DRAVET Syndrome UK

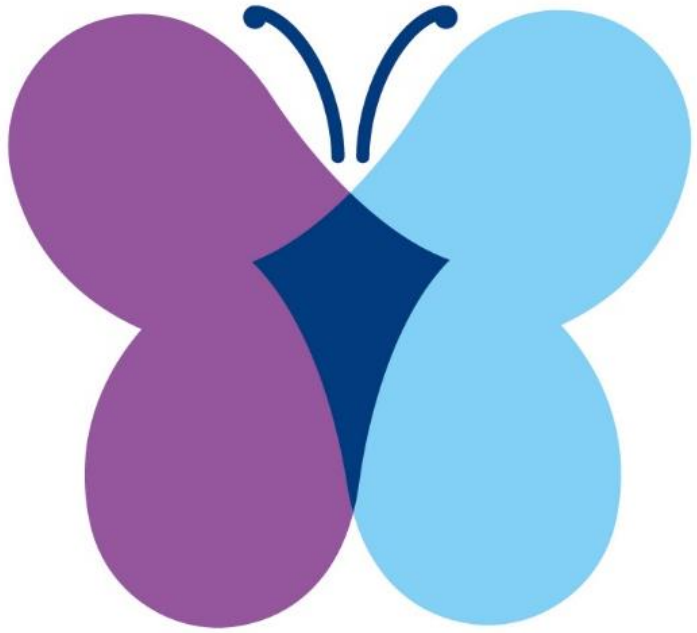
Hope for families with life-limiting epilepsy

# Parent/Carer & Professional Conference 2019

#DSUKLondon19

This Independent meeting is supported by an educational grant from GW Pharmaceuticals and Zogenix.
And also supported by XTX Markets

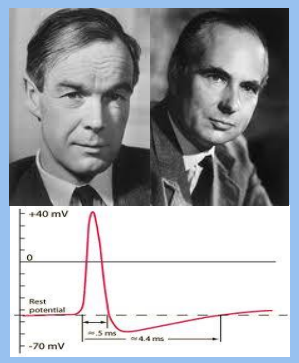
[XTX] MARKETS



# 10-year follow-up of patients with Dravet Syndrome in the UK

Dr Andreas Brunklaus

# How Dravet syndrome became a model for studying childhood genetic epilepsies




Hodgkin and Huxley

1952

1978

Charlotte Dravet

ARTICLES

**Stiripentol**

*C Chiron*
*Lancet 2000*

2000

2001

*SCN1A* mutations cause severe myoclonic epilepsy of infancy

*Claes et al. 2001*
*Am. J. Hum. Gent.*

The New York Times May 18, 1968

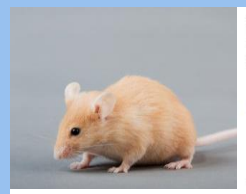
*Retarded Boy Awarded $651,783 in Drug Case*

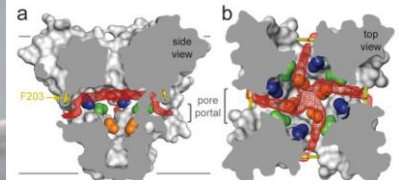
**De-novo mutations of the sodium channel gene *SCN1A* in alleged vaccine encephalopathy: a retrospective study**

***Berkovic et al. 2006*** ***Lancet Neurol***

2006

2006






Reduced Nav current in GABAergic interneurons in a mouse model of SMEI

Catterall et al. 2006 & 2011

nature neuroscience

2011

Low-dose fenfluramine

*European Journal of Neurology* 2017, **24:** 309–314

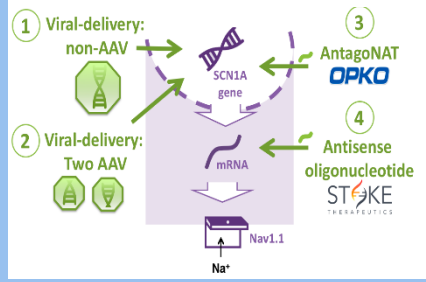
The NEW ENGLAND JOURNAL of MEDICINE

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

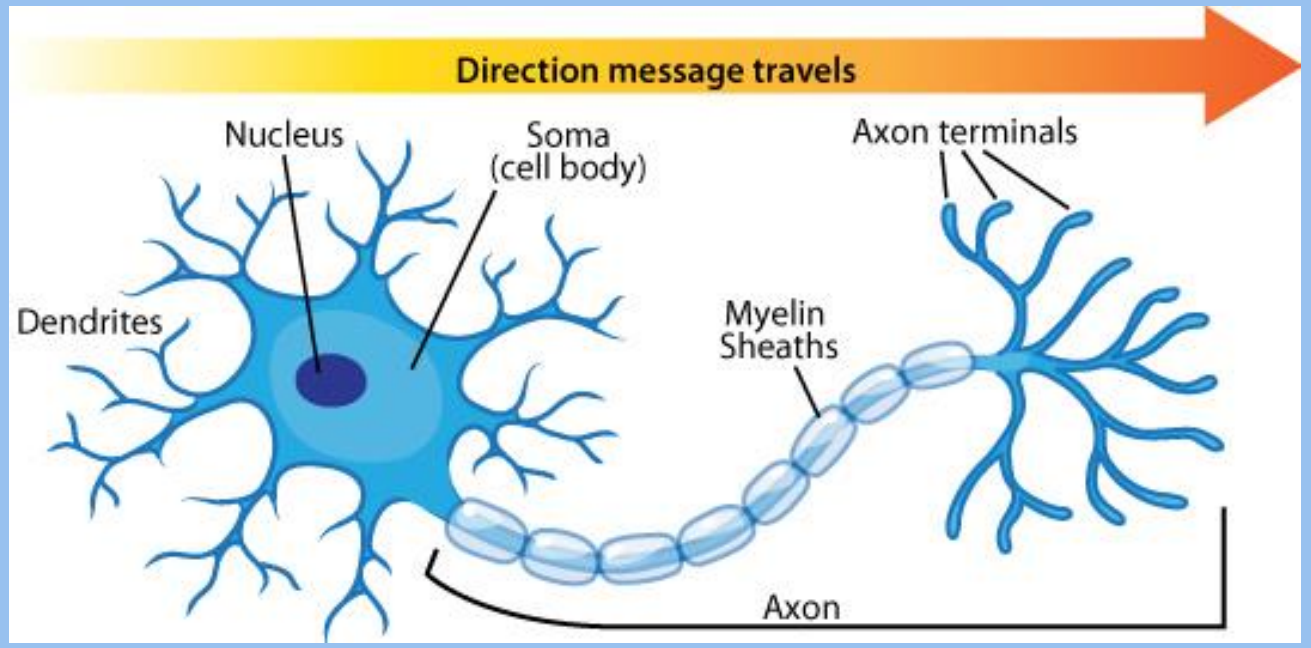
2017

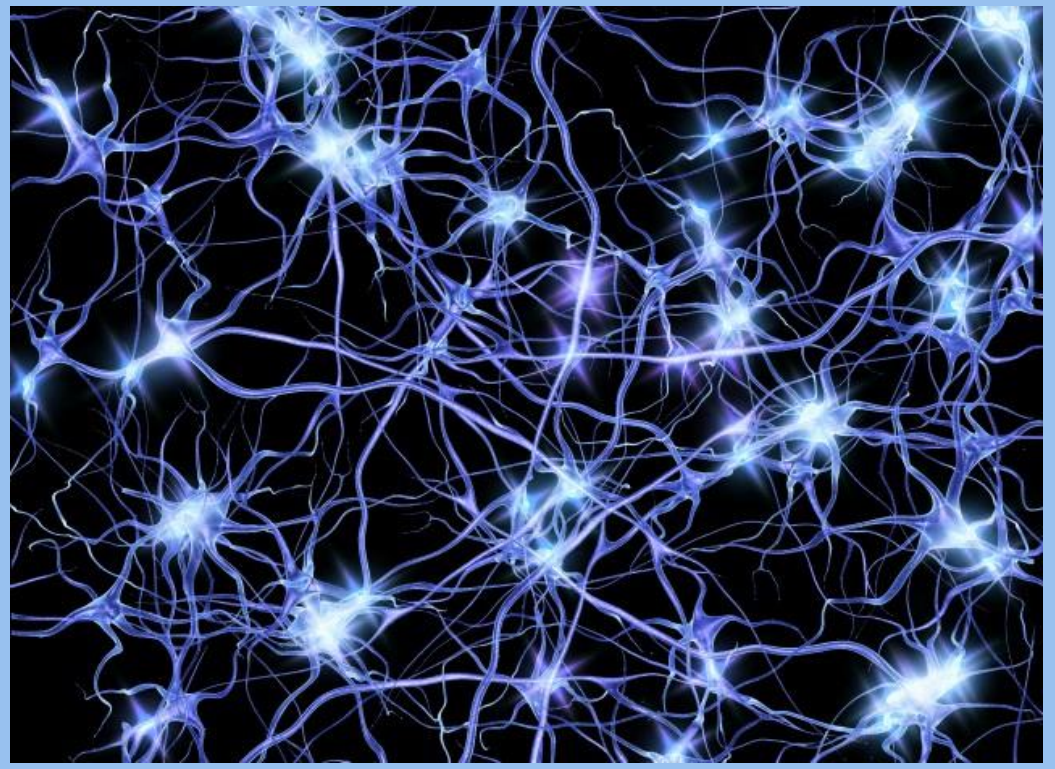
2020

**Gene Therapy for DS**

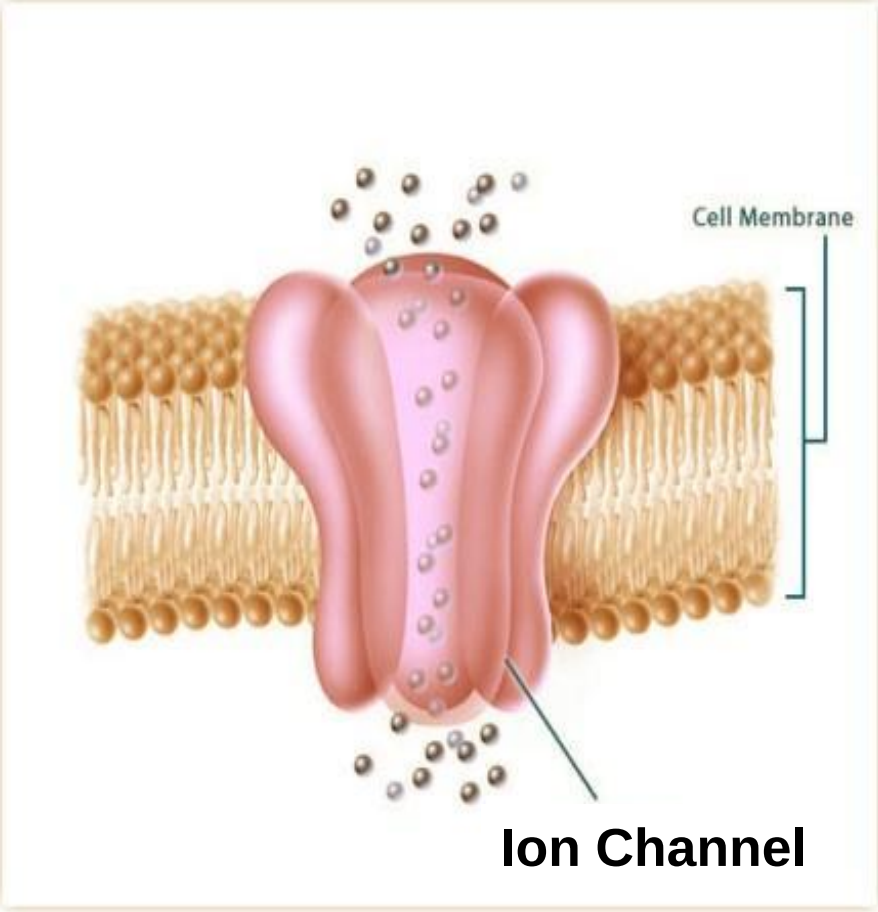


# The Brain = 100 billion nerve cells

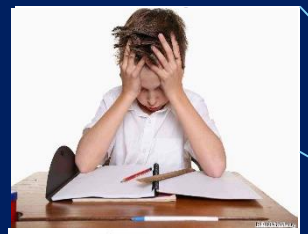


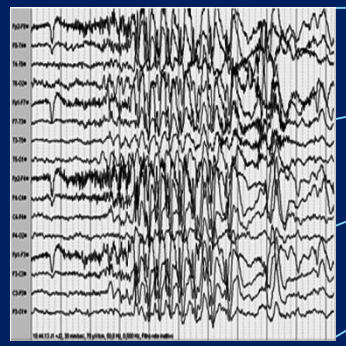



# Sodium channel alpha 1 subunit (*SCN1A*)




# Dravet syndrome – an ion channel disease



Nabbout et al. (2013) Orphanet J Rare Dis. 13;8:176; Brunklaus & Zuberi (2014) Epilepsia 55(7):979-984

# UK 2009 Dravet syndrome cohort study

doi:10.1093/brain/aws151 Brain 2012: 135; 2329–2336 | 2329

BRAIN
A JOURNAL OF NEUROLOGY

## Prognostic, clinical and demographic features in *SCN1A* mutation-positive Dravet syndrome

A. Brunklaus,[1,2] R. Ellis,[3] E. Reavey,[3] G.H. Forbes[3] and S.M. Zuberi[1]

*Epilepsia*, 52(8):1476–1482, 2011
doi: 10.1111/j.1528-1167.2011.03129.x

FULL-LENGTH ORIGINAL RESEARCH

## Comorbidities and predictors of health-related quality of life in Dravet syndrome

*†Andreas Brunklaus, *Liam Dorris, and *Sameer M. Zuberi

- 241 individuals (1 to 42 years)
- Analysis of UK birth cohort from 2003 – 2007 (n=88)
- Incidence at least 1 in 40,900 – now 1 in 15,000!
- 5 reported deaths (6%) at median of 5 years (status epilepticus 2 cases, SUDEP 3 cases)

# Dravet Syndrome UK Survey

**Dravet Syndrome UK families were asked to rate 5 areas in order of importance to them. The ranked them in the following order (with 1 being the most important):**

1) Autistic behaviours
2) Eating problems/difficulties
3) Sleeping issues
4) Mobility problems
5) Gait issues (particularly in older patients)

**Dravet Syndrome UK families were asked whether or not they saw a neurologist:**

85% said yes
3% said no
12% said other (epilepsy nurse)

# Dravet Syndrome UK Survey

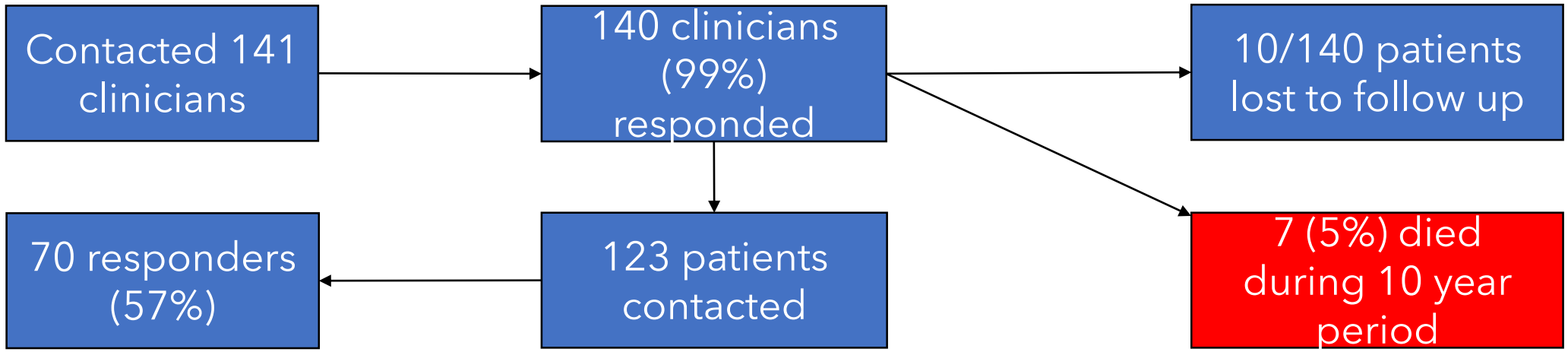
**Of those who answered yes to seeing a neurologist they were asked how often they saw them:**
5% less than once a year
5% once a year
54% twice a year
19% more than twice a year
17% other (including telephone appointments and variations depending on health of the patient)

**Dravet Syndrome UK families were asked to outline any other issues their families faced. Answers given (in no order) were:**
Behaviour (this was the most common answer)
Refusal behaviour
ADHD
Communication
Outreach issues - such as accessing respite for adults and physically being able to go out

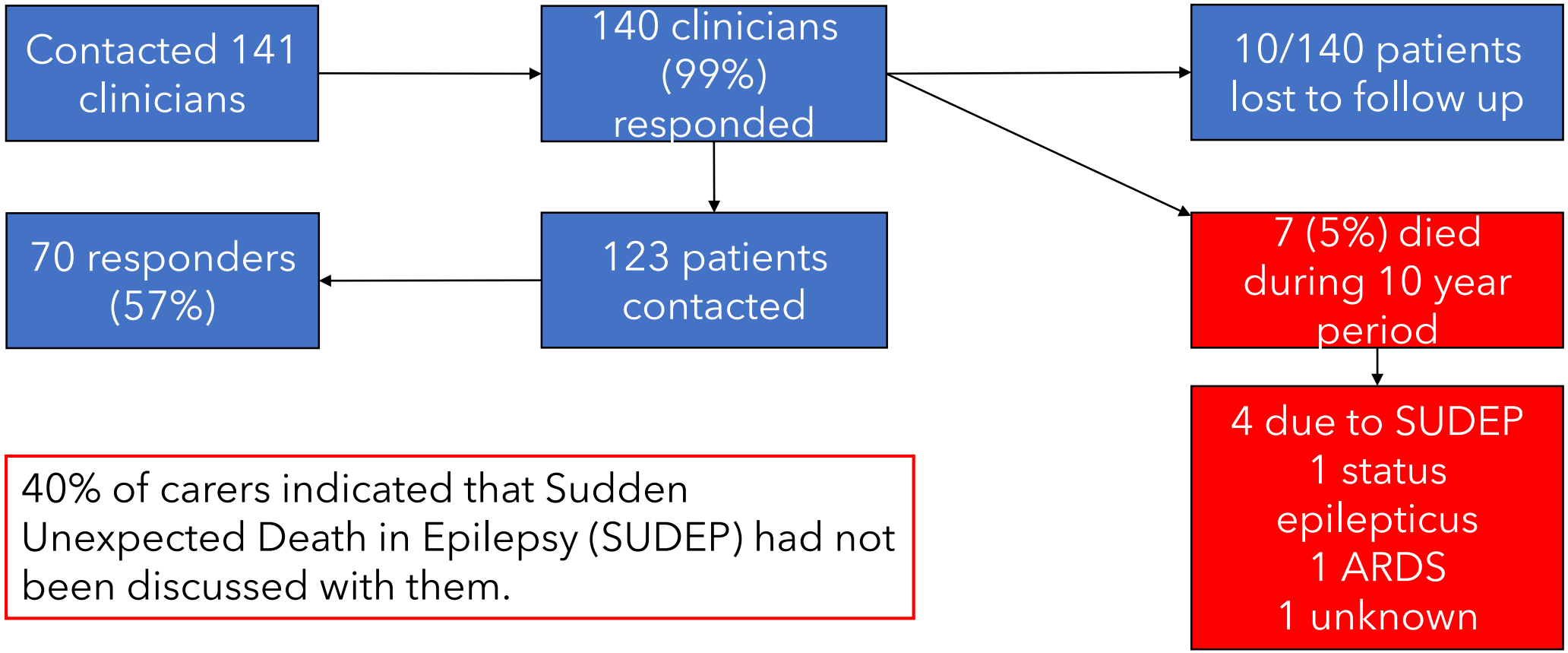
# Methods

- Longitudinal 10-year follow-up study from 2009 – 2019
- Structured Generic Questionnaire
- Adaptive Behaviour Assessment System, Third Edition (ABAS-3)
- Impact of Paediatric Epilepsy Scale (IPES)
- Epilepsy & Learning Disabilities Quality of Life Questionnaire (ELDQOL)
- Paediatric Quality of Life Inventory (PedsQL)
- Strength and Difficulties Questionnaire (SDQ)
- Sleep Disturbance Scale for Children

# Patient recruitment



# 10-year Mortality in Dravet syndrome




40% of carers indicated that Sudden Unexpected Death in Epilepsy (SUDEP) had not been discussed with them.

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Short communication

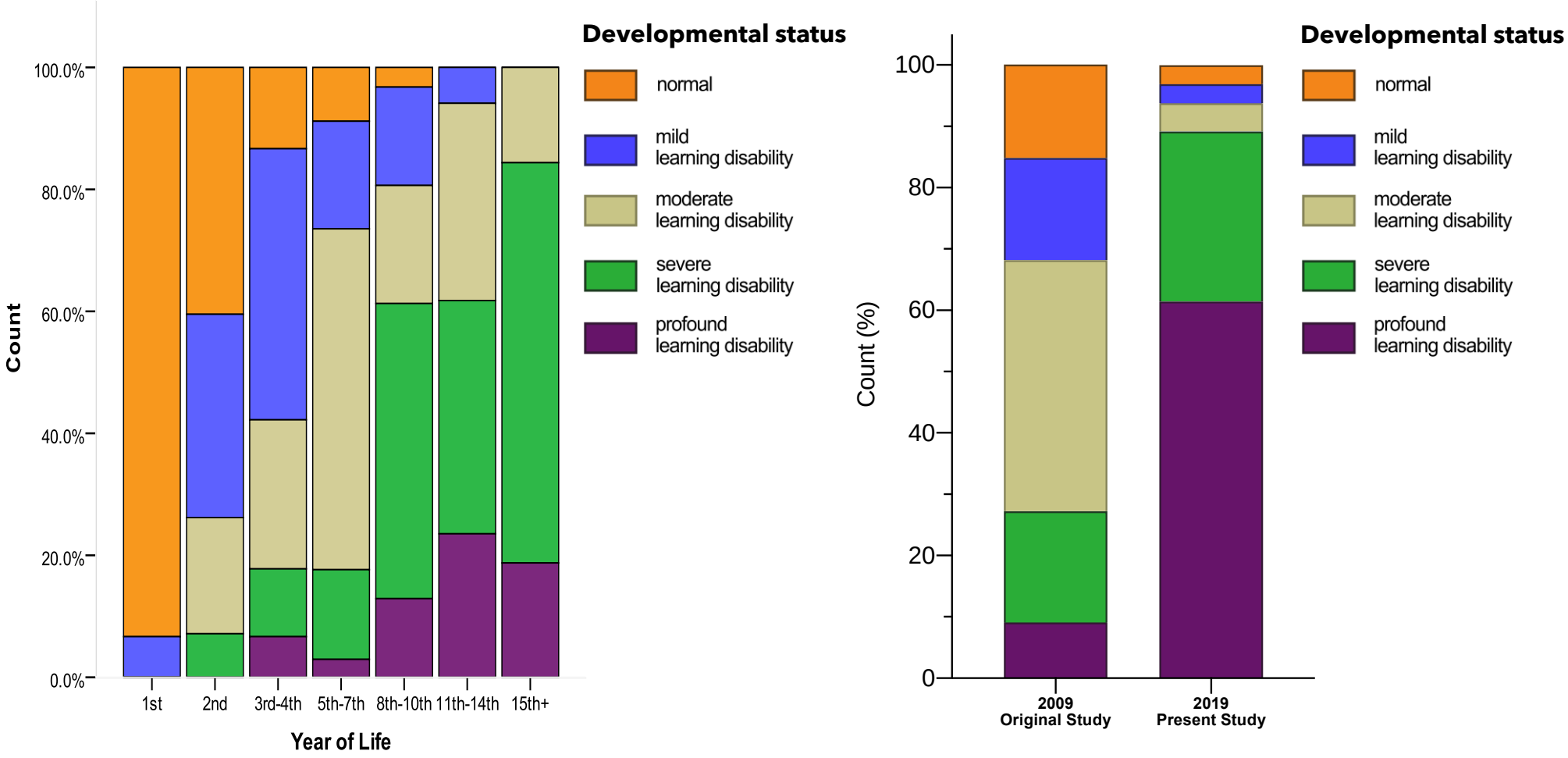
# Mortality in Dravet syndrome

Monica S. Cooper[a,b,c], Anne Mcintosh[d,e], Douglas E. Crompton[d,f], Jacinta M. McMahon[d], Amy Schneider[d], Kevin Farrell[g], Vijeya Ganesan[h], Deepak Gill[i], Sara Kivity[j], Tally Lerman-Sagie[k], Ailsa McLellan[l], James Pelekanos[m], Venkateswaran Ramesh[n], Lynette Sadleir[o,p], Elaine Wirrell[q], Ingrid E. Scheffer[b,d,r,*]

► 10% of children with DS die of SUDEP before their 20th birthday

► Dravet specific mortality is 9.32 per 1000-person-year

# Cross-sectional and longitudinal analysis of development in DS over time




Brunklaus et al (2012) Brain;135(8):2329-36

*Epilepsia*, 52(2):386–392, 2011
doi: 10.1111/j.1528-1167.2010.02925.x

FULL-LENGTH ORIGINAL RESEARCH

# Cognitive development in Dravet syndrome: A retrospective, multicenter study of 26 patients

*Francesca Ragona, *Tiziana Granata, †Bernardo Dalla Bernardina, †Francesca Offredi, †Francesca Darra, ‡Domenica Battaglia, *Monica Morbi, §Daniela Brazzo, ¶Simona Cappelletti, ‡Daniela Chieffo, *Ilaria De Giorgi, †Elena Fontana, *Elena Freri, **Carla Marini, ††Alessio Toraldo, ‡‡Nicola Specchio, §Pierangelo Veggiotti, ‡‡Federico Vigevano, **Renzo Guerrini, ‡Francesco Guzzetta, and §§Charlotte Dravet

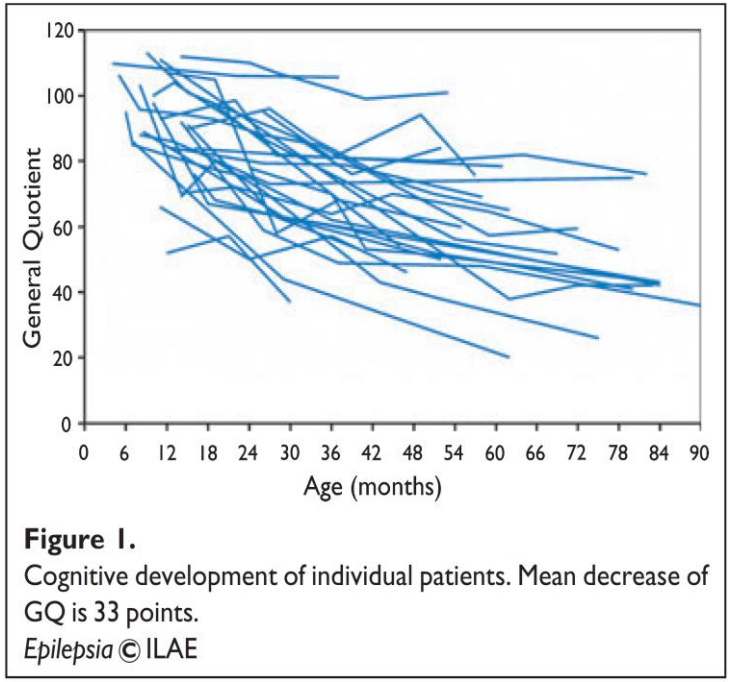



**Figure 1.**
Cognitive development of individual patients. Mean decrease of GQ is 33 points.
*Epilepsia* © ILAE

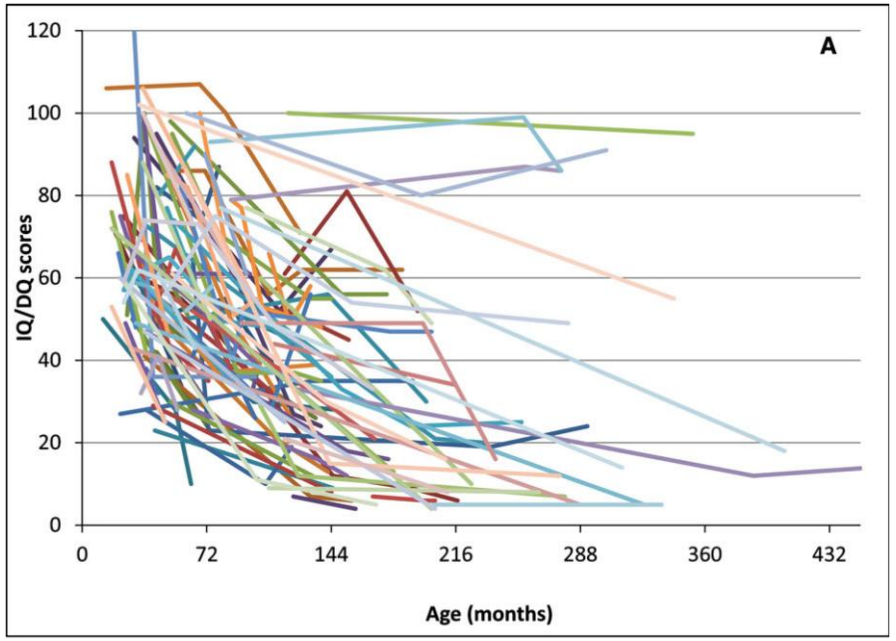
DOI: 10.1111/epi.14191

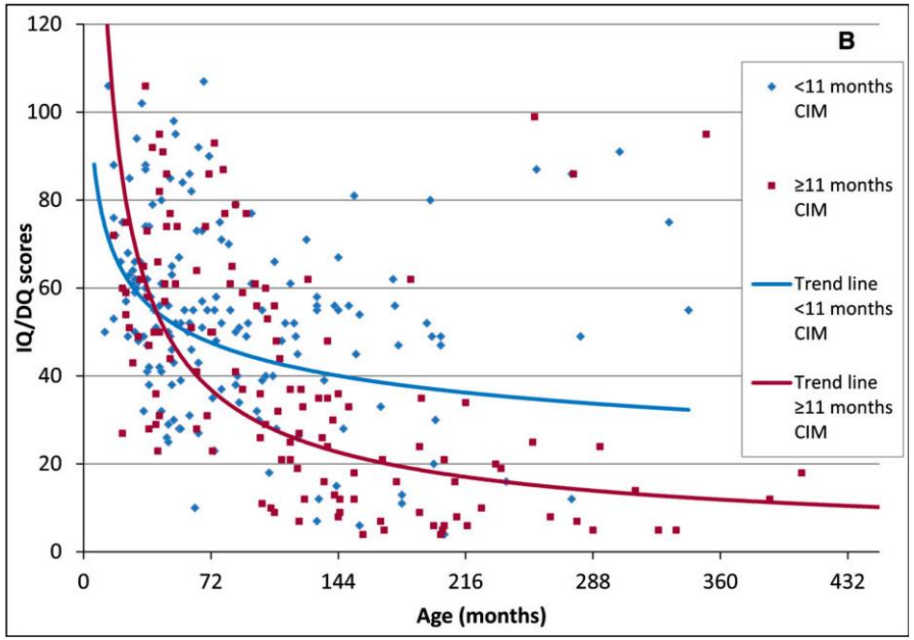
FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

# 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

Iris M. de Lange[1] | Boudewijn Gunning[2] | Anja C. M. Sonsma[1] | Lisette van Gemert[3] | Marjan van Kempen[1] | Nienke E. Verbeek[1] | Joost Nicolai[3] | Nine V. A. M. Knoers[1] | Bobby P. C. Koeleman[1] | Eva H. Brilstra[1]



# Impact on families

| Feature | Occurrence number/total responses |
|---|---|
| Child/adult is:<br>Completely independent<br>Partially dependent<br>Fully dependent | <br>2/68 (3%)<br>23/68 (34%)<br>43/68 (63%) |
| Child lives:<br>With family<br>In residential care | <br>62/68 (91%)<br>8/68 (13%) |
| Have access to respite<br>If yes, the respite received is sufficient | 47/65 (72%)<br>23/44 (52%) |
| Child/adult's illness has affected parent's health | 65/66 (98%) |
| Child/adult's illness has affected parent's career | 60/66 (90%) |

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY

Original article

# Burden-of-illness and cost-driving factors in Dravet syndrome patients and carers: A prospective, multicenter study from Germany

*Adam Strzelczyk* [a,b,c,*], *Malin Kalski* [a], *Thomas Bast* [d,e], *Adelheid Wiemer-Kruel* [d], *Ulrich Bettendorf* [f], *Lara Kay* [a,c], *Matthias Kieslich* [a,g], *Gerhard Kluger* [h,i], *Gerhard Kurlemann* [j],

**Table 3 – Total costs associated with Dravet syndrome for a 3-month period (in 2017 Euro) (source: questionnaire and diary *).**

| Cost components (n = 93 unless noted) | Mean cost | SD | Min | Median | Max | 95% CI[1] | Annual costs[2] |
|---|---|---|---|---|---|---|---|
| **Direct health care costs** | | | | | | | |
| Total including care grade allowances | | | | | | | |
| Informal care approach | 6,043 | 5,825 | 148 | 4,054 | 30,447 | 4,935–7,350 | 24,171 |
| Outpatient nursing approach | 7,468 | 6,180 | 148 | 6,004 | 32,505 | 6,351–8,833 | 29,872 |
| Total AED costs | 892 | 1,017 | 0 | 532 | 4,779 | 708–1120 | 3,569 |
| **Productivity costs** | | | | | | | |
| Total | 4,790 | 5,325 | 0 | 2,841 | 21,327 | 3,868–5,953 | 19,159 |
| Total maternal indirect costs | 4,399 | 4,989 | 0 | 2,339 | 20,191 | 3,466–5,551 | 17,594 |
| Quit work (n = 29) | 3,170 | 4,734 | 0 | 0 | 10,165 | 2,186–4,044 | 12,679 |
| Reduced working hours (n = 27)[6] | 732 | 1,522 | 0 | 0 | 10,030 | 491–1,188 | 2,930 |
| Missed days (n = 37) | 496 | 1,594 | 0 | 0 | 10,026 | 266–976 | 1,986 |

# Caregiver Burden Reports

- Stage 1: first year of life, emergence of febrile status
- Stage 2: around one year of life, other seizure types and emergence of behavioural problems
- Stage 3: children reaching early adolescence with seizure types decreasing and some improvement in behaviour

Nolan and Camfield 2006 & 2008

# Family Relationships

- Stage 1: 67% no change in extended family relationships, 21% improved relationships, 8% negative effects (increased strain on relationship). Regarding spousal relationships – 1/3 no change, 1/3 improved and 1/3 worsening relationships
- Anxiety around fever: 90% reported significant impact on personal and social life, 84% reported that fever had impact on their professional life.

Nolan and Camfield 2006 & 2008

# Family Relationships

- Stage 2: 54% of parents described this as being a particularly difficult time. Negative impact on relationships with family, friends and spouse. Sleep problems very common.
- Stage 3: Increasing difficulties in the friendships of children with DS in 80%. Family relationships can remain challenging.

Nolan and Camfield 2006 & 2008

*Epilepsia*, 52(8):1476–1482, 2011
doi: 10.1111/j.1528-1167.2011.03129.x

**FULL-LENGTH ORIGINAL RESEARCH**

# Comorbidities and predictors of health-related quality of life in Dravet syndrome

*†Andreas Brunklaus, *Liam Dorris, and *Sameer M. Zuberi

*The Paediatric Neurosciences Research Group, Royal Hospital for Sick Children, Glasgow, United Kingdom; and †School of Medicine, University of Glasgow, Glasgow, United Kingdom

**Table 1. PedsQL parent-proxy report in Dravet syndrome compared to normative data**

| Scales | N | Mean (SD) Dravet | Mean (SD) controls[a] | *t*-test[b] | p-value |
|---|---|---|---|---|---|
| PedsQL Generic Core Scale | | | | | |
| Total score | 158 | 46.85 (19.99) | 84.61 (11.19) | 22.90 | <0.001 |
| Physical functioning | 158 | 44.12 (28.85) | 89.06 (12.27) | 19.17 | <0.001 |
| Psychosocial health | 155 | 49.70 (17.58) | 82.21 (12.67) | 21.74 | <0.001 |
| Emotional functioning | 150 | 63.07 (20.85) | 78.28 (15.54) | 8.42 | <0.001 |
| Social functioning | 151 | 44.15 (24.11) | 86.82 (15.42) | 20.80 | <0.001 |
| School functioning | 139 | 40.63 (20.28) | 81.52 (16.09) | 22.34 | <0.001 |

[a]Summarized data from UK published norms for the PedsQL Core including 665 healthy children (Upton et al., 2005).
[b]Differences between published normative data and the observed data (mean and standard deviation) were calculated for each subscale, using a two-sample *t*-test of summarized data (Minitab statistical analysis package).

## KEY FINDINGS:

- Impact of epilepsy in Dravet syndrome was worse compared to epilepsy controls with and without learning difficulties
- Cross sectional analysis showed worse HRQOL in older age groups
- Overall 35% of children with Dravet syndrome scored in the abnormal range for “conduct problems” and 66% for “hyperactivity/inattention”

# HRQOL in Dravet Syndrome

**Table 2. Cross-sectional analysis of PedsQL, IPES, and SDQ scores across different age groups**

| | Age categories | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Scale | 2–3 years (n = 34) mean (SD) | 4–5 years (n = 28) mean (SD) | 6–9 years (n = 33) mean (SD) | 10–14 years (n = 30) mean (SD) | ≥15 years (n = 33) mean (SD) | d.f. | F | p-value[a] |
| PedsQL | | | | | | | | |
| Total score | 59 (21) | 54 (16) | 45 (18) | 44 (16) | 32 (16) | 4,153 | 11.79 | <0.001 |
| Physical functioning | 57 (27) | 58 (25) | 44 (28) | 41 (27) | 22 (22) | 4,153 | 9.81 | <0.001 |
| Psychosocial health | 62 (20) | 52 (13) | 45 (15) | 47 (15) | 42 (16) | 4,150 | 7.38 | <0.001 |
| Cognitive functioning | 43 (35) | 22 (18) | 21 (20) | 19 (18) | 17 (22) | 4,147 | 6.01 | <0.001 |
| IPES | | | | | | | | |
| Total impact score | 17 (9) | 21 (9) | 22 (8) | 22 (8) | 24 (7) | 4,156 | 3.47 | 0.009 |
| SDQ | | | | | | | | |
| Total score | 16 (6) | 18 (5) | 17 (5) | 18 (4) | 16 (6) | 4,133 | 0.64 | 0.631 |

PedsQL, Pediatric Quality of Life Inventory; IPES, Impact of Pediatric Epilepsy Scale; d.f., degrees of freedom.
[a]Based on Tukey Honestly Significant Difference post hoc analysis (ANOVA).

# HRQOL Follow-up Data

| | 10-15 years | | | | |
|---|---|---|---|---|---|
| **Scales** | N | Orig mean | N | FU mean | P |
| **PedsQL Generic Core Scale** | | | | | |
| Physical functioning | 28 | 54.89 | 27 | 30.63 | **0.002** |
| Emotional functioning | 28 | 68.57 | 27 | 63.66 | 0.365 |
| Social functioning | 28 | 47.79 | 28 | 32.44 | **0.042** |
| School functioning | 24 | 43.08 | 28 | 43.36 | 0.855 |
| **Total score** | 24 | 51.21 | 28 | 41.13 | **0.006** |
| | | | | | |
| Cognition | 28 | 33.71 | 24 | 20.49 | **0.009** |
| Eating | 28 | 61.64 | 27 | 49.63 | **0.042** |

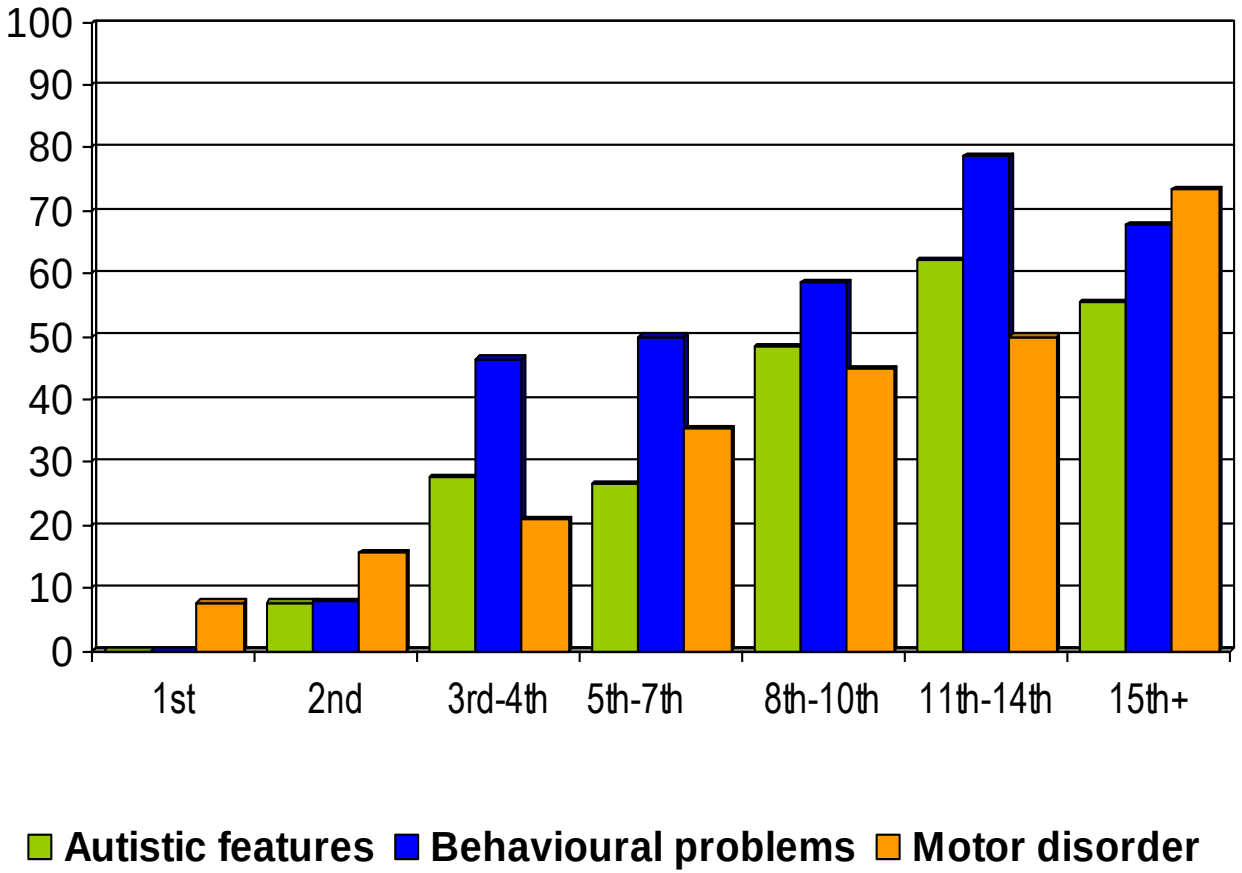
# HRQOL Follow-up Data

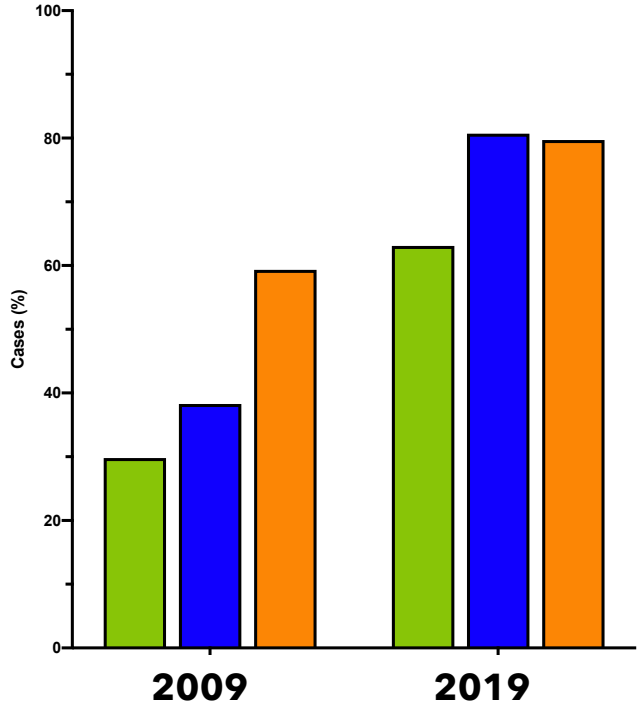
| | 10-15 years | | | | | ≥16 years | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Scales** | N | Orig mean | N | FU mean | P | N | Orig mean | N | FU mean | P |
| **PedsQL Generic Core Scale** | | | | | | | | | | |
| Physical functioning | 28 | 54.89 | 27 | 30.63 | **0.002** | 40 | 29.88 | 38 | 24.52 | **0.031** |
| Emotional functioning | 28 | 68.57 | 27 | 63.66 | 0.365 | 35 | 58.34 | 37 | 56.23 | 0.138 |
| Social functioning | 28 | 47.79 | 28 | 32.44 | **0.042** | 35 | 36.23 | 36 | 40.45 | 0.294 |
| School functioning | 24 | 43.08 | 28 | 43.36 | 0.855 | 36 | 30.83 | 26 | 35.13 | 0.187 |
| **Total score** | 24 | 51.21 | 28 | 41.13 | **0.006** | 33 | 39.78 | 36 | 37.15 | 0.557 |
| | | | | | | | | | | |
| Cognition | 28 | 33.71 | 24 | 20.49 | **0.009** | 39 | 16.69 | 34 | 20.89 | 0.08 |
| Eating | 28 | 61.64 | 27 | 49.63 | **0.042** | 39 | 50.51 | 37 | 49.05 | 0.345 |

# Comorbidities

| Feature | Occurrence number/total responses |
|---|---|
| Eating difficulties | 35/64 (55%) |
| Require gastrostomy/feeding tube | 6/68 (9%) |
| Dental problems | 20/63 (38%) |
| Mobility/walking problems | 51/64 (80%) |
| Require walking aids:<br>Insoles/splints/specialised boots<br>Wheelchair | 29/68 (42%)<br>25/68 (37%)<br>19/68 (28%) |
| Scoliosis | 7/68 (10%) |
| Experienced bone fractures | 27/68 (40%) |
| Access to:<br>PT<br>OT<br>SALT<br>Dietician | <br>34/68 (50%)<br>32/68 (47%)<br>33/68 (49%)<br>21/68 (31%) |
| Difficulties with sleep | 45/67 (67%) |

# Comorbidities

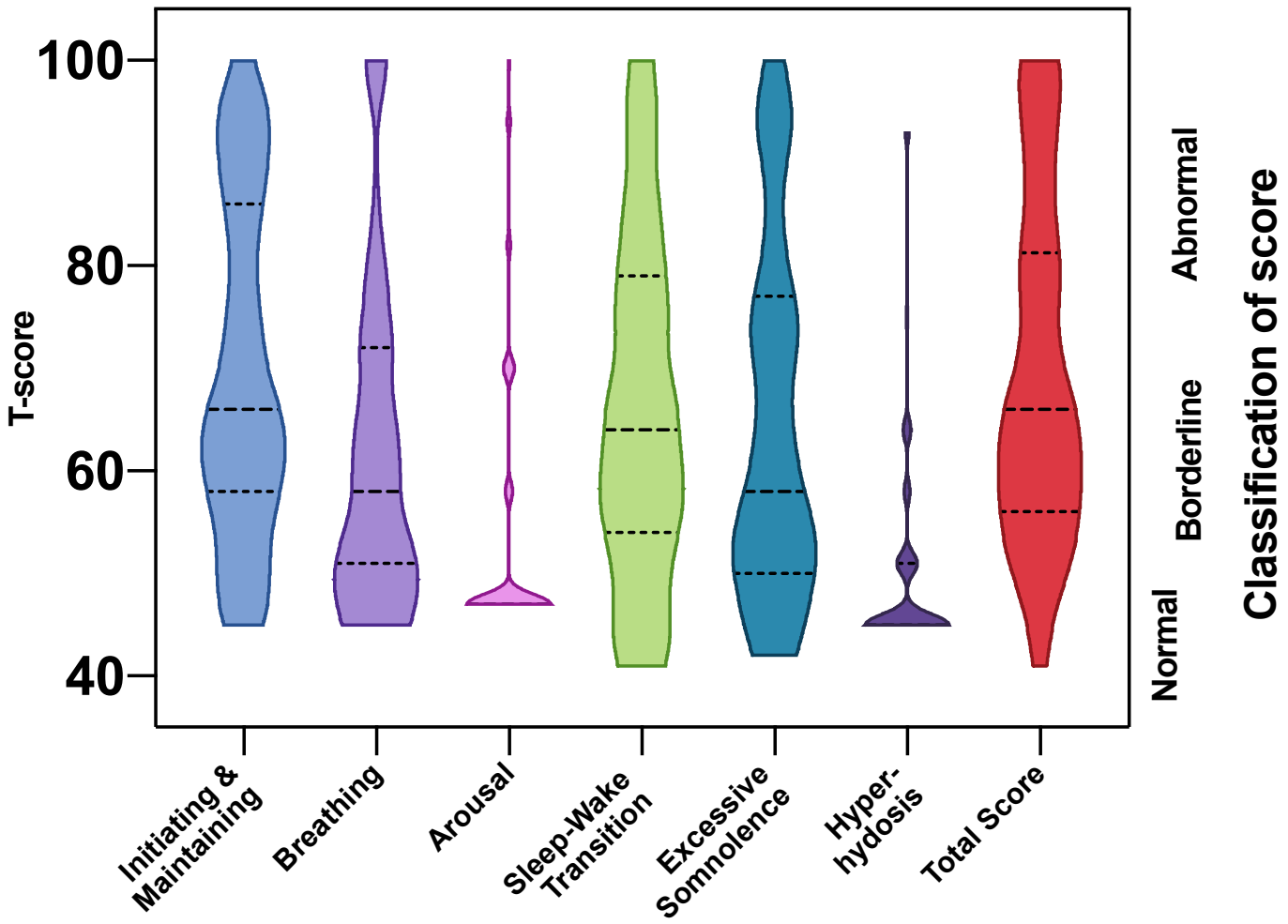


# Medication response

| Medications reported to have reduced seizure frequency | Number total (%) |
|---|---|
| | |
| Stiripentol | 21/46 (46%) |
| Clobazam | 18/46 (39%) |
| Sodium Valproate | 24/46 (52%) |
| | |
| **Medications reported to have increased seizure frequency** | **Number total (%)** |
| | |
| Lamotrigine | 17/40 (43%) |
| Carbamazepine | 7/40 (18%) |
| Phenytoin | 5/40 (13%) |

# Sleep Profile in Dravet Syndrome




- **Sleep Disturbance Scale for Children**
- Sleep, as measured by total sleep scale score, was abnormal in 40% of patients and borderline in 50%. Only 10% of patients with Dravet syndrome scored normal (n=58).
- Only 49% of individuals with abnormal sleep scores received treatment.
- Figure shows the distribution of sleep scores; mean=dashed line, IQR=dotted line, n=61 to 62, depending on sleep domain.

# Sleep summary

- **Forty four of 62 (71%) individuals had at least one abnormal category score or total sleep score**
- Disorders of excessive somnolence was the most common sleep problem in the older age group (17 out of 33, 51%)
- The most common sleep problem for those aged 10-15 years was disorders of initiating and maintaining sleep (10 out of 28, 36%)

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

# Sleep problems in Dravet syndrome: a modifiable comorbidity

SHANE H LICHENI[1] | JACINTA M MCMAHON[1] | AMY L SCHNEIDER[1] | MARGOT J DAVEY[2] | INGRID E SCHEFFER[1,3,4]

**1** Department of Medicine, Austin Health, University of Melbourne, Melbourne; **2** Melbourne Children's Sleep Centre, Monash Children's Hospital, Melbourne; **3** Florey Institute of Neuroscience and Mental Health, Melbourne; **4** Department of Neurology and Department of Paediatrics, University of Melbourne, Royal Children's Hospital, Melbourne, Australia.

## What this paper adds

- More than 70% of patients with Dravet syndrome have sleep problems.
- Difficulty initiating and maintaining sleep was most common, particularly in those older than 20 years.
- Second most common were sleep–wake transition disorders, affecting more than 50% of those younger than 5 years.
- Sleep breathing disorders were a frequent problem across all age groups.
- Oximetry was not diagnostic of sleep-disordered breathing or obvious seizures.

# Transition to adult services

Of the 34 patients that have left paediatric services:

- 18 (53%) received a formal transition process to adult services
- 3 patients (9%) are not under the care of a neurologist
- 21/28 (75%) are satisfied with the adult services

# Caregiver strategies to improve daily life

- Writing an emergency department protocol
- Establish emergency routines for the family
- Assigning a parent on-call to lessen the effect on siblings
- Creating personal time to decrease parental stress
- Finding respite care
- Contacting internet support groups

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

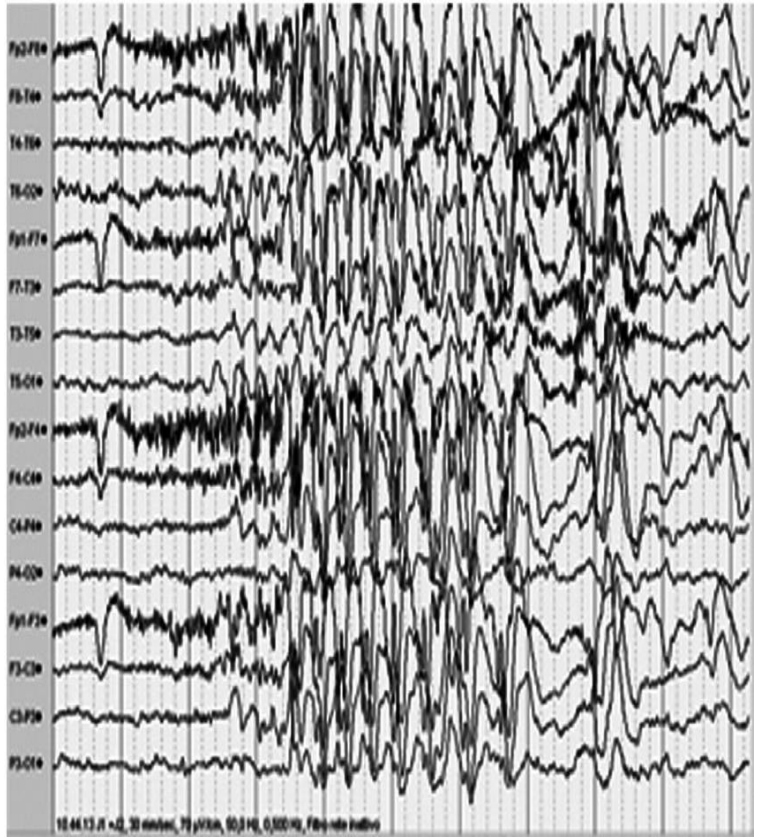
# The clinical utility of an *SCN1A* genetic diagnosis in infantile-onset epilepsy

ANDREAS BRUNKLAUS[1] | LIAM DORRIS[1] | RACHAEL ELLIS[2] | ELEANOR REAVEY[2] | ELIZABETH LEE[1] | GORDON FORBES[2] | RICHARD APPLETON[3] | J HELEN CROSS[4] | COLIN FERRIE[5] | IMELDA HUGHES[6] | ALICE JOLLANDS[7] | MARY D KING[8] | JOHN LIVINGSTON[5] | BRYAN LYNCH[8] | SUNNY PHILIP[9] | INGRID E SCHEFFER[10] | RUTH WILLIAMS[11] | SAMEER M ZUBERI[1]

- "We were very relieved when the results came back. It was like a weight had been lifted after 12 years"
- "It gave a reason for his epilepsy as before we kept blaming ourselves. More importantly it gives some indication to professionals what drugs to try"
- "Confirmed that management of condition is paramount, scans, tests, surgery routes no longer necessary "
- "It finally (after 14 years) gave a diagnosis - helpful in form filling!"
- "We now have a diagnosis and have set small goals for the future"

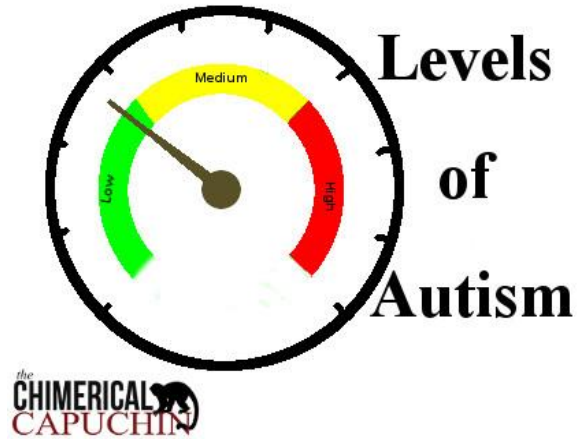
# Addressing Comorbidities

- Optimise seizure control
- Control status epilepticus
- Clear treatment protocols



# Behaviour problems, ADHD & ASD like features

- Neurodevelopmental assessments
- Identifying key issues
- Nurseries and schools already have a wealth of knowledge how to address this in day to day life
- Creating routines



# Mobility problems

- Physiotherapy assessment
- Orthotics review
- Need for insoles, mobility aids

# Diet and Sleep

- Monitor weight gain
- Dietician review
- Consider alternative feeding options
- Sleep review
- Sleep strategies

# Feeling stressed?

- Don’t keep it to yourself
- Supportive team of nurses, doctors and psychologists
- Dravet Syndrome UK

# Dravet Syndrome Natural History Study

- Emergence of drugs effective at reducing seizure burden, however impact on cognition and development unknown
- Without understanding the natural history of DS it will not be possible to measure treatment success beyond seizure control
- Need to characterise disease phenotype in detail
- A natural history study will allow us to provide standardized and better care for our patients tailored to their needs
- Model for other developmental & epileptic encephalopathies