A retrospective review of changes and challenges in the use of antiseizure medicines in Dravet syndrome in Norway

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Abstract

Objective: Dravet syndrome is a developmental and epileptic encephalopathy characterized by severe and drug-resistant seizures in early childhood, followed by developmental delay. The purpose of this study was to investigate aspects of pharmacological treatment of Norwegian patients with Dravet syndrome, focusing on the use of antiseizure medicines (ASMs) and identifying treatment challenges.

Methods: Patients were identified through medical registries at the National Center for Epilepsy in Norway and National Center for Rare Epilepsy Related Disorders during 2008-2018. Additional clinical data were obtained from medical records and laboratory request forms.

Results: We identified 53 patients with Dravet syndrome, 30/23 males/females, aged 2-50 years. The majority of patients with known seizure frequency experienced frequent seizures, 80% (n = 35/44). Only two patients were seizure-free. Valproate (n = 48), clobazam (n = 45), levetiracetam (n = 30), and stiripentol (n = 38) were most commonly used, previous or current use. More than one-third (n = 20) had tried sodium channel blockers (including lamotrigine), but these drugs were used less during the last decade. Polytherapy was common, 81% (n = 43) used two or more ASMs, and eight of these patients used 4-5 drugs (15%). Several challenges were identified: high seizure frequency, comorbidities, treatment changes with a wide range of ASMs, common use of oral gastro-tubes, extensive polypharmacy, and drug interactions.

Significance: The use of ASMs has changed over the last decade, in accordance with updated international recommendations. Various treatment challenges were identified. This vulnerable group of patients needs close follow-up for an optimal treatment outcome.

KEYWORDS
antiseizure medicines, Dravet syndrome, epilepsy, polypharmacy
1 | INTRODUCTION

Dravet syndrome is a rare developmental and epileptic encephalopathy characterized by severe, prolonged, and refractory seizures from the first year of life, placing the patients at risk of recurrent status epilepticus episodes (Figure 1A,B).1–6 The syndrome is associated with multiple comorbidities, including neurological and behavioral disorders and intellectual disability, as well as an increased mortality rate.1,2,5 It has a genetic cause, which is identified in the majority of patients, due to de novo mutations of SCN1A, a gene encoding a subunit of the voltage-gated sodium channel. This typically causes loss of function of neuronal voltage-gated sodium channels, resulting in a particularly low seizure threshold. Thus, sodium channel blockers should be avoided, as they are known to exacerbate seizures in Dravet syndrome.6–8

Treatment with various antiseizure medicines (ASMs) is necessary. ASMs are a heterogeneous group of drugs, with marked potential for drug interactions, many adverse effects, narrow therapeutic indexes, and extensive pharmacokinetic variability between and within patients.9–12

Polytherapy is common in the treatment of Dravet syndrome. Valproate and clobazam are recommended as first-line drug options, often in combination with the orphan drug stiripentol.13–17 Second-line options include levetiracetam, topiramate, and zonisamide, and a large number of ASMs are often tried over time.3,4,8

The purpose of the present study was to investigate aspects of pharmacological treatment of Norwegian patients diagnosed with Dravet syndrome, focusing on the use of ASMs. Furthermore, we wanted to identify treatment challenges in this patient group over time with a nationwide experience. Improved knowledge of pharmacological treatment in a real-life setting may contribute to better characterization and quality control of treatment and follow-up.

2 | METHODS

2.1 | Study material

In the period 2008-2018, we identified 53 patients diagnosed with Dravet syndrome through the medical registries at the National Center for Epilepsy in Norway and National Center for Rare Epilepsy Related Disorders. The medical registries were based on data from medical records of the patients, where the diagnosis was given by a neurologist/pediatrician. The therapeutic drug monitoring (TDM) database was used as an additional source to identify the use of stiripentol. As Dravet syndrome is the only approved indication for stiripentol, the request form for all patients having serum concentration measurement of this drug was screened and those containing the diagnosis of Dravet syndrome were included. The TDM data were further used in a pharmacokinetic study.18 The patients included in the present study cover the majority of Norwegian patients with Dravet syndrome, as it is highly likely that they at some point have been registered, referred to (diagnosed, treated, or monitored at) this center, or have been treated with stiripentol. The study is thus regarded to be population-based. Data regarding use of ASMs were collected from request forms for drug serum concentration measurements. Additional clinical patient data regarding genetic testing/mutation analysis, current seizure types and frequency (registered at the last medical checkup), and seizure onset were collected from the medical records with patients consent. All data were anonymized. The study was approved by the Regional Ethics Committee.

2.2 | Calculations

Antiseizure medicines in current use were restricted to the last three months. Retention rates/longest treatment periods were estimated by calculating the longest continuous period of use for each patient, based on available data. Patients with only one stated date of use or multiple nonconsecutive dates were excluded from these calculations. For statistical analyses, IBM SPSS Statistics version 22 was used. Mainly, descriptive analyses were performed. A direct logistic regression was performed to assess the impact of various variables on the seizure situation. Independent variables in the model were current use of drugs (mono- or polytherapy), gender, and age. P-values of <.05 were considered statistically significant in all analyses.

Key point

- This study demonstrates how treatment with ASMs in Dravet syndrome has changed over the last decade, with a nationwide experience not previously presented.
- This real-life retrospective study is of particular importance when new treatment options arrive and is an example of treatment patterns in Europe.
- Challenges: High seizure frequency, comorbidities, use of oral gastro-tubes, treatment changes, polypharmacy with ASMs, drug interactions, and adverse effects.
- Dravet patients need close follow-up for optimal treatment outcome, balancing seizure control, and tolerability of treatment.
3 | RESULTS

3.1 | Patient characteristics

Fifty-three patients with Dravet syndrome were identified. Mean age was 16 years, and 57% were men. A total of 20 patients were under the age of 13 years and thus considered to be children, while those from 13 to 17 years were classified as adolescents and from 18 as adults. Patient and clinical characteristics are summarized in Table 1. Seizure frequency was high: Of the 44 patients with a known seizure frequency, 35 (80%) suffered from daily or weekly seizures. Only two patients were seizure-free. The most common types of seizures, reported at the last medical checkup, were generalized tonic-clonic seizures (GTC), myoclonic seizures, and focal seizures. The seizure frequency was high, and the majority of patients suffered from daily or weekly seizures, with no significant difference in median age for the groups who had daily, weekly, and monthly seizures, respectively. Mutation or deletion of the SCN1A gene was identified in 45 (85%) patients. Intellectual disability was stated in the medical records in 37 (70%) of patients, eight patients were diagnosed with ADHD, and four patients with autism spectrum disorder. Thirteen patients used an oral gastro-tube for nutrition, pointing to difficulties in intake of oral tablet formulations. The patient characteristics show a similar pattern and development as described in the literature, as illustrated in Figure 1.

3.2 | Previous and present use of ASM

The most common ASMs in current use and during the entire study period were valproate, clobazam, levetiracetam, and stiripentol. These drugs were used by 48, 45, 30, and 38...
patients and in current use by 33, 25, 11, and 26 patients, respectively (Figure 2A-C). Twenty (38%) patients had used sodium channel blockers (lamotrigine, carbamazepine, or phenytoin) during the study period. Sodium channel blockers were still used by six patients, though in combinations with three to four other ASMs. Other treatments included cannabidiol and bromide in a few patients. On average, the patients had tried 5 (range 2-9) different ASMs during the study period. A total of 14 approved ASMs were in current use. Polytherapy was common, as 81% of the patients used 2-5 ASMs as their current therapy, and 25 different combinations of ASMs were in use, of which 10 combinations included valproate + clobazam + stiripentol. Valproate was widely used regardless of age (Figure 2A,C), in current use in more than half of patients across all age-groups. Use of lamotrigine was most common in the two oldest age-groups. The youngest age-group, 2-6 years, had the largest proportion of patients using valproate, clobazam, and stiripentol, one or more in combination. Regarding gender, there were no notable differences in the choice of ASMs between females and males. No significant correlations between the use of ASMs, use of polytherapy, and seizure situation (seizure types and frequency) were demonstrated by a multiple regression model. Only two patients were described as seizure-free: one used topiramate + clonazepam, and the other used levetiracetam + valproate + stiripentol. Regarding other Dravet syndrome treatment options, 25 patients (47%) had tried ketogenic diet during the study period (seven were still on the diet), and 23 (43%) had tried vagal nerve stimulation (still in use in six).

Figure 2B shows the most frequently used ASMs in 2008/09 (n = 31) and 2017/18 (n = 48). Valproate and clobazam were among the most commonly used drugs, both in 2008-2009 and 2018-2019. Clobazam use increased from 13% to 52% and valproate use from 45% to 60%. The use of the sodium channel blocker lamotrigine decreased from 35% to 13%, and carbamazepine which was used by one patient in 2008/2009 was not in use in 2017/2018. In 2008/2009 and 2017/2018, the majority of patients used a combination of two to three ASMs, while about one-fourth used monotherapy during both periods.
3.3 Longest treatment period

The longest continuous treatment periods for five different ASMs are illustrated in Figure 3. Valproate was used by a high percentage of patients and had the longest mean continuous treatment period of 50 months (SD 37) and 78% of patients were using it for periods longer than 12 months. In comparison, the mean treatment period for patients on lamotrigine had the lowest outcome; 34 months (SD 47). Only 44% of patients used lamotrigine for periods longer than 12 months. The mean continuous treatment periods were 38 months (SD 30) for clobazam, 38 (SD 34) for...
levetiracetam, and 40 (SD 38) for stiripentol, with 79%, 63%, and 60% of patients using these drugs for periods longer than 12 months, respectively.

### 3.4 | Case descriptions

Three patient cases with Dravet syndrome, all were young girls with SCN1A mutations, were chosen to present different treatment histories and individual differences in treatment requirements (Figure 4A-C). All of them had daily or weekly seizures, including GTC seizures. Case 1, followed for six years used the combination of valproate (20-25 mg/kg/day), stiripentol 400 mg/day, and clobazam 5 mg/day throughout the period. Levetiracetam and ketogenic diet were tried for short periods without efficacy. Case 2 was followed for a decade from below the age of five. She had severe intellectual disability, comorbid disorders, and 30-50 seizures per month. She tried eight different ASMs, including a sodium channel blocker, lamotrigine, but not clobazam, in addition to one year of vagal nerve stimulation, as well as ketogenic diet. Stiripentol was only used at the same dosage of 1000 mg/day. The dosage of valproate and levetiracetam increased steadily for each year, and the dosage of topiramate was frequently adjusted/titrated up and down. Valproate was a cornerstone in the treatment, being the only ASM continuously in use throughout the period. Case 3 was followed for eight years. She had a less complicated drug history and during the study period she used two ASMs, topiramate and clobazam. Topiramate was used at the same dose (100 mg/day) throughout the period, but the dosage of clobazam was not listed. In addition, ketogenic diet was used throughout the period. She had 8-10 seizures per month and no known comorbid disorders.

For the patient group as a whole, several challenges were identified: high seizure frequency, comorbidities, treatment changes with a wide range of ASMs, common use of oral gastro-tubes, extensive polypharmacy, risk of interactions, and adverse effects affecting the cognitive development.

### 4 | DISCUSSION

The present results describe long-term use of ASMs in patients with Dravet syndrome with a nationwide experience that has not been shown in previous studies. The most commonly used ASM were valproate, clobazam, and stiripentol. Polytherapy was common, as 81% used combinations of two to five ASMs. Sodium channel blockers (lamotrigine, carbamazepine, and phenytoin) were used to a small extent, and the use of lamotrigine was reduced during the past decade. Only two patients were completely free of seizures, and a difficult seizure situation and challenging treatment were common. The use of ASMs is in line with national and international treatment guidelines for Dravet syndrome. Treatment changes over time are especially important now when new treatment options arrive and more common use of genetic tests reveals the molecular background for the disease, which facilitates rational treatment choices.

### 4.1 | Patient characteristics

Out of the fifty-three patients with Dravet syndrome identified nationwide, 29 were children under the age of 18 years. This would correspond to 24 children under
the age of 18 years in the Norwegian population, which is in line with the population-based study with a prevalence from Sweden of 1:33,000 live births.\textsuperscript{19,20} The use of vagal nerve stimulation did not seem to be a persistent additional treatment option in most of these patients. In the present study population, there seemed to be no tendency of a reduction in seizure frequency with increasing age, which could be expected based on descriptions of the disease course.\textsuperscript{2,5,6} However, phenotypic differences in clinical course and severity of the disease are not uncommon.\textsuperscript{21,22}

\subsection*{4.2 Use of ASMs and polypharmacy aspects}

Dravet syndrome is regarded as therapy resistant, and seizure freedom or complete seizure control is rarely

\begin{figure}[h]
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\caption{A-C, Case presentations of different treatment histories in patients with Dravet syndrome, illustrating three individual patients with Dravet syndrome, cases 1, 2, and 3, all young girls with SCN1A mutations, followed up over an 6- to 10-year period.}
\end{figure}
Thus, the treatment goal is rather to reduce duration and frequency of seizures, avoid episodes of status epilepticus and seizure-related injuries, and to minimize adverse effects of ASMs. Valproate, stiripentol, and clobazam were the most commonly used ASMs, often in combination, during the entire study period, which is in accordance with international guidelines and recommendations. The combination of the three drugs is the only available ASM therapy for Dravet syndrome with demonstrated significant seizure reduction in randomized, controlled trials. Proper treatment is associated with a better outcome for cognitive functions. The patients were mainly treated with six different ASM, all of which are indicated as first or second treatment choices: valproate, clobazam, topiramate, stiripentol, clonazepam, and levetiracetam; most commonly in combinations of two to three ASMs, in line with other studies. However, in total 14 different ASMs were in current use. This may indicate that despite existing consensus regarding choice of treatment, treating Dravet syndrome is difficult and may require a wide range of ASMs to be tried in the attempt to optimize treatment. The wide use of polytherapy is possibly a consequence of the refractory trait of Dravet syndrome.

4.3 Changes in the use of ASM over the past decade

Valproate and stiripentol were widely used in both 2008-2009 and 2017-2018. Stiripentol was approved in Europe in 2007 and was already one of the most commonly used ASMs in the study population only one to two years later. Stiripentol was used by half of the study population. It has an indication of use in combination with valproate and clobazam only. This may explain the increased use of clobazam during this decade, as the combination is required for reimbursement of stiripentol therapy in Norway. More than one-third had tried sodium channel blockers during the study period, despite the recognition made in the 1990s that these drugs may exacerbate seizures in Dravet syndrome and generally should be avoided. Lamotrigine was still in use in six patients and may support anecdotal evidence that some patients may experience beneficial effect of lamotrigine. However, long-term use of sodium channel blockers in the first five years after disease onset may result in poorer cognitive functions in Dravet syndrome. The retention rates demonstrated that treatment periods were longest for valproate, followed by clobazam, stiripentol, and levetiracetam. Duration of treatment was shortest for lamotrigine, as discussed above.

4.4 Treatment challenges

Optimizing treatment of Dravet syndrome is challenging and requires an individualized approach for each patient. The treatment history of the patient cases 1 and 2 is a reflection of how challenging optimizing treatment of Dravet syndrome can be, as compared to case 3.

In this vulnerable patient group as a whole, several challenges were identified: high seizure frequency, use of polytherapy with ASMs, and treatment changes. Furthermore, many have comorbidities with additional treatment requirements such as use of oral gastro-tube for nutrition and drug administration. This may be a complicating factor affecting the pharmacokinetics of ASMs due to limitations in drug administration forms, where measurements of drug levels are recommended, prior to and after insertion of the gastro-tube. The use of gastro-tubes is a cause of concern and a challenge, when it comes to proper absorption of ASMs, finding appropriate drug formulations and designing optimal dosing schemes. Many children were identified in this study, and they are particularly vulnerable for cognitive adverse effects of ASMs during development.

Therefore, designing optimal drug regimens and close monitoring in order to minimize the adverse effect burden is of importance.

The use of polypharmacy with ASMs that are susceptible to cause interactions and that exhibit large inter- and intranidividual pharmacokinetic variability was common, such as valproate, clobazam, and stiripentol. Stiripentol has demanding pharmacokinetic properties, such as saturation kinetics, being a potent enzyme inhibitor and may displace other highly protein-bound drugs from plasma proteins, such as valproate and clobazam. The metabolism of clobazam is susceptible to enzyme inhibitors as stiripentol and cannabidiol.

Recent advances point to new insights into early mechanisms based on a genetic zebrafish model for Dravet syndrome and possible future targeted treatment options. When upcoming treatment choices such as cannabidiol or fenfluramine might be added, the complexity of the treatment will increase and call for careful monitoring of the patients. The patients have difficult-to-treat epilepsy, experience various seizure types, are at risk of life-threatening status epilepticus episodes, and often have comorbidities that need to be treated. It is difficult to find an optimal balance between efficacy and tolerability, contributing to challenges in managing everyday life.

4.5 Methodological considerations

The present study represents the majority of patients with Dravet syndrome in Norway, with the highest inclusion among the youngest patients who are referred to our
national center for diagnostic and clinical evaluation. This gives an advantage to study the use of drugs over time when new treatment options arrive. There may be a selection bias regarding the patients included in the registries for clinical evaluation. The National Center for Epilepsy serves the most refractory patients in the country, but most patients were followed locally in collaboration with the regional university hospitals with access to genetic testing, and with consultations at or admission to our center based on individual needs. A limitation in exact information on duration of treatment periods could impact the calculation of retention rates in some patients and would lead to an underestimation. Information on seizure types, duration and the incidence of status epilepticus was sparse, and medical records may be incomplete. Retrospective studies may, however, be valuable to study subgroups of patients and elucidate a real-life setting.\(^\text{36}\)

\section{Conclusions}

This study demonstrates how treatment with ASMs in Dravet syndrome has changed over the last decade, with a nationwide experience not previously presented. This is of particular importance when new treatment options arrive. The study draws a picture of the treatment in the Norwegian study population which may serve as an example of Dravet syndrome populations also in other countries and is in accordance with recent guidelines. Several challenges were identified: high seizure frequency, comorbidities, treatment changes with a wide range of ASMs, common use of oral gastro-tubes, extensive polypharmacy, risk of interactions, and adverse effects affecting the cognitive development. Despite existing consensus regarding choice of treatment, treating Dravet syndrome is difficult and may require a wide range of ASMs to be tried. This vulnerable patient group needs close follow-up and monitoring for an optimal treatment outcome, balancing seizure control, tolerability, and other factors affecting their daily life.

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\section{Conflict of Interest}

The authors have no conflicts of interest or any financial disclosures regarding this manuscript. 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.

\section{Authors’ Contribution}

The contribution of the authors of this manuscript has been as follows: Caroline Lund and Cecilie Johannessen Landmark planned and designed the study. Katrine Heger did the data collection and has written the first draft of the manuscript and been responsible for revisions. Katrine Heger, Caroline Lund, and Cecilie Johannessen Landmark analyzed and evaluated the results. Margrete Larsen Burns, Svein I. Johannessen, Marit Bjørnvold, and Erik Sætre contributed with clinical evaluation and discussion. All authors have contributed in developing the manuscript and approved the final manuscript.

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