment and management of DS was responded by 29 European experts (see Supplementary Table S3) using a 1 to 5 score (1, strongly disagree; 2, somewhat disagree; 3, neither agree nor disagree; 4, somewhat agree; 5, strongly agree). Statements are listed in this Figure. Shown are means and standard deviations of the scores given to each statement. DS, Dravet syndrome; MRI, magnetic resonance imaging; EEG, electroencephalogram; VPA, valproate; STP, stiripentol; CLB, clobazam; CBD, cannabidiol; FFA, fenfluramine; KD, ketogenic diet; VNS, vagus nerve stimulation.

Figure 4. Proposed treatment algorithm for DS. CBD, cannabidiol; FFA, fenfluramine.

Supplementary Figure S1. Drugs in the pipeline for DS. 5-HT, serotonin; HTR, serotonin receptor; GABA, γ-aminobutyric acid; NMDAR, N-methyl-D-aspartate receptor; CH24H, cholesterol 24-hydroxylase; AChE, acetylcholinesterase; P-gp, P-glycoprotein; CYP3A4, cytochrome P450 3A4 enzyme; TSPO, translocator protein; CBC, cannabichromene; CBCA, cannabichromenic acid; CBCVA, cannabichromevarinic acid; CBR, cannabinoid receptor; TRPA1, transient receptor potential ankyrin 1; GLP-1, glucagon-like peptide-1; NP-

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OT, Nanoparticle encapsulated oxytocin; OXTR, oxytocin receptor. At present, there are no studies announced with trazodone.

Supplementary Figure S2. Current advanced therapeutic options in development for DS. NAT, natural antisense transcript; AAV, adeno associated virus; AdV, adenovirus; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; Cas9, CRISPR-associated protein 9; tRNA, transfer RNA.

Supplementary Table S1. KD studies on DS patients.

Supplementary Table S2. VNS studies on DS patients.

Supplementary Table S3. European experts participating in the Delphi study.

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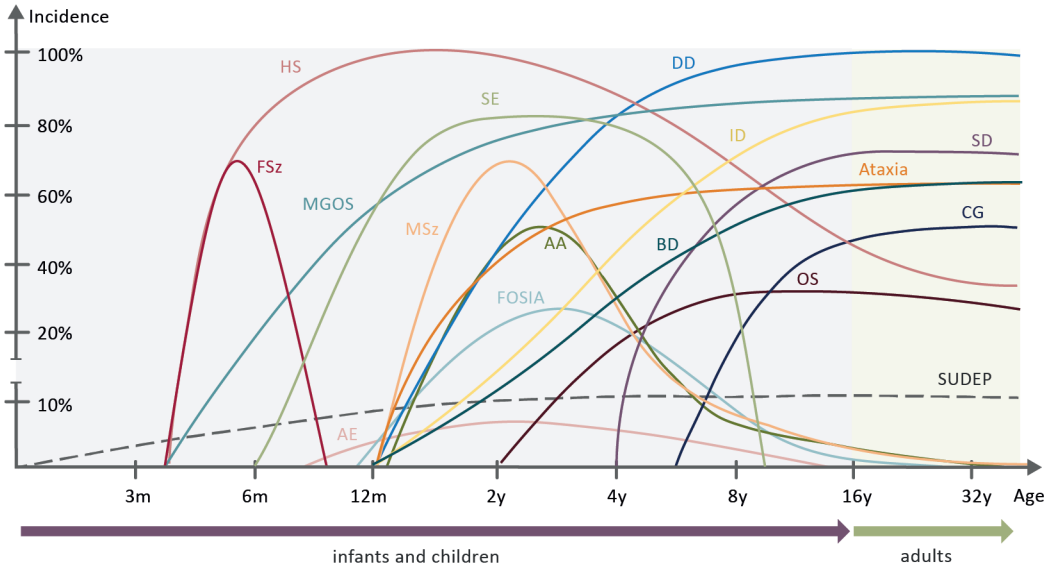

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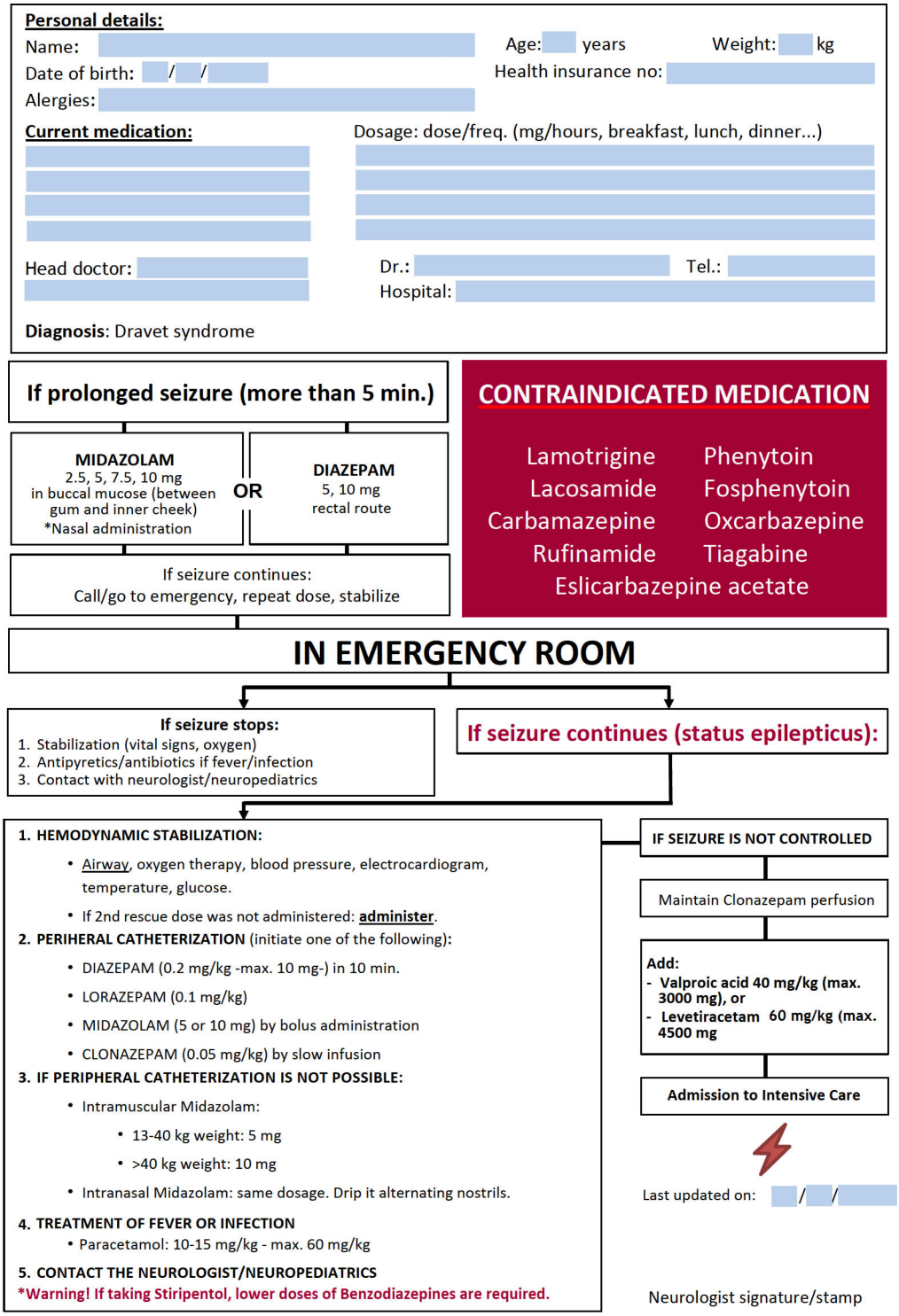

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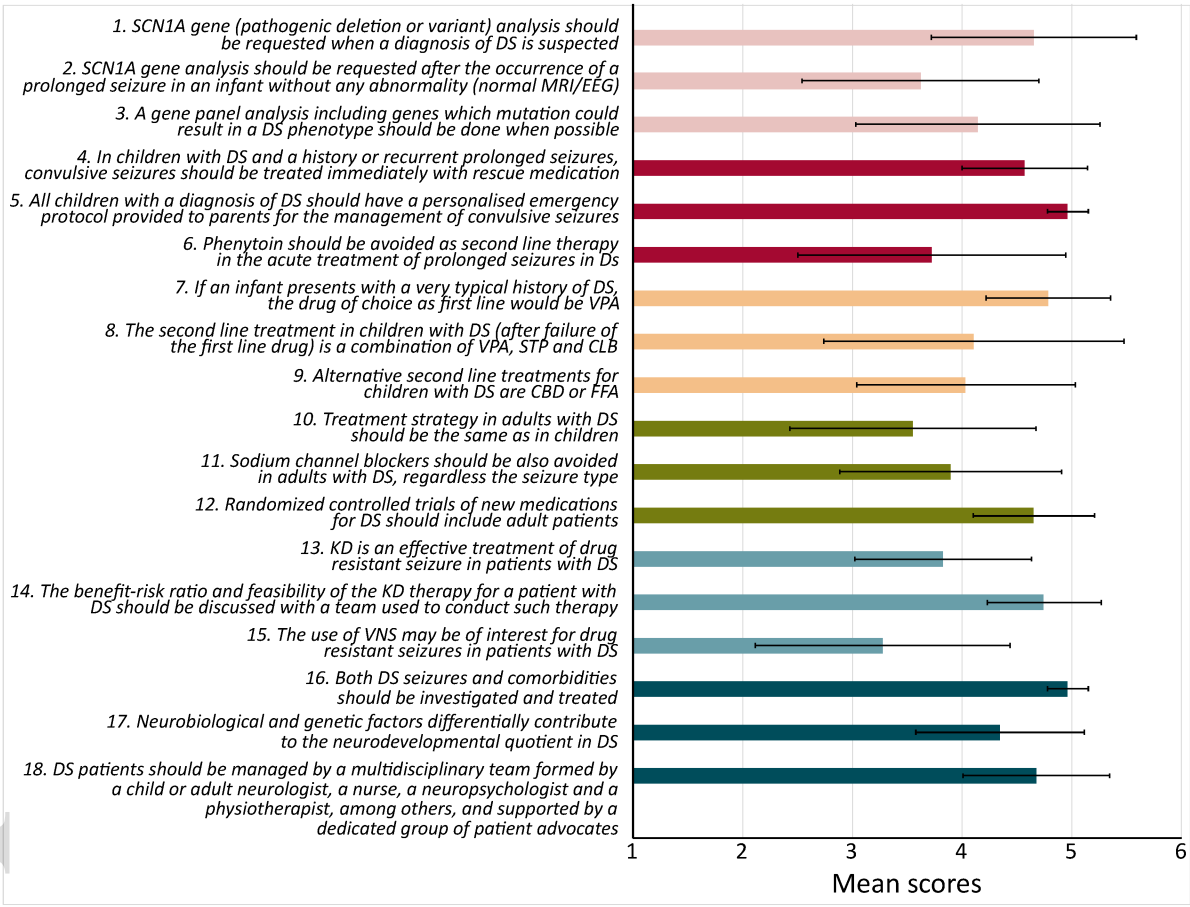

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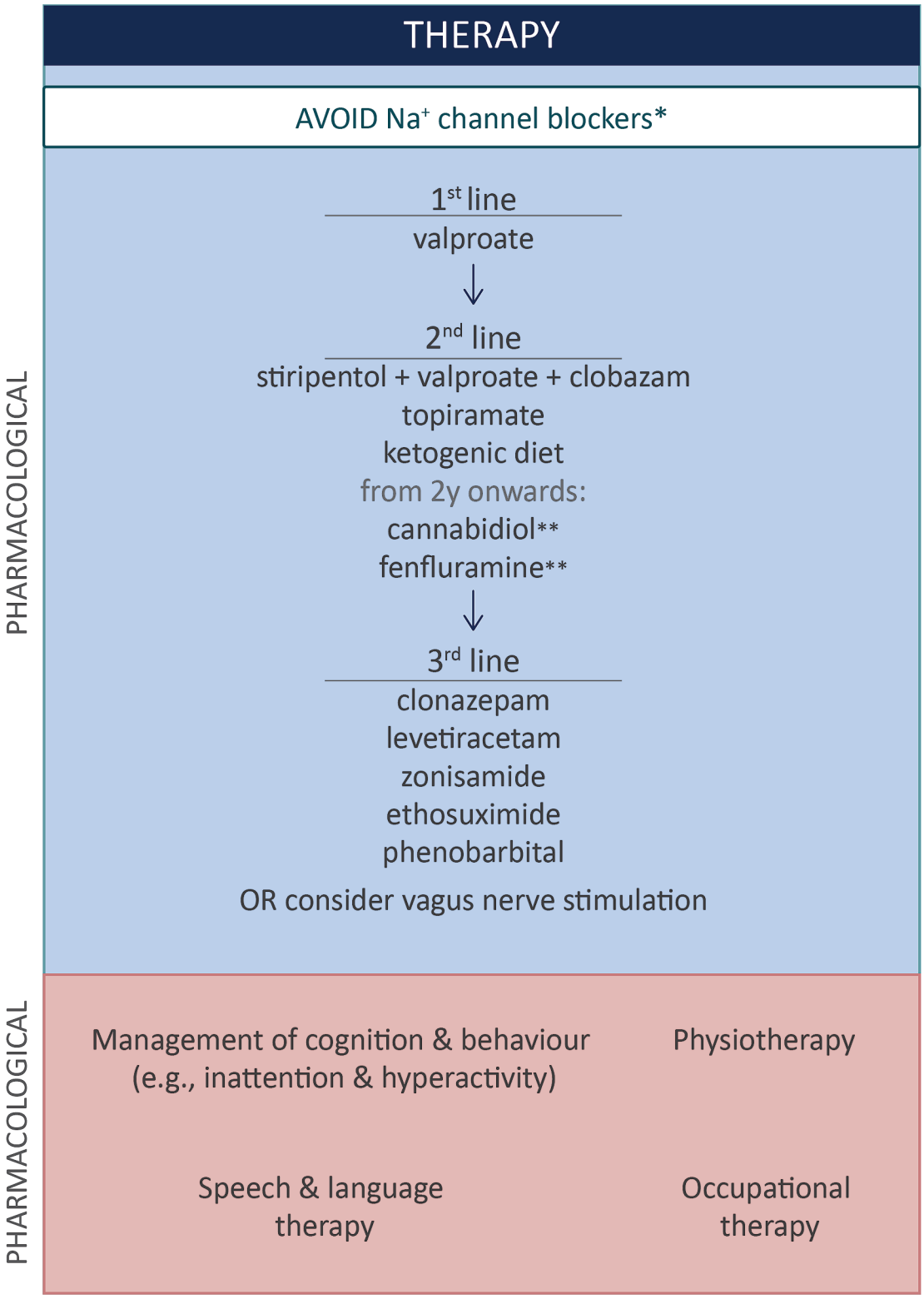

*Na+ channel blockers should also be avoided in adults. However, further studies are needed to ensure that these drugs produce, as the disease evolves, the same negative effects as in childhood. If already introduced with no apparent negative effect, Na+ channel blockers may be considered as 2nd line therapy in adults.

**To now, there is limited evidence on the use of CBD and FFA in adults.