More than epilepsy - a parent-initiated collaborative analysis of the research landscape and research needs in Dravet syndrome

- Long version with 66 references -

Carsten Konrad[1,2]

Simona Borroni[3]

Serpil Budak[2]

Silke Flege[2]

Daniel Kiper[4]

Affiliations:

[1] Medial Center for Adults with Disabilities (MZEB) and Department of Psychiatry and Psychotherapy, AGAPLESION Diakonieklinikum Rotenburg, Elise-Averdieck-Str. 17, 27256 Rotenburg, Germany, c.konrad@diako-online.de

[2] Dravet Syndrom e.V. (Frankfurt a.M., Germany)

[3] Gruppo Famiglie Dravet Associazione APS (Milan, Italy)

[4] Vereinigung Dravet Syndom Schweiz (Zurich, Switzerland)

Abstract

Background: Dravet syndrome (DS) is a complex developmental and epileptic encephalopathy associated with mutations or deletions in the SCN1A gene (2q24.3). Symptoms highly impact patients and their families. Therefore, patient and family associations (PFA) have become important players in stimulating and supporting research. Three European PFAs initiated the current analysis to advance DS research, to identify unmet research needs and suggest future DS research directions.

Methods: A SCOPUS and PubMed literature review was performed on DS research, including 3003 publications. Further insights were gathered from interviews with selected stakeholders and opinion leaders. The resulting landscape analysis was instrumental to identify the state of knowledge and actual research priorities and provided a platform for the discussion involving representatives of all stakeholders during two workshops held 16th and 20th January 2023.

Results: Major advances have been made in the epidemiology, clinical characterization, pathophysiology, and therapy of DS. However, major issues remain poorly investigated, including the mechanisms, development, and management of cognitive, behavioral, social, motor, speech and language, sleep problems. DS in adulthood and SUDEP are poorly understood. Many patients suffer from difficult-to-treat seizures and the side effects of polypharmacy.

Discussion: PFAs point out that DS is more than epilepsy. Research on the mechanisms of SUDEP as well as cognitive, behavioral, social, motor, speech, and sleep problems is of very high priority. PFAs suggest further research on the longitudinal course as well as pharmacological and non-pharmacological treatment of DS's non-epileptic symptoms. Therapeutic studies should include standardized behavioral, cognitive, and motor measures, as well as mortality rates. Direct comparisons of DS treatments across populations are necessary. More emphasis should be laid on adult DS.

Keywords: Dravet syndrome, epileptic encephalopathy, treatment, caregiver perspectives

Zusammenfassung

Hintergrund: Das Dravet-Syndrom (DS) ist eine komplexe Entwicklungsstörung und epileptische Enzephalopathie, die mit Mutationen oder Deletionen im SCN1A-Gen (2q24.3) einhergeht. Die Symptomatik des DS wirkt sich stark auf Patienten und ihre Familien aus. Daher sind Patienten- und Familienverbände zu wichtigen Akteuren geworden, die die Forschung anregen und unterstützen. Drei europäische PFAs haben die aktuelle Analyse initiiert, um die DS-Forschung voranzutreiben, ungedeckte Forschungsaspekte zu identifizieren und zukünftige Richtungen für die die DS-Forschung vorzuschlagen.

Methoden: Es wurde eine SCOPUS- und PubMed-Literaturrecherche zur DS-Forschung durchgeführt, die 3003 Veröffentlichungen umfasste. In Interviews mit ausgewählten Interessenvertretern und Meinungsführern wurden weitere Einblicke gewonnen. Die resultierende Landscape-Analyse bot eine Plattform für die Diskussion mit Vertretern aller Interessengruppen während zweier Workshops am 16. und 20. Januar 2023.

Ergebnisse: In der DS-Forschung wurden große Fortschritte in der Epidemiologie, klinischen Charakterisierung, Pathophysiologie und Therapie erzielt. Wichtige Aspekte sind jedoch unzureichend erforscht, darunter die Mechanismen, die Entwicklung und das Management von kognitiven, verhaltensbezogenen, sozialen, motorischen, sprachlichen und schlafbezogenen Problemen. DS im Erwachsenenalter und SUDEP sind unzureichend erforscht. Viele Patienten leiden unter schwer behandelbaren Anfällen und den Nebenwirkungen von Polypharmazie.

Diskussion: Die PFAs weisen darauf hin, dass DS mehr als eine Epilepsie ist. Die Erforschung der Mechanismen von SUDEP sowie kognitiven, verhaltensbezogenen, sozialen, motorischen, Sprach- und Schlafproblemen hat höchste Priorität. PFAs schlagen weitere Forschung zum Längsschnittverlauf sowie zur pharmakologischen und nicht-pharmakologischen Behandlung der nicht-epileptischen Symptome von DS vor. Therapiestudien sollten standardisierte verhaltensbezogene, kognitive und motorische Messungen sowie die Sterblichkeitsraten umfassen. Direkte Vergleiche von DS-Behandlungen in verschiedenen Populationen sind notwendig. Ein größeres Augenmerk sollte auf erwachsene DS gelegt werden.

Introduction

Dravet syndrome (DS), initially described as Severe Myoclonic Epilepsy of Infancy (SMEI), is a genetic, developmental, and epileptic encephalopathy characterized by the early onset of recurrent convulsive seizures, usually within the first year of life in normally developed infants. Mortality of DS is high at 15.84 per 1000 person-years, as well as the rate of sudden unexpected death in epilepsy (SUDEP) at 9,32 per 1000 person-years [1]. In addition to epileptic seizures, other symptoms such as behavioral problems (aggression, dangerous behavior, impulsivity, hyperactivity, or compulsive habits) motor deterioration, and cognitive deficits emerge during development [2,3,4]. DS significantly impacts patients' and caregivers' lives [2, 3].

To advance DS research, an innovative approach, the landscape analysis, was carried out to depict the global landscape of research in DS, identify research obstacles and define priorities for research support, develop a roadmap for future research, and enable stakeholder engagement and collaboration.

Methods

This landscape analysis was initiated and sponsored by three Patient and Family Associations (PFAs) for DS: the Gruppo Famiglie Dravet Associazione APS (Milan, Italy), the Vereinigung Dravet Syndrom Schweiz (Zurich, Switzerland), and the Dravet Syndrom e.V. (Frankfurt a.M., Germany). Commissioned research was carried out by the research consulting agency Science Compass (Milan, Italy), which applied an innovative landscape analysis approach.

A literature search was conducted in February 2021 using both SCOPUS and PubMed databases, searching for the keywords “Dravet OR SCN1a,” which revealed 2000 (SCOPUS) and 531 (PubMed) additional publications. 197 reviews published since 2015 were selected as the basis of the landscape analysis. The literature search was repeatedly updated until June 2022, based on the same selection criteria, and ultimately included 3003 publications. The results of the literature review are described in three consecutive articles, covering the topics “basic and preclinical research,” “clinical manifestations,” and “treatment options.” Although other aspects, such as “population and market size” and “databases, patient registries, and biobanks,” were included in the full study, they are not discussed in the three consecutive papers due to space limitations. We invite readers to consult the complete study for information on these aspects (see below).

Finally, several key opinion leaders with longstanding expertise in Dravet research were invited to participate in web-based interviews and round-table discussions conducted between October 2021 and March 2022. The experts were selected with the assistance of each Dravet Association’s scientific advisory boards for their central role in DS research. All experts are listed in the Acknowledgments section.

Materials from the original research report by Science Compass are available upon request by writing to gruppofamiglie@sindromedidravet.org.

Results

1. Gene, protein, and disease mechanisms

1.1. Genetics

DS is highly associated with mutations or deletions in the SCN1A gene on chromosome 2q24.3, coding for the alpha subunit of the NaV1.1 voltage-gated sodium channel. Over 80% of DS patients have mutations at this locus. Other implicated genes include PCDH19 (Xq22.1, about 5% of female cases), GABRG2 (5q34), GABRA1 (5q34), STXBP1 (9q34.11), and SCN2A (2q24.3). The etiology is unknown in approximately 10% of cases [4, 5].

However, there is no clear genotype-phenotype correlation. Genetic mutations do not always predict the type of disease or disease severity, and SCN1A alterations have been linked to other disorders, such as Genetic Epilepsy with Febrile Seizures Plus (GEFS+), Myoclonic-Atonic Epilepsy (MAE), Epilepsy of Infancy with Migrating Focal Seizures, Early-Onset Developmental Epileptic Encephalopathy, or Familial Hemiplegic Migraine 3 (FHM3).

SCN1A haploinsufficiency is not only linked to epilepsy but also ataxia (cerebellum), crouch gait (basal ganglia, motor neurons), thermoregulation and sleep disturbances (hypothalamus), and psychomotor delay (all of these structures) [6]. Disease mechanisms concerning these functions are still elusive.

1.2. Proteins

The sodium channel NaV1.1 affected by SCN1A alterations is primarily found in the axonal initial segment of inhibitory GABAergic interneurons [7]. Research indicates that NaV1.1 channels are critical for maintaining inhibitory network stability, and their dysfunction leads to hyperexcitability. SCN1A mutations primarily cause NaV1.1 loss-of-function (LOF), reducing inhibitory neuron excitability and leading to network hyperexcitability. Functional studies suggest a spectrum of effects, from mild to severe phenotypes, influenced by modifying factors and environmental variables. Truncating mutations generally lead to more severe outcomes, whereas missense mutations display variable phenotypic presentations. The study of these mutations is key to understanding DS pathogenesis.

1.3. Expert opinions

Experts emphasize that more basic and preclinical research is warranted in DS. The exact genotype-phenotype correlation remains unclear, and modifying variables such as mosaicism, epigenetics, and environmental factors remain elusive. Examining mosaicism and the whole genome may be worthwhile. At the protein level, the contribution of SCN1A-related dysfunction on ion channels in different types of interneurons, as well as the specific contribution of SCN1A-expressed relative to SCN2A- or SCN8A-expressed sodium channels, is unknown. New technical approaches, such as high-throughput electrophysiology, may allow for quicker and more automated functional studies.

2. Research infrastructure

Several in vitro and in vivo disease models have been developed to study DS. In vitro models provide insight into disease mechanisms, the effect of different mutations, the role of cellular compounds involved, and provide a tool for testing pharmacological compounds. In vivo animal models, such as rodents, zebrafish, and Drosophila melanogaster, provide significant insights into understanding DS and facilitate screening of potential pharmacological targets.

2.1. In vitro models

2.1.1. Heterologous expression systems

Electrophysiological studies of SCN1A mutation effects on channel function are often performed in cultured cells, such as human embryonic kidney (HEK) cells, the tsA-201 cell line, or Chinese hamster ovary (CHO) cells. Depending on the type of mutation, channels gain or lose function (GOF or LOF), with LOF mutations associated with more severe DS phenotypes. While electrophysiological properties can be studied in detail, these models are far from the complexity of a human brain, do not inform about network effects, and cannot model effects of interacting proteins, splicing, and other factors unique to neurons. Therefore, in vitro expression systems can be considered a first step in understanding the effects of a genetic mutation and testing pharmacological approaches [8].

2.1.2. Transfected / transgenic neurons

In vitro models can be generated by introducing patient mutations into neuronal cells, either by transfecting cell lines with the mutation of interest or by deriving neuronal cells from transgenic animal models. These models enable the study of channel functions in disease-relevant cells, supporting the development of therapies and personalized medicine. They facilitate relatively fast functional screening of mutants and contribute to the development of therapies or testing of personalized medicine.

2.1.3. Patient-derived induced pluripotent stem cells (iPSCs)

The development of pluripotent stem cell technology opens up the possibility of designing patient-specific cell models of DS. Pluripotent cells may be derived from fibroblasts by skin biopsy or blood-derived hematopoietic cells. After pushing these cells back to a pluripotent state, differentiation and editing of the genome become possible, e.g., by TALEN (transcription activator-like effector nuclease) or by CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats / CRIPSR-associated protein-9 nuclease). iPSCs can help understand disease progression at the cellular, tissue, and organ levels. Therefore, iPSCs might help to elucidate non-epileptic dysfunctions in DS.

2.2. In vivo models

2.2.1. Rodents

Genetic engineering designs different mutant mice, including knockout mice, knock-in mice, and conditional mutants. Knockout mice allow us to study the effects of lacking a specific gene. The first SCN1A knockout mouse was obtained by targeting the last coding exon of SCN1A [9], showing spontaneous seizures. Exon 1 was also deleted to create the Scn1atm1Kea knockout mouse [10]. Knock-in mice allow for studying introduced genetic mutations. Substitution of exon 21 leads to the R1407X mutation, a nonsense mutation

found in patients [11]. The SCN1A R1648H mouse carries a specific mutation found in a large GEFS+ family [12]. The SCN1A E1099X knock-in mouse demonstrates spontaneous and hyperthermia-induced seizures [13]. Conditional null mutants allow the deletion of a specific gene under controlled conditions during a lifetime. Conditional SCN1A deletion in forebrain GABAergic neurons demonstrates that targeting this specific neuronal population leads to spontaneous and hyperthermia-induced seizures [14]. Genetic background modifies seizure phenotype [10]. Rodent models of SCN1A mutations suggest that SCN1A mutations increase cortical excitability by reducing the excitability of cortical and hippocampal inhibitory interneurons, which is underlined by conditional cell-specific Nav1.1 inactivation [15, 16].

2.2.2. Zebrafish

Zebrafish models have the advantage that subdivisions of the central nervous system are similar to mammals and optically accessible. Zebrafish are used in high-throughput screening of new compounds, such as the scn1lab552/—containing a null allele of the voltage-gated sodium channel. Models such as scn1lab morphant or 4—and 7-dfp scn1labmut/mut larvae helped to identify the antiseizure effects of clemizole, lorcaserin, trazodone[17], and fenfluramine [18].

2.2.3. Drosophila melanogaster

This species has only one gene, Para, encoding voltage-gated sodium channels. The channel structure differs from human nav1.1. channels, so there are concerns about transferring research results from drosophila to humans. The two knock-ins of human mutations SCN1A K1270T and SCN1A S1231R show heat-induced seizures and gain (K1270T) and loss (S1231R) of function. Dose-dependent effects of 5-hydroxytryptophan could be shown in these models. R1648C and R1648H mutations created by CRISPR-Cas9 gene editing were associated with DS and GEFS+, respectively, suggesting that disorders of different severity in humans may have different genetic backgrounds [19].

2.3. Expert opinion

Experts underline that the development of iPCS technology enables research with “artificial” DS, building mutations found in human patients. However, there is doubt that IPSCs can mirror the alterations during the progression of the disease. The possibilities of genetic technologies open new horizons in DS research. In vivo models allow to observe more complex interactions of different neuronal systems.

3. Clinical knowledge

DS is considered to be the prototype of developmental and epileptic encephalopathies (DEE). It comprises a wide range of clinical manifestations beyond epilepsy, including intellectual disability, behavioral disorders, increased risk of SUDEP, ataxia, gait disturbance, speech disorder, and sleep abnormalities [20], impacting the quality of life of people with DS and their families [21].

3.1. Epilepsy

Seizure onset in DS is between 1-18 months when neurodevelopment appears still normal, with a majority of first seizures observed below the age of 1 year. Seizures are typically triggered by hyperthermia, e.g., induced by fever, high outdoor temperature, hot baths, or physical activation. They may be prolonged, sometimes leading to status epilepticus. At disease onset, generalized tonic-clonic or hemiclonic seizures predominate, but at age two or later, additional seizure types appear, including absence seizures or myoclonic seizures [22]. Seizure frequency is high within the first decade, and seizures are often drug-resistant. The application of contraindicated medicines has adverse long-term outcomes. Therefore, early diagnosis followed by correct treatment is essential [23]. A significant problem is that epilepsy is often pharmaco-resistant. Polypharmacy is frequently used, and side effects affect quality of life.

3.2. Cognitive, behavioral, and social functioning

While neurodevelopment appears normal during the first age of life, slowing of psychomotor development may become evident from 12 to 60 months of age, sometimes following episodes of status epilepticus. Most patients develop profound learning disabilities [3, 21]. Behavioral difficulties are highly relevant for patients and caregivers. DS patients show significant deficits in adaptive behavior, and signs of autism spectrum disorder are highly prevalent (31-38%) [24, 25]. Cognitive, behavioral, and social problems are major contributors to disease burden and caregiver concerns. They severely impact patients' and caregivers' quality of life [2, 26, 27].

3.3. Motor development and gait abnormalities

The course of motor development in DS is not well understood yet. Most children with DS older than 2 years show delayed motor development [28]. Crouch gait with increased hip and knee flexion and ankle dorsiflexion is common. In addition, muscle weakness, spasticity, and contractures are observed. DS patients show progressive gait deterioration in the second decade of life [29, 30]. Many teenagers require a wheelchair to overcome long distances. Motor difficulties add significantly to decreased mobility and social inclusion. Nevertheless, studies with larger numbers of participants and systematic assessment of therapeutic interventions are still lacking.

3.4. Speech and language function

Limited data are available on speech and language problems in DS. Speech problems such as imprecise articulation, breathy voice, unusual resonance, pitch, and prosody errors are common in DS [32], while language impairment is congruent with cognitive skills [31]. Considering that speech and language are highly relevant social skills, it becomes clear that they have not received enough attention.

3.5. Sleep

Sleep problems are frequent in DS [32]. While younger DS children are often affected by sleep-wake transition disorders, patients older than 20 years have difficulties initiating and maintaining sleep, and breathing disorders during sleep occur across all ages [20]. It is unclear which role SCN1A plays in sleep regulation. The first experiments in knock-out mice showed abnormalities in sleep architecture, such as reduced non-rapid and rapid eye movement sleep in R1648H mice [33]. However, there is a significant lack of understanding of sleep disturbances and their therapy in DS. Considering that sleep deprivation is a risk factor for seizures and has negative impacts on learning, and that sleep disorders in DS affect the whole family, more research on sleep in DS is necessary.

3.6. Sudden unexpected death in epilepsy (SUDEP)

The rate of SUDEP is exceptionally high in DS, with up to 50% of deaths in DS caused by SUDEP, 73% of these before the age of 10 [34]. Research on cardiac and autonomic functions in DS is controversial, with studies reporting abnormalities [35, 36] versus others finding normal function [37]. SCN1A-R1407X knock-in mice show increased myocyte excitability and different forms of arrhythmias [38]. Abnormalities in myocytes derived from DS pluripotent stem cells suggest a predisposition of DS patients to cardiac arrhythmia [39]. Other mechanisms under discussion are intracranial pressure and edema [40], epilepsy severity, seizure frequency, drug polytherapy, or postictal ventilatory abnormalities [41]. Although SUDEP is an active field of research in DS, SUDEP mechanisms and prevention are still unresolved. Considering the very high mortality in DS, further examination into the causes and prevention of SUDEP is crucial.

3.7. DS in adulthood

Over the years, seizure severity and frequency decrease, and status epilepticus becomes less frequent. Parkinsonian symptoms progress, and behavior problems associated with a lower health-related quality of life persist in adulthood [42]. Although no specific treatment guidelines exist for adults, a treatment algorithm developed in consultation has been suggested [20]. DS research has so far focused on children, with a 7:1 children-to-adult ratio of DS studies [42]. There is a substantial lack of information about the course of the disease in adulthood, as well as pharmacological strategies in adulthood.

3.8. Expert opinion

Experts underline that early diagnosis and intervention of DS are critical for long-term outcomes. More clinical studies on the evolution of DS in the longitudinal course are required, and more standardized assessments of all symptoms, including non-epileptic symptoms of DS, are essential. It is also important to ensure that companies conduct clinical trials in adults. The presentation and treatment of DS in adulthood have so far received too little attention. The impact of different treatment strategies on non-epileptic symptoms, such as gait- and speech disturbances, and behavioral and social problems, should be investigated. This includes pharmacological as well as non-pharmacological and behavioral treatments. There is a paucity of data on how to treat behavioral problems and autism spectrum disorder in DS, even though these problems are a priority for parents and represent a considerable source of concern. In total, there is a vast gap in knowledge on the clinical development of different DS symptoms, especially non-epileptic symptoms, and their treatment, especially in adulthood. More studies are urgently needed.

4. Therapeutic Pipeline

An international consensus on diagnosing and managing DS suggests valproate as a first-line treatment [43]. There is also consensus for using clobazam, fenfluramine, or stiripentol as first—or second-line treatment. Valproate and ethosuximide are effective in absence seizures in DS, and valproate is effective in myoclonic seizures in DS. Valproate and fenfluramine are highly tolerated. Dietary interventions should be considered when 3 or 4 antiseizure drugs have failed. Lamotrigine is contraindicated in DS [43].

4.1. Approved symptomatic treatments

So far, three anti-seizure medications —stiripentol, cannabidiol, and fenfluramine — have been approved for treating DS in Europe.

Stiripentol (Diacomid®) was developed by the French company Biocodex and obtained conditional marketing authorization in Europe in 2007 and full authorization without age restriction in 2014. It is used as an adjunctive therapy for DS in combination with valproate and clobazam. Stiripentol increases the GABA concentration in synaptic and extra-synaptic compartments and increases the duration of $GABA_A$ receptor activation. Efficacy and safety were demonstrated in 2 phase-III double-blind, placebo-controlled randomized trials, STICLO France and STICLO Italy [44, 45]. Stiripentol reduces the risk of status epilepticus by 70% [46]. The main side effects are anorexia and weight loss, sedation, behavioral changes including hyperexcitability and aggression, neutropenia, insomnia, abdominal pain, ataxia, drooling, and dystonia. Stiripentol improves long-term seizure frequency in about 50% of patients

Cannabidiol as a liquid formulation of cannabidiol was developed by GW Pharmaceuticals, which Jazz Pharmaceuticals later acquired. It was approved as adjunctive therapy in 2018 in the US as Epidiolex® and in 2019 in Europe as Epidyolex®, the latter in conjunction with clobazam in children aged 2 or more. Two phase-III double-blind randomized-controlled trials (GWPCARE1 and GWPCARE2) demonstrated the efficacy and safety of cannabidiol [47, 48], with an average reduction of seizure frequency of 39%, and the main side effects being somnolence, diarrhea, anorexia, fatigue, behavioral disorders, vomiting, and hepatic cytolysis. Although, according to international consensus, cannabidiol is only a third-line treatment, it has gained high popularity and extraordinarily high sales numbers [49].

Fenfluramine is a derivative of amphetamine and 5HT2C serotonin receptor agonist, which was first used in the 1970ies as an anorectic drug but was withdrawn due to cardiac valvopathies. It was developed for DS therapy by Zogenic, later acquired by UCB, with the commercial name Fintepla®. The safety and efficacy of fenfluramine in DS were assessed in three phase-III, double-blind, randomized controlled trials (NCT02682927, NCT02826863, NCT02926898) [50, 51]. It is approved for patients aged two and above without concomitant medication. Additional data on patients ages 1-2 is currently obtained (NCT06118255). The main side effects are anorexia, diarrhea, fatigue, sedation, and lethargy. It does not require concomitant treatment with clobazam. Fenfluramine may improve cognitive functions [52] and reduce mortality, including SUDEP [53].

In a recent network meta-analysis, stiripentol was at least as effective as fenfluramine in reducing convulsive seizures, and both were more effective than cannabidiol [54].

4.2. Treatments under development

Several symptomatic compounds are in different stages of development. In the following text, we adopt the categorization suggested by Mingorance, differentiating between “first-generation / first-in-class” treatments based on an innovative new pharmacological strategy, “second-generation / second-in-class” treatments optimizing existing pharmacological strategies, and “disease-targeting / disease-modifying therapies” targeting SCN1A haploinsufficiency in DS [49]. As most of the treatments under development focus primarily on their anti-epileptic efficacy, it is difficult, if not impossible, at this stage to assess their impact on non-epileptic symptoms of DS. Further studies will be necessary to assess and document such potential effects.

4.2.1. First-generation (first-in-class) treatments

Takeda Pharmaceuticals developed **Soticlestat (TAK-935)** in collaboration with Ovid Therapeutics to treat rare developmental and epileptic syndromes. It inhibits the enzyme cholesterol-24-hydroxylase in the brain, reducing glutamatergic signaling. It effectively reduced seizure frequency in many DS animal models and two pediatric clinical trials, ELEKTRA and ARCADE. The phase-III trial SKYLINE missed the primary endpoint in DS, although secondary endpoints were met. An open-label extension phase will end in 2025, and it remains unclear whether soticlestat will be further developed [49].

Huperzine A (SPN-817) is a natural alkaloid used in Traditional Chinese Medicine. It is a brain-penetrant acetylcholine-esterase inhibitor with antiseizure properties in preclinical models. Supernus Pharmaceuticals has performed an open-label phase-2 trial in adults with treatment-resistant seizures showing seizure reduction in an interim analysis [55].

BL-001 by Bloom Science is a combination of bacterial populations designed to induce changes in gut microbiome as observed in the ketogenic diet. The company describes this approach as the “reverse engineering of the ketogenic diet.” The probable mechanism of action is the modulation of the GABAergic system. The company announced it would prepare a phase-2 trial in DS [56].

There is not enough information about ongoing trials on other first-generation treatments. It is known that additional companies made efforts to develop new compounds, such as **IAMA-6** (IAMA Therapeutics), an inhibitor of a Na^+-K^+-Cl^- cotransporter (NKCC1), modulating the sensitivity to GABA [57], **JBPOS-0101** (Bio-Pharm Solutions), an antagonist of metabotropic glutamate receptors, and **NT102** (Neuroene Therapeutics) that targets mitochondria dysfunction and gained FDA orphan drug status and FDA Rare Pediatric Disease Designation, but the current status is unknown. The development of **ReS3-T** (reMYND), which had been accepted into the NINDS Epilepsy Therapy Screening Program in 2021, seems to be paused or discontinued [49, 58].

4.2.2. Second generation (Second-in-class) treatments under development

Lorcaserin (Belviq® by Eisai) is a serotonin-receptor agonist with comparable mechanism of action to fenfluramine. It had to be withdrawn from the market in 2020 due to the enhanced risk of cancer.

Bexicaserin (Longboard / Lundbeck Pharmaceuticals) has a comparable mechanism of action to fenfluramine with selective 5HT2C agonism but without cytochrome P 450 metabolization. The phase-2 PACIFIC trial showed positive results [59], and Lundbeck announced a phase-3 program including DS (DEEp SEA, NCT06660394) [49].

Clemizole (EPX-100), lorcaserin (EPX-200), and **trazodone (EPX-300)** are some compounds of the Epigenics / Harmony Biosciences Pipeline modulating the serotonergic pathways. DS patients' recruitment for clemizole add-on started in 2020 and was later expanded (ARGUS trial, NCT04462770, https://argustrial.com). Results are expected in 2026 [49].

BMB-101 (Bright Mind Biosciences) also has agonist properties at the 5HT2C receptor. An open-label phase 2 study in adults with either absence epilepsy or developmental epileptic encephalopathy is still recruiting [60].

Information about the development of GABAergic compounds is scarce. NCT10004 (NeuroCycle), after Engrail Therapeutics's acquisition, is no longer listed on the company's pipeline. There is also no news about DSP-0378 (Sumitomo Pharma) or XP-0863 (Xeris

Pharmaceutical) [49]. Transdermal treatment with a cannabidiol gel (**ZYN002**, Zynerba Pharmaceuticals) was safe, well tolerated, and reduced seizures in children with DEEs (ACTRN12618000516280) [61]. However, the company informs that further development focuses on fragile X (FXS) and 22q11.2 deletion syndrome (22q) [62].

4.2.3. Disease-targeting (Disease-modifying) therapies

Disease-modifying therapies attempt to target SCN1A haploinsufficiency in DS by applying either antisense oligonucleotides (ASOs) or gene therapy by viral vectors (adeno-associated viral vectors, AAV-vectors).

Zorevunersen (STK-001, Stoke Therapeutics) is an ASO requiring intrathecal injection, allowing SCN1A pre-mRNA to upregulate Nav1.1 protein expression. After two successful phase 1/2a open-label studies (MONARCH, ADMIRAL), a phase-3 trial (EMPEROR) has been announced for the second quarter of 2025 [63]. Data suggest improvements not only in seizure activity but also in cognitive, behavioral, and motor domains [64].

ETX101 (Encoded Therapeutics) designed an AAV vector upregulating the SCN1A expression in GABAergic cells specifically. In 2024, the company started a phase 1/2 trial program consisting of three studies: ENDEAVOR, WAYFINDER, and EXPEDITION. EXPEDITION enrolls children in the UK and is the first study in DS with a primary endpoint on behavioral measures [65].

RT101 (Regel Therapeutics) is also an AAV vector targeting interneurons in DS. The company is preparing an investigational new drug application [49, 66]. Tevard Biosciences is developing **mRNA modulators** for haploinsufficiency and for nonsense mutations in DS. Viral vectors are used to increase the amount of protein to normal levels or repair the gene's bad copy by introducing the normal amino acid. There is not enough actual information to comment on a gene therapy designed to upregulate SCN1A (Sangamo Therapeutics), elevation of gene transcription by CMP-SCN (CAMP4 Therapeutics), and small-molecule ion-channel modulators for Nav1.1 activation (Xenon Pharma). Other companies such as Lundbeck and academic programs such as the Gladstone Institute of Neurological Disease, the Florey Institute of Neuroscience and Mental Health, and the University of Melbourne are researching Nav1.1. activation as well [49].

Discussion

The number of patients with DS is relatively high for a rare disease, with approximately 11,000 in Europe [22] and 35,000 in the major markets [23], offering promising economic gain for companies developing effective medications. DS with SCN1A alterations may be considered prototypical for monogenetic brain disorders, although the genotype-phenotype correlation is not yet fully understood. Thus, research results on SCN1A may also inform about other genetically determined diseases. And there are many compelling reasons to optimize treatment for Dravet Syndrome (DS): DS has a significant impact on the lives of patients and caregivers. Quality of life for DS patients is often limited, and there is a significant increase in mortality rates [29]. Many patients are impaired in education, social interactions, and mobility, and there is much polypharmacy with unknown interactions and side effects for the patients. For caregivers, the burden of DS is enormously high as well. Caregivers indicate limited availability of free time, dependence on family support, emotional

challenges, and concerns about their child's future healthcare requirements [3]. DS influenced the career choices of as much as 80% of the caregivers [3], and 28% had missed over three working days in the past four weeks due to the disease of their child. Depressive symptoms were reported in 47% to 70% of caregivers. For society, the direct and indirect costs of DS are high [2]. As the number of patients with DS is relatively high for a rare disease, companies are investing in developing effective medications.

Gaps identified in basic and preclinical research include genotype-phenotype correlation and the influence of modifying variables such as mosaicism, epigenetics, and environmental factors. The contribution of SCN1A deficiency to different types of interneurons and the specific relationship between SCN1A-expressed channels and other sodium channels remain unknown. The contributions of SCN1A and other genetic factors to non-epileptic symptoms are elusive. From the perspective of PCAs, it is crucial to elucidate the underlying mechanisms of the evolution of different DS symptoms during aging. This includes in vitro and in vivo models of epileptic, cognitive, behavioral, social, motor, speech, language, and sleep symptoms. There is no clear pathophysiological concept explaining the development of motor, cognitive, or behavioral skills, speech, language, or sleep problems. Mortality in DS remains a significant topic, especially concerning the risk of SUDEP, which is exceptionally high in DS [34]. Therefore, SUDEP mechanisms and prevention should be a focus of clinical research.

There are also research gaps in clinical fields of DS. The evolution of different DS symptoms during aging, including epileptic, cognitive, behavioral, social, motor, speech and language, and sleep symptoms, requires considerable research efforts. Especially, symptoms in adulthood are not sufficiently studied. Behavioral and social problems are among the most significant concerns for caregivers of DS patients, contributing mainly to their burden of disease. Cognitive and learning impairments limit the patients' social integration. However, there is no clear pathophysiological concept for these symptoms. The development of motor skills requires much more attention. Speech and language problems are insufficiently explored. Sleep problems require much more attention because they interact with seizures, learning, and the family's health status. Mortality in DS remains a significant concern, especially concerning the risk of SUDEP, which is exceptionally high in DS [34]. Therefore, SUDEP mechanisms and prevention should be a focus of clinical research.

Therapeutic advances in DS are enormous, and the field is very competitive. With stiripentol, cannabidiol, and fenfluramine, three disease-specific symptomatic therapies have been approved in recent years. Several first-generation drugs are currently being researched, e.g., soticlestat, BL-001, SPN-817. Second-generation drugs reproduce the effects of first-generation drugs using novel compounds, e.g., bexicaserin. Most notably, new disease-modifying approaches targeting genetic defects in DS are on the way, e.g., increasing the function of Nav1.1 ion channels by antisense oligonucleotides, viral vectors, or small molecules. Targeting the underlying genetic mechanisms holds the promise of influencing the natural course of the disease and ameliorating development in different domains, including cognitive, behavioral, and motor domains.

Despite these advances, the burden of disease remains too high for patients and caregivers so far. From the perspective of PFAs, it is essential to consider behavioral, cognitive, and

motor measures as well as mortality rates as important endpoints for clinical studies. Standardization of measures would support comparability. Head-to-head comparisons of DS treatments in different populations are greatly needed to develop and validate treatment algorithms and prevent irrational polypharmacy.

In summary, this landscape analysis reveals a wealth of knowledge and ongoing research activity in DS. It highlights the need for basic and clinical research efforts focused on the development of non-epileptic symptoms. This landscape analysis indicates the potential of future symptomatic and disease-modifying treatments in DS. As developments continue in the therapeutic pipeline, PFAs claim to address all patient-related symptoms rather than only antiepileptic properties.

Acknowledgments
We thank the Consultant Scientific Officer Francesca Sofia, Science Compass (Milan, Italy) , and Serena Bertoldi, Science Compass, for performing the landscape analysis.
We thank the following DS experts for sharing their time and expert opinions in expert interviews: Andreas Brunklaus (University of Glasgow, UK), Daniel Fisher (Tevard Biosciences, Cambridge, Massachusetts, USA), Shinichi Hirose (Fukuoka University, Japan), Jennifer Kearney (Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA), Massimo Mantegazza (Institute of Molecular and Cellular Pharmacology, Nice, France)), Miriam Meisler (University of Michigan Medical Center, Ann Arbor, Michigan, USA), Ingrid Sheffer (University of Melbourne, Australia), and Elaine C. Wirrell (Mayo Clinic, Rochester, Minnesota, USA) for sharing their time and expert opinions to support our landscape analysis.
We thank the following DS experts for their participation in the round tables and sharing their time and expert opinions to support our landscape analysis: Danielle Andrade (University of Toronto, Toronto, Canada), Scott Baraban (University of California, San Francisco, USA), Andreas Brunklaus (University of Glasgow, Glasgow, UK), Andre Elferink (EMA Medicine Evaluation Board, Amsterdam, The Netherland), Alfred George (Northwestern University, Chicago, USA), Jackie Gofshteyn (Encoded Therapeutics, San Francisco USA), Renzo Guerrini (Azienda Ospedaliero Universitaria Meyer, Firenze, Italy), Jennifer Helfer (Encoded Therapeutics, San Francisco, USA), Lori Isom (University of Michigan Medical School, Ann Arbor, USA), Lieven Lagae (UZ Leuven, Leuven, Belgium), Massimo Mantegazza (Institute of Molecular and Cellular Pharmacology, Nice, France), Megan Murphy (Takeda Pharmaceutical Co., Cambridge, USA), Rima Nabbout (Imagine Institute Necker Enfants Malades, Paris, France), Kimberly Parkerson (Stoke Therapeutics, Bedford, USA), Gopi Shanker (Tevard Biosciences, Cambridge, USA), Barry Ticho (Stoke Therapeutics, Bedford, USA), Francoise Truong-Berthoz (Takeda Pharmaceutical Co., Cambridge, US), Konrad Werhahn (UCB, Bruxelles, Belgium), Elaine Wirrell (Mayo Clinic, Rochester, USA).
Data availability: The materials from the original research report by Science Compass are available upon request by writing to gruppofamiglie@sindromedidravet.org.
Funding Declaration: Funding was provided by the Gruppo Famiglie Dravet Associazione APS (Milan, Italy), the Vereinigung Dravet Syndrom Schweiz (Zurich, Switzerland), and the Dravet Syndrom e.V. (Frankfurt a.M., Germany).
Authors contribution: CK wrote the manuscript and updated the data. SBo, SBu, SF and DK drafted and organized the study on behalf of the PFAs and corrected the manuscript.
Conflicts of interest: CK, SBo, SBu, SF, and DK are members of PFAs. CK has received speakers and advisory honorariums concerning psychiatric topics that do not affect Dravet research. SBo, SBu, SF, and DK have no conflicts of interest to declare.

References

1. Cooper MS, Mcintosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, Ganesan V, Gill D, Kivity S, Lerman-Sagie T, McLellan A, Pelekanos J, Ramesh V, Sadleir L, Wirrell E, Scheffer IE (2016) Mortality in Dravet syndrome. Epilepsy Res 128:43–47. https://doi.org/10.1016/j.eplepsyres.2016.10.006

2. Strzelczyk A, Lagae L, Wilmshurst JM, Brunklaus A, Striano P, Rosenow F, Schubert-Bast S (2023) Dravet syndrome: A systematic literature review of the illness burden. Epilepsia Open 8:1256–1270. https://doi.org/10.1002/epi4.12832

3. Lagae L, Irwin J, Gibson E, Battersby A (2019) Caregiver impact and health service use in high and low severity Dravet syndrome: A multinational cohort study. Seizure 65:72–79. https://doi.org/10.1016/j.seizure.2018.12.018

4. Marini C, Scheffer IE, Nabbout R, Suls A, De Jonghe P, Zara F, Guerrini R (2011) The genetics of Dravet syndrome. Epilepsia 52 Suppl 2:24–29. https://doi.org/10.1111/j.1528-1167.2011.02997.x

5. Lagae L (2021) Dravet syndrome. Curr Opin Neurol 34:213–218. https://doi.org/10.1097/WCO.0000000000000902

6. Gataullina S, Dulac O (2017) From genotype to phenotype in Dravet disease. Seizure 44:58–64. https://doi.org/10.1016/j.seizure.2016.10.014

7. Hu H, Jonas P (2014) A supercritical density of Na(+) channels ensures fast signaling in GABAergic interneuron axons. Nat Neurosci 17:686–693. https://doi.org/10.1038/nn.3678

8. Mantegazza M, Rusconi R, Scalmani P, Avanzini G, Franceschetti S (2010) Epileptogenic ion channel mutations: from bedside to bench and, hopefully, back again. Epilepsy Res 92:1–29. https://doi.org/10.1016/j.eplepsyres.2010.08.003

9. Yu FH, Mantegazza M, Westenbroek RE, Robbins CA, Kalume F, Burton KA, Spain WJ, McKnight GS, Scheuer T, Catterall WA (2006) Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. Nat Neurosci 9:1142–1149. https://doi.org/10.1038/nn1754

10. Miller AR, Hawkins NA, McCollom CE, Kearney JA (2014) Mapping genetic modifiers of survival in a mouse model of Dravet syndrome. Genes Brain Behav 13:163–172. https://doi.org/10.1111/gbb.12099

11. Ogiwara I, Miyamoto H, Morita N, Atapour N, Mazaki E, Inoue I, Takeuchi T, Itohara S, Yanagawa Y, Obata K, Furuichi T, Hensch TK, Yamakawa K (2007) Nav1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. J Neurosci 27:5903–5914. https://doi.org/10.1523/JNEUROSCI.5270-06.2007

12. Tang B, Dutt K, Papale L, Rusconi R, Shankar A, Hunter J, Tufik S, Yu FH, Catterall WA, Mantegazza M, Goldin AL, Escayg A (2009) A BAC transgenic mouse model reveals neuron subtype-specific effects of a Generalized Epilepsy with Febrile Seizures Plus (GEFS+) mutation. Neurobiol Dis 35:91–102. https://doi.org/10.1016/j.nbd.2009.04.007

13. Tsai M-S, Lee M-L, Chang C-Y, Fan H-H, Yu I-S, Chen Y-T, You J-Y, Chen C-Y, Chang F-C, Hsiao JH, Khorkova O, Liou H-H, Yanagawa Y, Lee L-J, Lin S-W (2015) Functional and structural deficits of the dentate gyrus network coincide with emerging spontaneous seizures in an Scn1a mutant

Dravet Syndrome model during development. Neurobiol Dis 77:35–48. https://doi.org/10.1016/j.nbd.2015.02.010

14. Cheah CS, Yu FH, Westenbroek RE, Kalume FK, Oakley JC, Potter GB, Rubenstein JL, Catterall WA (2012) Specific deletion of NaV1.1 sodium channels in inhibitory interneurons causes seizures and premature death in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A 109:14646–14651. https://doi.org/10.1073/pnas.1211591109

15. Dutton SB, Makinson CD, Papale LA, Shankar A, Balakrishnan B, Nakazawa K, Escayg A (2013) Preferential inactivation of Scn1a in parvalbumin interneurons increases seizure susceptibility. Neurobiol Dis 49:211–220. https://doi.org/10.1016/j.nbd.2012.08.012

16. Ogiwara I, Iwasato T, Miyamoto H, Iwata R, Yamagata T, Mazaki E, Yanagawa Y, Tamamaki N, Hensch TK, Itohara S, Yamakawa K (2013) Nav1.1 haploinsufficiency in excitatory neurons ameliorates seizure-associated sudden death in a mouse model of Dravet syndrome. Hum Mol Genet 22:4784–4804. https://doi.org/10.1093/hmg/ddt331

17. Baraban SC, Dinday MT, Hortopan GA (2013) Drug screening in Scn1a zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment. Nat Commun 4:2410. https://doi.org/10.1038/ncomms3410

18. Zhang Y, Kecskés A, Copmans D, Langlois M, Crawford AD, Ceulemans B, Lagae L, de Witte PAM, Esguerra CV (2015) Pharmacological characterization of an antisense knockdown zebrafish model of Dravet syndrome: inhibition of epileptic seizures by the serotonin agonist fenfluramine. PLoS One 10:e0125898. https://doi.org/10.1371/journal.pone.0125898

19. Roemmich AJ, Vu T, Lukacsovich T, Hawkins C, Schutte SS, O'Dowd DK (2021) Seizure Phenotype and Underlying Cellular Defects in Drosophila Knock-In Models of DS (R1648C) and GEFS+ (R1648H) SCN1A Epilepsy. eNeuro 8:ENEURO.0002-21.2021. https://doi.org/10.1523/ENEURO.0002-21.2021

20. Cardenal-Muñoz E, Auvin S, Villanueva V, Cross JH, Zuberi SM, Lagae L, Aibar JÁ (2022) Guidance on Dravet syndrome from infant to adult care: Road map for treatment planning in Europe. Epilepsia Open 7:11–26. https://doi.org/10.1002/epi4.12569

21. Brunklaus A, Dorris L, Zuberi SM (2011) Comorbidities and predictors of health-related quality of life in Dravet syndrome. Epilepsia 52:1476–1482. https://doi.org/10.1111/j.1528-1167.2011.03129.x

22. Scheffer IE, Nabbout R (2019) SCN1A-related phenotypes: Epilepsy and beyond. Epilepsia 60 Suppl 3:S17–S24. https://doi.org/10.1111/epi.16386

23. de Lange IM, Gunning B, Sonsma ACM, van Gemert L, van Kempen M, Verbeek NE, Nicolai J, Knoers NVAM, Koeleman BPC, Brilstra EH (2018) 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 59:1154–1165. https://doi.org/10.1111/epi.14191

24. Jansson JS, Hallböök T, Reilly C (2020) Intellectual functioning and behavior in Dravet syndrome: A systematic review. Epilepsy Behav 108:107079. https://doi.org/10.1016/j.yebeh.2020.107079

25. Ouss L, Leunen D, Laschet J, Chemaly N, Barcia G, Losito EM, Aouidad A, Barrault Z, Desguerre I, Breuillard D, Nabbout R (2019) Autism spectrum disorder and cognitive profile in children with Dravet syndrome: Delineation of a specific phenotype. Epilepsia Open 4:40–53. https://doi.org/10.1002/epi4.12281

26. Postma A, Milota M, Jongmans MJ, Brilstra EH, Zinkstok JR (2023) Challenging behavior in children and adolescents with Dravet syndrome: Exploring the lived experiences of parents. Epilepsy Behav 138:108978. https://doi.org/10.1016/j.yebeh.2022.108978

27. Sullivan J, Deighton AM, Vila MC, Szabo SM, Maru B, Gofshteyn JS, James ES, Rico S, Zuberi SM (2022) The clinical, economic, and humanistic burden of Dravet syndrome - A systematic literature review. Epilepsy Behav 130:108661. https://doi.org/10.1016/j.yebeh.2022.108661

28. Verheyen K, Verbecque E, Ceulemans B, Schoonjans A-S, Van De Walle P, Hallemans A (2019) Motor development in children with Dravet syndrome. Dev Med Child Neurol 61:950–956. https://doi.org/10.1111/dmcn.14147

29. Selvarajah A, Gorodetsky C, Marques P, Zulfiqar Ali Q, Berg AT, Fasano A, Andrade DM (2022) Progressive Worsening of Gait and Motor Abnormalities in Older Adults With Dravet Syndrome. Neurology 98:e2204–e2210. https://doi.org/10.1212/WNL.0000000000200341

30. Wyers L, Van de Walle P, Hoornweg A, Tepes Bobescu I, Verheyen K, Ceulemans B, Schoonjans A-S, Desloovere K, Hallemans A (2019) Gait deviations in patients with dravet syndrome: A systematic review. Eur J Paediatr Neurol 23:357–367. https://doi.org/10.1016/j.ejpn.2019.03.003

31. Turner SJ, Brown A, Arpone M, Anderson V, Morgan AT, Scheffer IE (2017) Dysarthria and broader motor speech deficits in Dravet syndrome. Neurology 88:743–749. https://doi.org/10.1212/WNL.0000000000003635

32. Schoonjans A-S, De Keersmaecker S, Van Bouwel M, Ceulemans B (2019) More daytime sleepiness and worse quality of sleep in patients with Dravet Syndrome compared to other epilepsy patients. Eur J Paediatr Neurol 23:61–69. https://doi.org/10.1016/j.ejpn.2018.09.012

33. Papale LA, Makinson CD, Christopher Ehlen J, Tufik S, Decker MJ, Paul KN, Escayg A (2013) Altered sleep regulation in a mouse model of SCN1A-derived genetic epilepsy with febrile seizures plus (GEFS+). Epilepsia 54:625–634. https://doi.org/10.1111/epi.12060

34. Shmuely S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD (2016) Mortality in Dravet syndrome: A review. Epilepsy Behav 64:69–74. https://doi.org/10.1016/j.yebeh.2016.09.007

35. Lyu SY, Nam SO, Lee Y-J, Kim G, Kim YA, Kong J, Ko A, Kim YM, Yeon GM (2019) Longitudinal change of cardiac electrical and autonomic function and potential risk factors in children with dravet syndrome. Epilepsy Res 152:11–17. https://doi.org/10.1016/j.eplepsyres.2019.02.018

36. Perulli M, Battista A, Sivo S, Turrini I, Musto E, Quintiliani M, Gambardella ML, Contaldo I, Veredice C, Mercuri EM, Lanza GA, Dravet C, Delogu AB, Battaglia DI (2022) Heart rate variability alterations in Dravet Syndrome: The role of status epilepticus and a possible association with mortality risk. Seizure 94:129–135. https://doi.org/10.1016/j.seizure.2021.11.023

37. Shmuely S, Surges R, Helling RM, Gunning WB, Brilstra EH, Verhoeven JS, Cross JH, Sisodiya SM, Tan HL, Sander JW, Thijs RD (2020) Cardiac arrhythmias in Dravet syndrome: an observational multicenter study. Ann Clin Transl Neurol 7:462–473. https://doi.org/10.1002/acn3.51017

38. Auerbach DS, Jones J, Clawson BC, Offord J, Lenk GM, Ogiwara I, Yamakawa K, Meisler MH, Parent JM, Isom LL (2013) Altered cardiac electrophysiology and SUDEP in a model of Dravet syndrome. PLoS One 8:e77843. https://doi.org/10.1371/journal.pone.0077843

39. Frasier CR, Zhang H, Offord J, Dang LT, Auerbach DS, Shi H, Chen C, Goldman AM, Eckhardt LL, Bezzerides VJ, Parent JM, Isom LL (2018) Channelopathy as a SUDEP Biomarker in Dravet Syndrome Patient-Derived Cardiac Myocytes. Stem Cell Reports 11:626–634. https://doi.org/10.1016/j.stemcr.2018.07.012

40. Dibué M, Spoor JKH, Dremmen M, von Saß CF, Hänggi D, Steiger H-J, Ryvlin P, Kamp MA (2020) Sudden death in epilepsy: There is room for intracranial pressure. Brain Behav 10:e01838. https://doi.org/10.1002/brb3.1838

41. Kim Y, Bravo E, Thirnbeck CK, Smith-Mellecker LA, Kim SH, Gehlbach BK, Laux LC, Zhou X, Nordli DR, Richerson GB (2018) Severe peri-ictal respiratory dysfunction is common in Dravet syndrome. J Clin Invest 128:1141–1153. https://doi.org/10.1172/JCI94999

42. Selvarajah A, Zulfiqar-Ali Q, Marques P, Rong M, Andrade DM (2021) A systematic review of adults with Dravet syndrome. Seizure 87:39–45. https://doi.org/10.1016/j.seizure.2021.02.025

43. Wirrell EC, Hood V, Knupp KG, Meskis MA, Nabbout R, Scheffer IE, Wilmshurst J, Sullivan J (2022) International consensus on diagnosis and management of Dravet syndrome. Epilepsia 63:1761–1777. https://doi.org/10.1111/epi.17274

44. Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, Dulac O, Pons G (2000) Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet 356:1638–1642. https://doi.org/10.1016/s0140-6736(00)03157-3

45. Guerrini R, Chancharme L, Serraz B, Chiron C (2024) Additional Results from Two Randomized, Placebo-Controlled Trials of Stiripentol in Dravet Syndrome Highlight a Rapid Antiseizure Efficacy with Longer Seizure-Free Periods. Neurol Ther 13:869–884. https://doi.org/10.1007/s40120-024-00623-8

46. Specchio N, Auvin S, Strzelczyk A, Brigo F, Villanueva V, Trinka E (2024) Efficacy and safety of stiripentol in the prevention and cessation of status epilepticus: A systematic review. Epilepsia Open 9:2017–2036. https://doi.org/10.1002/epi4.13036

47. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S, Cannabidiol in Dravet Syndrome Study Group (2017) Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med 376:2011–2020. https://doi.org/10.1056/NEJMoa1611618

48. Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, Saneto RP, Checketts D, Dunayevich E, Knappertz V, GWPCARE2 Study Group (2020) Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol 77:613–621. https://doi.org/10.1001/jamaneurol.2020.0073

49. Mingorance A (2024) Dravet syndrome pipeline 2024. https://www.draccon.com/s/Dracaena-Dravet-syndrome-pipeline-review-2024.pdf. Accessed 13 Feb 2025

50. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, Devinsky O, Cross JH, Guerrini R, Talwar D, Miller I, Farfel G, Galer BS, Gammaitoni A, Mistry A, Morrison G, Lock M, Agarwal A, Lai WW, Ceulemans B, FAiRE DS Study Group (2019) Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet 394:2243–2254. https://doi.org/10.1016/S0140-6736(19)32500-0

51. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, Stephani U, Laux L, Wirrell E, Knupp K, Chiron C, Farfel G, Galer BS, Morrison G, Lock M, Agarwal A, Auvin S, FAiRE, DS Study Group (2020) Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol 77:300–308. https://doi.org/10.1001/jamaneurol.2019.4113

52. Bishop KI, Isquith PK, Gioia GA, Knupp KG, Scheffer IE, Nabbout R, Specchio N, Sullivan J, Auvin S, Helen Cross J, Guerrini R, Farfel G, Galer BS, Gammaitoni AR (2023) Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (<5 years) with Dravet syndrome: A critical period for early neurodevelopment. Epilepsy Behav 138:108994. https://doi.org/10.1016/j.yebeh.2022.108994

53. Cross JH, Galer BS, Gil-Nagel A, Devinsky O, Ceulemans B, Lagae L, Schoonjans A-S, Donner E, Wirrell E, Kothare S, Agarwal A, Lock M, Gammaitoni AR (2021) Impact of fenfluramine on the expected SUDEP mortality rates in patients with Dravet syndrome. Seizure 93:154–159. https://doi.org/10.1016/j.seizure.2021.10.024

54. Guerrini R, Chiron C, Vandame D, Linley W, Toward T (2024) Comparative efficacy and safety of stiripentol, cannabidiol and fenfluramine as first-line add-on therapies for seizures in Dravet syndrome: A network meta-analysis. Epilepsia Open 9:689–703. https://doi.org/10.1002/epi4.12923

55. Khattar J, Rubin J (2024) SPN 817 Phase 2a Study Exploratory Open Label Study in Adult Patients with Treatment Resistant Epilepsy

56. Bloom Science Announces Positive Topline Data from a Phase 1 Clinical Trial of BL-001, a Potential First-in-Class Therapeutic Being Developed for Both Dravet Syndrome and ALS. https://bloomscience.com/bloom-science-bl-001-phase1-topline-data/. Accessed 19 Feb 2025

57. Savardi A, Borgogno M, De Vivo M, Cancedda L (2023) Selective NKCC1 Inhibitors for the Treatment of Neurodevelopmental and Neurological Disorders with Defective NKCC1/KCC2 expression-ratio (P2-12.003). Neurology 100:3708. https://doi.org/10.1212/WNL.0000000000203467

58. reMYND Platfor and products. https://www.remynd.com/platform-products. Accessed 19 Feb 2025

59. Lundbeck announces positive results from 12-month Open-Label Extension (OLE) of the PACIFIC trial evaluating bexicaserin in participants with Developmental and Epileptic Encephalopathies. https://news.cision.com/h--lundbeck-a-s/r/lundbeck-announces-positive-results-from-12-month-open-label-extension--ole--of-the-pacific-trial-ev,c4098079. Accessed 19 Feb 2025

60. BMB-101 in Absence Epilepsy and DEE. https://clinicaltrials.gov/study/NCT06401538. Accessed 19 Feb 2025

61. Scheffer IE, Hulihan J, Messenheimer J, Ali S, Keenan N, Griesser J, Gutterman DL, Sebree T, Sadleir LG (2021) Safety and Tolerability of Transdermal Cannabidiol Gel in Children With Developmental and Epileptic Encephalopathies: A Nonrandomized Controlled Trial. JAMA Netw Open 4:e2123930. https://doi.org/10.1001/jamanetworkopen.2021.23930

62. ZygelTM (ZYN002 Cannabidiol Gel). https://www.zynerba.com/in-development/zygel/. Accessed 19 Feb 2025

63. Clinical studies. https://www.stoketherapeutics.com/patients-families/clinical-studies/. Accessed 19 Feb 2025

64. Sullivan J, Perry MS, Brunklaus A, Cross JH, Desurkar A, Laux L, Schreiber JM, Knupp KG, Brathwait C, Concon C, Dandurand A, Lynch J, Stutely J, Wang F, Meena, Parkerson KA, Ticho barry (2024) Patients with Dravet syndrome in open-label extension studies of zorevunersen (STK-001) have durable reductions in seizure frequency and ongoing improvements in cognition and behavior. Los Angeles, California, USA

65. ETX101 for Dravet Syndrome. https://encoded.com/programs/etx101-for-dravet-syndrome/. Accessed 19 Feb 2025

66. Targeted Gene Therapy to transform the lives of people living with severe genetic diseases. https://regeltherapeutics.com. Accessed 19 Feb 2025