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

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Summary
Objective: Pathogenic variants in SCN1A can give rise to extremely variable disease severities that may be indistinguishable at their first presentation. We aim to find clinical features that can help predict the evolution of seizures into Dravet syndrome and clinical features that predict cognitive outcome in Dravet syndrome. We specifically investigate the role of contraindicated medication (CIM) as a possible modifier of cognitive decline.

Methods: A cohort of 164 Dutch participants with SCN1A-related seizures was evaluated. Clinical data were collected from medical records and semistructured telephone interviews. Cognitive function was classified by a child neurologist, neuropsychologist, and clinical geneticist. Several clinical variables, including duration of CIM use in the first 5 years of disease, were evaluated in univariate and multivariate analyses.

Results: A longer duration of CIM use in the first 5 years after seizure onset was significantly associated with a worse cognitive outcome at time of inclusion, and with lower interpolated intelligence quotient/developmental quotient scores after the first 5 years of disease in Dravet syndrome patients. CIM use remained a significant predictor for cognitive outcome in a multivariate regression model, as did age at the first observation of developmental delay and age at first afebrile seizure. Age at first afebrile seizure was the most accurate predictor for evolution of seizures into Dravet syndrome for the complete cohort.

Significance: Our data suggest that a longer CIM use in the first 5 years of disease can have negative effects on cognitive outcome in Dravet syndrome. An early diagnosis is essential to avoid these drugs. Furthermore, we identified age at first afebrile seizure as an important predictor for evolution of seizures into Dravet syndrome and for the severity of Dravet syndrome, which can be used to counsel parents of young patients with SCN1A-related seizures.

KEYWORDS
cognition, Dravet syndrome, GEFS+, SCN1A, sodium-channel blockers
INTRODUCTION

Pathogenic variants in SCN1A can give rise to extremely variable disease severities. On the severe end of the spectrum is Dravet syndrome, characterized by intractable epileptic seizures, diminishing psychomotor development that results in mild to severe intellectual disability, and often walking difficulties and behavioral problems. Recently, an SCN1A epileptic encephalopathy that is even more severe than Dravet syndrome has been described in 9 patients. Milder phenotypes include genetic epilepsy with febrile seizures plus (GEFS+) syndrome and febrile seizures, in which intellectual disability is usually absent. Furthermore, there is a large phenotypic variability between Dravet syndrome patients; whereas some are severely disabled and suffer from ongoing seizures, others live much more independent lives. An accurate prediction of the prognosis in affected children is understandably very important to parents.

SCN1A encodes for the α-subunit of a neuronal sodium channel, Nav1.1. Pathogenic variants that lead to a complete loss of function of the channel are nearly always associated with severe phenotypes. Such variants include genomic rearrangements, splice-site, nonsense, and frameshift variants. Certain missense variants can also lead to complete loss of function when located in critical regions of the gene (eg, the pore region and voltage sensor). However, other missense variants can result in milder disturbances of channel function and thus lead to milder phenotypes, although variants causing partial loss of function or gain of function may also be associated with Dravet syndrome. Although missense variant location is a strong indicator for the severity of channel disruption, it still cannot fully predict the effect of the variant on channel function and phenotype. Physicochemical changes due to missense variants are similarly difficult to predict. Several genetic factors have already been suggested to modify the clinical outcome of SCN1A-related diseases, such as variants in the SCN1A promoter region, the 5′- and 3′-untranslated regions, and variants in other genes. In clinical practice, it remains difficult to predict whether a missense variant will lead to Dravet syndrome or a milder disease. A few studies have identified clinical features that can help discriminate between Dravet syndrome and milder phenotypes, such as age at seizure onset, seizure types, and number of seizures. Perhaps even more important are studies that focus on factors that clinicians can influence. Although it is clear that sodium channel blockers such as lamotrigine and carbamazepine can result in more frequent or severe seizures in this patient group, and many studies have suggested a positive effect of an early diagnosis and appropriate treatment on long-term cognitive outcomes, this has not been established in large patient groups. Increasing knowledge about the effects of sodium channel blockers is crucial, because they are prescribed to a large proportion of patients with Dravet syndrome at some point during their disease course (21%-100%), often before a diagnosis is established.

Parents often experience great uncertainty about the prognosis of their children when a pathogenic SCN1A variant is found early in life, because accurate prediction of the consequences of an SCN1A variant is still not possible, and different SCN1A-related phenotypes may be indistinguishable at their first presentation. Consequently, there is still a critical necessity to identify more accurate predictors. Here, we study the effect of contraindicated medication (CIM) on cognitive function in Dravet syndrome patients and perform retrospective analyses of possible clinical predictors in a large cohort of Dutch patients with SCN1A pathogenic variants (n = 164).

MATERIALS AND METHODS

2.1 Participants

A cohort of 164 participants with SCN1A pathogenic variants was evaluated. A portion of this cohort (n = 124) has previously been evaluated for mosaicism. We included only symptomatic participants with pathogenic variants (class V) or likely pathogenic variants (class IV) in SCN1A, according to the American College of Medical Genetics and Genomics criteria. SCN1A variants had been detected in diagnostic laboratories (University Medical Center Utrecht, Utrecht, The Netherlands; Laboratory for
Neurogenetics, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium; Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands; Duncan Guthrie Institute of Medical Genetics, Glasgow, UK) by Sanger sequencing, next generation sequencing epilepsy gene panels, whole exome sequencing, or multiplex ligation-dependent probe amplification.

All eligible individuals of at least 4 years of age known to the University Medical Center Utrecht were approached for study inclusion. We excluded patients younger than 4 years because clinical experience has shown that syndrome classification and estimation of disease severity are less reliable for younger children. Informed consent was obtained from participants or their legal caretakers, according to the Declaration of Helsinki. The study was approved by the Ethical Committee of the University Medical Center Utrecht.

2.2 | Clinical data

Detailed clinical data were collected from medical records for all participants, and from semistructured telephone interviews when possible (n = 155). Data on several clinical variables, depicted in Table 1, were obtained. Variables were selected based on literature and clinical experience. Afebrile seizures were defined as seizures with a body temperature < 38°C, or seizures for which medical records reported “no fever” without mentioning the exact temperature. Our main outcome was cognitive function at the time of inclusion, which was classified in a consensus meeting by a child neurologist, neuropsychologist, and clinical geneticist. Cognitive function at the moment of inclusion was rated on a 5-point scale based on available data on intelligence quotient (IQ) and developmental level, adjusted for age at assessment (1 = no intellectual disability [ID]; IQ or developmental quotient [DQ] > 85, 2 = borderline ID [IQ or DQ = 70-85], 3 = mild ID [IQ or DQ = 50-70], 4 = moderate ID [IQ or DQ = 30-50], 5 = severe or profound ID [IQ or DQ < 30]). When no (recent) IQ or DQ was available, the assessment was made based on function in school, communication, and adaptive behavior. All participants were categorized into 2 clinical subgroups: Dravet syndrome or non–Dravet syndrome. Dravet syndrome was diagnosed based on previously published criteria35 and in line with recently published recommendations.36 The non–Dravet group consisted of patients with either GEFS+ or febrile seizures.

2.3 | Statistical analyses

We investigated predicting factors for Dravet syndrome versus non–Dravet syndrome, and for the severity of Dravet syndrome. We specifically tested the influence of CIM use on cognitive function. Univariate analyses were performed, and variables for which statistically significant differences between groups were observed were included in multivariate regression analyses, adjusted for age at cognitive assessment. Adjusting the models for age at cognitive assessment is necessary, because average cognition declines with older age in Dravet syndrome patients. Furthermore, sensitivity, specificity, positive and negative predictive values, and receiver operating characteristic (ROC) curves were calculated. Statistical analyses were performed using SPSS statistics software (SPSS Statistics for Windows V21; IBM, Armonk, NY, USA). All reported tests were performed 2-tailed with an alpha-level for significance of P < .05.

2.3.1 | Predicting factors for Dravet syndrome versus non–Dravet syndrome

Differences between the Dravet and non-Dravet groups were calculated with either Pearson chi-square test or Fisher’s exact test for binary and categorical variables (type of variant, whether a patient had ever been admitted to an intensive care unit [ICU], secondary seizure types before the age of 12 months [comprising absences, myoclonias, focal seizures, and focal seizures with impaired awareness], and the presence of mosaicism for the pathogenic variant) or Mann-Whitney U test for continuous and ordinal variables (age at seizure onset and age at first afebrile seizure). A multivariate binomial logistic regression analysis was performed with statistically significant variables.

2.3.2 | Predicting and influencing factors for cognitive outcome in Dravet syndrome

Univariate binomial logistic regression analyses, adjusted for age at cognitive assessment, were performed in the subgroup of Dravet syndrome patients. Patients were divided into 2 groups: mild cognitive dysfunction (score = 1-3) and severe cognitive dysfunction (score = 4-5). The following variables were assessed: age at seizure onset, age at first afebrile seizure, age at first observation of developmental delay, variant type, whether the patient had ever been admitted to an ICU, secondary seizure types before the age of 12 months (as defined previously), the presence of mosaicism for the pathogenic SCN1A variant, the duration of CIM use (defined as sodium channel blockers: lamotrigine, phenytoin, carbamazepine, oxcarbazepine, vigabatrin), and age at diagnosis. The cumulative number of months CIM was used in the first 5 years after seizure onset was calculated for each patient with seizure onset at least 5 years before assessment. This time frame was chosen because cognitive decline is generally most severe in the first years following disease onset.6,25,26 We chose to
### TABLE 1  Characteristics of the study population and univariate analyses

| Variable                                      | 1a: All participants | 1b: Dravet syndrome patients |
|-----------------------------------------------|-----------------------|------------------------------|
| n                                             | Total | Dravet | Non-Dravet | p   | Cognition score 1-3 | Cognition score 4-5 | p   |
| Age, y, median (range)                        | 164   | 116    | 48         |     | 33                 | 83              |     |
| Sex: male, n                                  | 83    | 65 (56%) | 18 (38%)  |     | 16 (48%)           | 49 (59%)        |     |
| Variant type, n                               |       |        |            | <.0005 |        |        | .562 |
| Missense                                      | 87    | 44 (38%) | 43 (90%)  | 14 (42%) | 30 (36%)        |        |     |
| Pore/pore loop/voltage sensor                 | 58    | 29     | 29         | 7  | 24                 |        |     |
| Elsewhere                                     | 29    | 15     | 14         | 13 (39%) | 66 (49%)        |        | .007 |
| Splicing                                      | 16    | 13 (11%) | 3 (6%)    | 4 (12%) | 9 (11%)          |        |     |
| Nonsense/frameshift/rearrangement             | 61    | 59 (51%) | 2 (4%)   | 15 (45%) | 44 (53%)        |        |     |
| Mosaicism: yes, n                            | 9     | 8 (7%)  | 1 (2%)    | .286 | 5 (15%)           | 3 (4%)      | .03  |
| Cognition score n\(^a\)                       | 1     | 46     | 3 (3%)    | 3 (9%) | 0 (0%)          |        |     |
| 2                                             | 15    | 10 (9%) | 5 (10%)   | 10 (30%) | 0 (0%)          |        |     |
| 3                                             | 20    | 20 (17%) | 0 (0%)   | 20 (61%) | 0 (0%)          |        |     |
| 4                                             | 31    | 31 (27%) | 0 (0%)   | 0 (0%) | 31 (37%)        |        |     |
| 5                                             | 52    | 52 (45%) | 0 (0%)   | 0 (0%) | 52 (63%)        |        |     |
| Age at seizure onset, mo, median (range)      | 8     | 5 (1-30) | 15 (4-72) | <.0005 | 7.6 (3-30) | 5.2 (1-18) | .007 |
| Secondary seizure types at <12 months: yes, n | 71    | 68 (59%) | 3 (6%)    | <.0005 | 13 (39%) | 55 (66%) | .008 |
| Admission to intensive care unit: yes, n      | 60    | 54 (47%) | 6 (13%)  | <.0005 | 13 (39%) | 41 (49%) | .185 |
| Age at first observation of developmental delay, n |       |        |            | <.0005 |        |        |     |
| <12 months                                    | 15    | 15 (13%) | 0 (0%)    | 1 (3%) | 14 (17%)        |        |     |
| 12-23 months                                  | 43    | 43 (38%) | 0 (0%)    | 5 (16%) | 38 (47%)        |        |     |
| 24-35 months                                  | 24    | 23 (21%) | 1 (2%)    | 9 (29%) | 14 (17%)        |        |     |
| 36-47 months                                  | 24    | 20 (18%) | 4 (8%)    | 9 (29%) | 11 (14%)        |        |     |
| ≥48 months                                    | 15    | 11 (10%) | 4 (8%)    | 7 (23%) | 4 (5%)          |        |     |
| No delay                                      | 39    | 0 (0%)  | 39 (81%)  | 0 (0%) | 0 (0%)          |        |     |
| Missing                                       | 4     | 4       | 0         | 2     | 2               |        |     |
| Age at first afebrile seizure, n\(^c\)        |       |        |            | <.0005 |        |        | .001 |
| <12 months                                    | 70    | 70 (65%) | 0 (0%)    | 10 (34%) | 60 (77%)        |        |     |
| 12-23 months                                  | 31    | 27 (25%) | 4 (9%)    | 15 (52%) | 12 (15%)        |        |     |
| 24-47 months                                  | 14    | 5 (5%)  | 9 (20%)   | 1 (3%) | 4 (5%)          |        |     |
| ≥48 months                                    | 21    | 5 (5%)  | 16 (36%)  | 3 (10%) | 2 (3%)          |        |     |
| Never                                         | 16    | 0 (0%)  | 16 (36%)  | 0 (0%) | 0 (0%)          |        |     |
| Missing                                       | 12    | 9       | 3         | 4     | 5               |        |     |

(Continues)
analyze the duration of CIM use rather than whether CIM had ever been used, because only a small number of patients had never used CIM, thereby reducing the power of this analysis. Furthermore, we hypothesized that if CIM use is damaging, a longer use will result in more severe effects.

A multivariate binomial logistic regression analysis, adjusted for age at cognitive assessment, was performed with all statistically significant variables.

Duration of CIM use was further investigated in relation to cognitive outcome scores 1-5 (ordinal logistic regression analysis, in contrast to the previously used dichotomy 1-3 vs 4-5) and interpolated IQ/DQ scores after 5 years of disease (linear regression analysis). To obtain these approximated scores, all IQ and developmental assessment scores of each patient, conducted at different ages, were interpolated by linear regression. When the first official assessment was made >5 years after seizure onset, we used the age at which a developmental delay was first observed (by either parents or clinicians) as the first moment of decline, and IQ/DQ scores up until that age were estimated to be average (=100). The duration of CIM use may depend on disease severity. To avoid confounding, clinical variables that were shown to have significant predictive value in our main analysis were added to these last 2 regression models.

We furthermore analyzed the effects of CIM use in year 1, 2, 3, 4, and 5 after seizure onset separately in univariate and multiple regression analyses, to investigate whether different effects are seen in different years.

### RESULTS

The characteristics of the study population are depicted in Table 1a, Table 1b, Table 2, and Figure 1A. The Dravet syndrome subgroup consisted of 116 patients, and the non-Dravet group of 48. The median ages of the participants were 14 and 22 years, respectively. Almost half of all Dravet syndrome patients had a cognition score of 5 (45%), whereas almost all non-Dravet patients had normal cognitive capacities (score = 1, 90%) except for 5 who had a slight delay (score = 2, 10%). In 104 Dravet syndrome patients, seizure onset was at least 5 years prior to cognitive assessment. After 5 years of disease, the average interpolated IQ/DQ score was 62 and the median duration of CIM use was 11 months. Patients older than 12 years were more likely to have used CIM for longer periods of time and to be diagnosed at a later age. It was not possible to accurately perform an ordinal logistic regression analysis with age at diagnosis as a variable and the cognitive score as outcome, as there was a very strong multicollinearity between age at diagnosis and age at cognitive assessment (variance inflating factor = 15.375; Figure S1).
been diagnosed at a later age), it is difficult to calculate the separate contributions of each variable to the outcome. Because a younger age at diagnosis can only positively influence outcome if clinical management is adjusted, we focused on the duration of CIM use instead.

3.1 Predicting factors for Dravet syndrome versus non–Dravet syndrome

Five tested variables showed a significant difference between the Dravet syndrome and non–Dravet subgroups in univariate analyses (all \( P < .0005 \); Table 1a). Missense variants were the predominant variant type in non-Dravet patients (90%), and nonsense/frameshift/rearrangements were present in half of Dravet syndrome patients (51%). Dravet syndrome patients had a significantly earlier age of seizure onset (median 5 vs 12 months), more often had secondary seizure types before the age of 12 months (59% vs 6%), and were more likely to have been admitted to an ICU (47% vs 12%). Additionally, Dravet syndrome patients had their first afebrile seizure at an earlier age, with 65% before 12 months, whereas 36% of non-Dravet patients experienced their first afebrile seizure only after 48 months and 36% never had an afebrile seizure. Specificity, sensitivity, positive and negative predictive values, and ROC areas of all 5 significant variables are shown in Table S1a. Occurrence of a first afebrile seizure before the age of 24 months was shown to be the best predictor for Dravet syndrome, with a positive predictive value of 96% and a negative predictive value of 81%.

The multivariate binomial logistic regression model, including all 5 significant variables, showed that the variables most significantly associated with Dravet syndrome were age at first afebrile seizure (\( P < .0005 \)), a truncating or splice-site variant (\( P = .006 \)), and admittance to an ICU (\( P = .039 \); Table 3a).

3.2 Predicting and influencing factors for cognitive outcome in Dravet syndrome

Six variables analyzed in univariate binomial regression analyses differed significantly between the mild and severe groups of Dravet syndrome patients: mosaicism of the pathogenic variant (\( P = .03 \)), age at seizure onset (\( P = .007 \)), secondary seizure types before the age of 12 months (\( P = .008 \)), age at first observation of developmental delay (\( P < .005 \)), age at first afebrile seizure (\( P = .001 \)), and the duration of CIM use in the first 5 years of disease (\( P = .015 \); Table 1b). Specificity, sensitivity, positive and negative predictive values, and ROC areas of all 6 significant models are shown in Table S1b. Age at first observation of delay and age at first afebrile seizure without fever were the best clinical predictors (ROC area under curve = 0.797 and 0.792, respectively).

The multivariate binomial logistic regression model, including all 6 statistically significant variables, showed that the best predictors for a worse cognitive outcome were age at first observation of developmental delay (\( P = .004 \)), age at first afebrile seizure (\( P = .019 \)), and duration of CIM use (\( P = .022 \); Table 3b).

### Table 2 CIM use in Dravet syndrome patients per age group

| Dravet syndrome patients with disease onset >5 years ago, n = 104 | 5-8 years | 9-12 years | 13-16 years | 17-20 years | 21+ years |
|---|---|---|---|---|---|
| n | 12 | 22 | 24 | 9 | 32 |
| CIM use in first 5 years of disease, mo | | | | | |
| Mean | 2.6 | 10.3 | 23.1 | 31.9 | 23.7 |
| Median | 1.5 | 7.5 | 14 | 40 | 21.5 |
| Range | 0-11 | 0-34 | 0-56 | 1-57 | 0-59 |
| Missing | 0 | 0 | 0 | 0 | 5 |
| Age at diagnosis, mo | | | | | |
| Mean | 26 | 39.6 | 74.8 | 117 | 239.6 |
| Median | 19.5 | 31.5 | 66 | 110 | 239 |
| Range | 12-90 | 10-115 | 39-135 | 83-148 | 110-516 |
| Used CIM, prescribed at some point during the disease course to % of patients | | | | | |
| Lamotrigine | 25 | 64 | 92 | 100 | 63 |
| Phenytoin | 33 | 36 | 67 | 56 | 47 |
| Carbamazepine | 33 | 45 | 71 | 89 | 88 |
| Oxcarbazepine | 0 | 23 | 29 | 33 | 22 |
| Vigabatrin | 0 | 9 | 21 | 44 | 50 |

CIM, contraindicated medication (sodium channel blockers).
Ordinal logistic regression analysis, corrected for age at inclusion, age at first observation of developmental delay, and age at first afebrile seizure, showed a significantly higher chance of a worse cognitive outcome category score with a longer duration of CIM use ($P = .001$; Table 3c, Figure 2). Linear regression analysis, corrected for age at first observation of developmental delay and age at first afebrile seizure, showed that a longer duration of CIM use was also a significant predictor for a lower interpolated IQ/DQ score 5 years after disease onset ($B = -0.237, P = .05$ without the 29 patients for whom estimated IQ/DQ scores were used, and $B = -0.244, P = .011$ when the IQ/DQ scores before the first notice of delay were estimated to be 85 instead of 100. We furthermore found the strongest effect for the second year of disease when analyzing the first 5 years separately ($B = 1.961, P = .002$; Table S2).

4 | DISCUSSION

We studied several clinical variables in patients with pathogenic $SCN1A$ variants to determine those that can be used as predictors for the development of Dravet syndrome and its
### TABLE 3 Regression analyses

| Variable                                                                 | 3a. Outcome: Dravet syndrome vs non-Dravet; binomial regression, all non-Dravet patients (Nagelkerke $R^2 = 0.831$) | 3b. Outcome: “mild” vs “severe” cognitive dysfunction; binomial regression, Dravet syndrome patients with disease onset >5 years ago (Nagelkerke $R^2 = 0.647$) | 3c. Outcome: cognition scores at inclusion (1-5); ordinal regression, Dravet syndrome patients with disease onset >5 years ago ($\chi^2 = 51.84$) | 3d. Outcome: interpolated IQ/DQ scores after 5 years of disease; linear regression, Dravet syndrome patients with disease onset >5 years ago ($R^2 = 0.386$) |
|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Age at inclusion                                                        | 1.074 0.992-1.162 .077                                                                                            | 1.250 1.050-1.488 .012                                                                                            | 1.105 1.036-1.179 .002                                                                                            | 3.658 −0.920 to 8.236 .116 |
| Age at first seizure                                                     | 0.956 0.824-1.110 .558                                                                                            | 0.919 0.657-1.284 .620                                                                                            | 0.341 0.139-0.835 .019                                                                                            | 0.380-1.093 .103 |
| ICU admittance                                                          | 6.044 1.097-33.294 .039                                                                                            | 0.101 0.035-0.287 <.0005                                                                                        | 0.644 0.380-1.093 .103                                                                                            | 0.644-1.093 .103 |
| Secondary seizure types at <12 months                                   | 5.450 0.655-45.354 .117                                                                                            | 0.101 0.035-0.287 <.0005                                                                                        | 0.341 0.139-0.835 .019                                                                                            | 0.380-1.093 .103 |
| Variant type, truncating/splice-site vs missense                        | 16.591 2.253-122.178 .006                                                                                            | 0.101 0.035-0.287 <.0005                                                                                        | 0.341 0.139-0.835 .019                                                                                            | 0.380-1.093 .103 |
| Age at first observation of developmental delay                         | 0.238 0.089-0.636 .004                                                                                            | 0.255-0.607 <.0005                                                                                              | 9.510 6.104-12.917 <.0005                                                                                              | 9.510-12.917 <.0005 |
| Mosaicism                                                               | 1.981 0.110-35.552 .643                                                                                            | 0.275 0.056-1.358 .113                                                                                            | 0.394 0.255-0.607 <.0005                                                                                              | 0.394-0.607 <.0005 |
| Duration of CIM use in first 5 years of disease                        | 1.091 1.012-1.175 .022                                                                                            | 1.057 1.022-1.092 .001                                                                                            | 1.057 1.022-1.092 .001                                                                                            | 1.057-1.092 .001 |

Significant $P$-values are in boldface.

CI, confidence interval; CIM, contraindicated medication (sodium channel blockers: lamotrigine, phenytoin, carbamazepine, oxcarbazepine, vigabatrin); DQ, developmental quotient; ICU, intensive care unit; ID, intellectual disability; IQ, intelligence quotient.

$^a$Based on available data on IQ and developmental level, adjusted for age at assessment (1 = no ID [IQ or DQ > 85], 2 = borderline ID [IQ or DQ = 70-85], 3 = mild ID [IQ or DQ = 50-70], 4 = moderate ID [IQ or DQ = 30-50], 5 = severe or profound ID [IQ or DQ < 30]. When no (recent) IQ or DQ was available, the assessment was made based on function in school, communication, and adaptive behavior.

$^b$Defined as seizures with a body temperature < 38°C or seizures for which medical records reported “no fever” without mentioning the exact temperature.

$^c$Absences, myoclonias, focal seizures, and focal seizures with impaired awareness.
severity. The most novel finding of our study is negative influence of longer CIM use on cognition in Dravet syndrome patients. Previous studies have suggested that appropriate treatment may have a positive effect on long-term cognitive outcomes in Dravet syndrome.\textsuperscript{10,16,29,30} To our knowledge, only one study tried to correlate CIM to cognitive outcomes and found no effect\textsuperscript{25}; however, only 17 participants (25\%) had used CIM and none of them had taken it for >3 months. In our current study, 86\% of Dravet syndrome patients had used CIM and the median duration of use in the first 5 years of disease was 11 months. We identify a significantly higher probability of a worse cognitive outcome, as well as a more severe cognitive decline in the first 5 years of the disease, when CIM was used for longer periods of time. Although reliable data on seizure frequency during CIM use are not available for our cohort, increases in seizure frequency due to sodium channel blocker use have been reported previously.\textsuperscript{6,27,28} High seizure frequency has been associated with a worse cognitive outcome in Dravet syndrome patients,\textsuperscript{26,37} and similar findings have recently been shown in $\text{SCN1A}^+$ mice.\textsuperscript{38} Furthermore, if CIM is used, indicated medication is less likely to be prescribed, and therefore the negative effects of CIM can also partly be due to the deprivation of optimal treatment. It is therefore likely that an increased seizure severity, at least to some extent, explains the worse cognitive outcome associated with longer CIM use, in accordance with the epileptic encephalopathy disease model. However, because we did not observe an association between longer CIM use and ICU admittances (data not shown), the worse cognitive outcome is probably not due to an increase in status epilepticus. Furthermore, multiple authors have suggested that cognition in Dravet syndrome patients declines independent of seizures due to the direct impact of sodium channel dysfunction on cognitive processes,\textsuperscript{25,39} which may also explain the negative effects of CIM use on cognition. We specifically observed the largest effect of CIM use in the second year of disease, indicating that the developing brain might be particularly sensitive to CIM during this time frame. This finding emphasizes the importance of an early diagnosis and correct clinical management as soon as possible in the disease course. We suggest that $\text{SCN1A}$ analysis should be considered in every child with atypical febrile seizures at the moment that maintenance treatment is indicated. Not surprisingly, older patients were more likely to be diagnosed at a later age and to have used CIM for a longer period of time, likely due to the upcoming availability of $\text{SCN1A}$ genetic testing and evolving insights regarding best treatments. Better cognitive outcomes and a shorter duration of CIM use are to be expected if a younger and more recent cohort would be studied. Future research could therefore also focus on the effects of indicated treatment in this patient group.

There are a few limitations to our strategy of IQ/DQ interpolation. Different testing methods have been used, and IQ scores are not necessarily completely comparable to DQ scores. Furthermore, interpolated values become less reliable as the difference between the ages at which the tests are performed increases, as deterioration might not have been linear but might have fluctuated or was logarithmic instead. This can especially be a problem when a first assessment is performed a long time after a period of steep decline. Most importantly, it is likely that development had already began to decrease before it was first observed by parents or clinicians, and although the assumption of an IQ/DQ of 100 before this moment might be correct for the group as a whole, in reality individual scores will differ. However, the same estimation was made for patients with longer and shorter CIM use and it therefore has probably not affected our results; repeated analyses without the 29 patients for whom estimated IQ/DQ scores were used and analyses in which the IQ/DQ scores before the first observation of delay were estimated to be 85 instead of 100 yielded very similar results. Ideally, CIM use should be tested in a prospective cohort with regular IQ/DQ assessments at similar ages for all participants, including an assessment before developmental delay is present. However, because of the known negative effects of CIM use, this is not ethically responsible. Our method, although probably not completely accurate, seems to lead to a close approximation of the real situation, as all different approaches, including our main analysis, show the same effect of CIM use on cognition.

A previous study has suggested that older patients respond differently to CIM use than younger patients.\textsuperscript{40}
Although there is anecdotal evidence for improved cognition after withdrawal of CIM following long-term use in adults,\textsuperscript{37} there are also adult patients in whom CIM discontinuation cannot be established because of increased seizure severity.\textsuperscript{40} It is hypothesized that this could be due to secondary lesions or compensatory mechanisms after a long disease course, leading to seizures that respond to sodium channel blockers.\textsuperscript{40} Eighty-one percent of adults in our cohort have a severe or profound intellectual disability (score = 4-5), and only one patient had never used CIM. The small group of mildly affected participants (score = 1-3, n = 8) gives us little power to show an effect of CIM use in adulthood. We can therefore not state whether continued CIM use at higher ages results in further cognitive deterioration. Ideally, a cohort of adults would be analyzed prospectively, with functional assessment before and after withdrawal. If discontinuing CIM in adult patients is shown to have a better predictor than age at seizure onset, a variable that was previously mentioned as the most relevant parameter associated with Dravet syndrome.\textsuperscript{21} Having a truncating or splice-site variant, a well-known predictor,\textsuperscript{13} added significant predictive value to the regression model, as was expected. ICU admittances were also significantly associated with the outcome. Interestingly, 6 non–Dravet syndrome patients (13%) also experienced ICU admittances. These patients were not classified as having Dravet syndrome because of their readily achieved seizure control and absence of intellectual disability at the time of inclusion. Having secondary seizure types at a young age, previously described as having predictive value,\textsuperscript{16,22} was in our cohort only significant in univariate analysis.

A younger age at first afebrile seizure was also shown to be a significant predictor in analyses of the cognitive outcome in Dravet syndrome, together with a longer duration of CIM use and an earlier onset of developmental delay. Although age at the start of developmental delay was already identified as a significant prognostic factor,\textsuperscript{6} age at first afebrile seizure was not mentioned in previous studies. That age at the first afebrile seizure is a significant predictor for distinguishing between Dravet syndrome and non–Dravet syndrome, as well as for the severity of Dravet syndrome itself, provides support for the theory that febrile seizures, GEFS+, and Dravet syndrome are all part of the same disease spectrum, as previously proposed.\textsuperscript{16,42} Having secondary seizure types at an early age, another variable that was found to be significant in other studies,\textsuperscript{6,23,25} was again only significant in a univariate analysis.

**5 | CONCLUSION**

Our data suggest that longer use of CIM in the first 5 years of disease may have negative effects on cognitive outcomes in Dravet syndrome patients and should therefore be
avoided. An early diagnosis is essential to achieve this result. The negative effect of CIM might be mediated through a direct impact on cognitive processes and/or an increased seizure frequency, caused by the medication itself or by deprivation of indicated treatment. We furthermore identified age at first afebrile seizure as an important predictor for evolution of seizures into Dravet syndrome, as well as for the severity of Dravet syndrome, which can be used to counsel parents of young patients with SCN1A-related seizures.

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DISCLOSURE OF CONFLICTS OF INTEREST

B.G. has served on an advisory board for GW Pharmaceuticals (Pan-EU Advisory Board on Dravet Syndrome, on Epidiolex) and an advisory board for Zogenix (Belgium/Netherlands advisory board, on fenfluramine). None of the other authors has any conflict of interest to disclose. 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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.