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Dravet Syndrome Natural History: Placebo-Treated Patients in Clinical Trials

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INTRODUCTION

- Dravet syndrome (DS) is a rare developmental and epileptic encephalopathy associated with severe, treatment-resistant seizures.[1]
- The natural history of DS is variable and imprecisely characterized.[2]
- Since seizures and seizure clusters are linked to morbidity, reduced quality of life, and premature mortality, a greater understanding of the natural history could improve trial designs.[3]

OBJECTIVE

- This analysis explored seizure types, seizure clusters and factors affecting seizure cluster variability in DS patients across age groups, to improve the understanding of DS natural history.

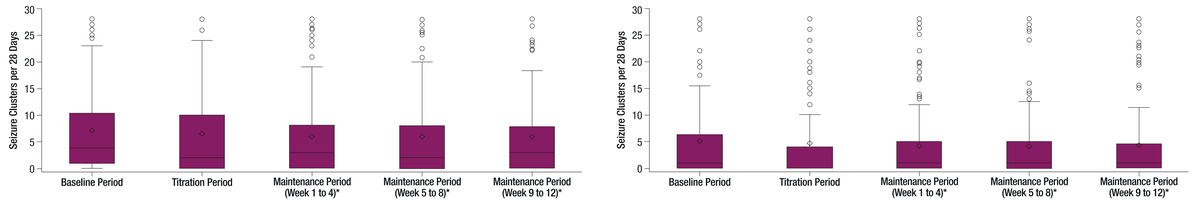
METHODS

- Pooled post-hoc analyses were performed on data from placebo-treated patients from the GWPCARE1B and GWPCARE2 randomized controlled phase III trials in DS patients aged 2–18 years.[4, 5]
- Seizure clusters were defined as either ≥2 or ≥3 seizures occurring within a 24-hour period.
- Multivariate stepwise analysis of covariance (ANCOVA) of log-transformed seizure cluster frequency during the 14-week treatment period (2 weeks dose escalation; 12 weeks dose maintenance) was performed to explore whether any patient characteristics were associated with convulsive seizure clustering.
- Explanatory variables included body weight and body mass index (BMI), antiseizure medication use, sex, race, geographic region, baseline seizure cluster frequency, DS history and age group (2–5; 6–12; 13–18 years). The full list of all variables considered is available via QR code.
- Incidence of adverse events (AEs) was assessed during the treatment period.

RESULTS

- The analysis included 124 placebo-treated patients across both studies (2–5 years: n=35; 6–12 years: n=52; 13–18 years: n=37). Details on antiseizure medication use are available via QR code.
- Generalized tonic-clonic seizures followed by myoclonic seizures were the most common seizure types across all age groups during the study period **(Table 1)**.
- For both seizure cluster definitions, mean and median convulsive seizure cluster frequency numerically decreased between the baseline and maintenance period, but did not change in a meaningful way during the maintenance period **(Figure 1)**.
- There was variation in the mean and median seizure cluster frequency across the different age groups; the youngest age group (2–5 years) experienced the largest numerical reductions in the mean number of seizure clusters and variability of seizure cluster frequency **(Figures 2 and 3)**.
- Multivariate analysis revealed that seizure cluster frequency (when defined as ≥3 seizures in 24 hours) had a positive correlation with age and a negative correlation with BMI **(Table 2)**.
- Over the observation period, most patients across age groups presented constant body weight z-scores (age/sex-adjusted, standardised measures), although the youngest age group (2–5 years) had the greatest degree of fluctuations in body weight and BMI z-scores.
- AEs were generally infrequent, with "somnolence, fatigue, lethargy and sedation" being the most common type of AE across the three age groups.

Figure 1. Summary of convulsive seizure cluster frequency, defined as (a) ≥2 or (b) ≥3 convulsive seizures in 24 hours

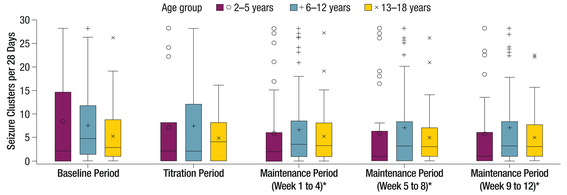


	Analysis period	n	Mean (SD)	Median (IQR)
Average per 28 days	Baseline Period	124	7.09 (8.365)	3.87 (1.00–10.31)
	Maintenance Period	124	6.00 (7.96)	2.74 (0.53–8.74)
	Maintenance Period (Week 1 to 4)*	123	6.01 (7.801)	3.00 (0.00–8.00)
	Maintenance Period (Week 5 to 8)*	121	6.00 (8.217)	2.00 (0.00–8.00)
	Maintenance Period (Week 9 to 12)*	120	5.95 (8.069)	3.00 (0.00–7.78)
Percent change from baseline	Baseline Period	104	0.00 (0.00)	0.00 (0.00–0.00)
	Maintenance Period	104	-16.37 (80.173)	-26.49 (-65.92–0.42)
	Maintenance Period (Week 1 to 4)*	103	-13.64 (82.274)	-25.00 (-61.65–3.57)
	Maintenance Period (Week 5 to 8)*	101	-20.14 (82.613)	-28.57 (-75.00–3.70)
	Maintenance Period (Week 9 to 12)*	100	-16.58 (96.953)	-27.67 (-74.46–1.79)

	Analysis period	n	Mean (SD)	Median (IQR)
Average per 28 days	Baseline Period	124	5.07 (8.023)	1.00 (0.00–6.40)
	Maintenance Period	124	4.28 (7.408)	0.54 (0.00–4.61)
	Maintenance Period (Week 1 to 4)*	123	4.27 (7.251)	1.00 (0.00–5.00)
	Maintenance Period (Week 5 to 8)*	121	4.10 (7.380)	1.00 (0.00–5.00)
	Maintenance Period (Week 9 to 12)*	120	4.37 (7.666)	1.00 (0.00–4.65)
Percent change from baseline	Baseline Period	75	0.00 (0.000)	0.00 (0.00–0.00)
	Maintenance Period	75	-25.85 (83.869)	-34.12 (-83.33–2.47)
	Maintenance Period (Week 1 to 4)*	75	-22.76 (94.321)	-40.00 (-100.00–0.00)
	Maintenance Period (Week 5 to 8)*	73	-30.21 (83.175)	-44.64 (-100.00–0.00)
	Maintenance Period (Week 9 to 12)*	73	-27.08 (85.934)	-31.03 (-100.00–3.57)

Footnotes: GWPCARE1B and GWPCARE2, Intention-To-Treat Analysis Set, Placebo subjects. Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures. Baseline period includes all data prior to Day 1. Treatment period was defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit. Maintenance period was defined as Day 15 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit. *Patients with at least 7 days of seizure data within the period. **Abbreviations:** IQR, interquartile range; SD, standard deviation.

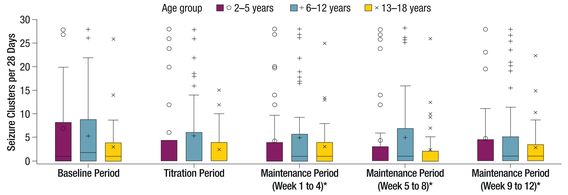
Figure 2. Summary of convulsive seizure cluster frequency by age group (≥2 convulsive seizures in 24 hours)



	Analysis period	n	Mean (SD)	Median (IQR)
Average per 28 days (2–5 years)	Baseline Period	35	8.3 (10.8)	2.1 (0.0–14.5)
	Maintenance Period	35	7.1 (10.7)	2.0 (0.0–8.0)
	Maintenance Period (Week 1 to 4)*	34	5.9 (8.3)	2.0 (0.0–6.0)
	Maintenance Period (Week 5 to 8)*	34	5.8 (9.4)	1.0 (0.0–6.0)
	Maintenance Period (Week 9 to 12)*	34	5.6 (9.5)	1.0 (0.0–6.0)
Average per 28 days (6–12 years)	Baseline Period	52	7.6 (7.8)	4.7 (1.4–11.6)
	Maintenance Period	52	7.4 (9.2)	2.0 (0.0–12.0)
	Maintenance Period (Week 1 to 4)*	52	6.6 (8.2)	3.5 (1.0–8.5)
	Maintenance Period (Week 5 to 8)*	50	7.0 (8.8)	3.2 (0.0–8.3)
	Maintenance Period (Week 9 to 12)*	49	6.9 (8.5)	3.9 (1.0–7.8)
Average per 28 days (13–18 years)	Baseline Period	37	5.3 (6.1)	2.9 (1.0–8.7)
	Maintenance Period	37	4.8 (5.1)	4.0 (0.0–8.0)
	Maintenance Period (Week 1 to 4)*	37	5.3 (6.1)	3.2 (1.0–8.0)
	Maintenance Period (Week 5 to 8)*	37	4.9 (6.0)	3.0 (1.0–7.0)
	Maintenance Period (Week 9 to 12)*	37	4.9 (5.8)	3.0 (1.0–7.7)

Footnotes: GWPCARE1B and GWPCARE2, Intention-To-Treat Analysis Set, Placebo subjects. *Patients with at least 7 days of seizure data within the period. **Abbreviations:** IQR, interquartile range; SD, standard deviation.

Figure 3. Summary of convulsive seizure cluster frequency by age group (≥3 convulsive seizures in 24 hours)



	Analysis period	n	Mean (SD)	Median (IQR)
Average per 28 days (2–5 years)	Baseline Period	35	6.9 (10.7)	0.9 (0.0–8.3)
	Maintenance Period	35	6.1 (10.4)	0.0 (0.0–4.3)
	Maintenance Period (Week 1 to 4)*	34	4.3 (8.1)	0.0 (0.0–4.0)
	Maintenance Period (Week 5 to 8)*	34	4.4 (8.7)	0.0 (0.0–3.0)
	Maintenance Period (Week 9 to 12)*	34	4.8 (9.2)	0.0 (0.0–4.5)
Average per 28 days (6–12 years)	Baseline Period	37	2.9 (5.0)	1.0 (0.0–3.9)
	Maintenance Period	37	2.5 (3.9)	0.0 (0.0–4.0)
	Maintenance Period (Week 1 to 4)*	37	3.1 (5.3)	1.0 (0.0–4.0)
	Maintenance Period (Week 5 to 8)*	37	2.5 (5.0)	0.0 (0.0–2.1)
	Maintenance Period (Week 9 to 12)*	37	2.8 (4.8)	1.0 (0.0–3.5)
Average per 28 days (13–18 years)	Baseline Period	37	5.2 (6.1)	2.9 (1.0–8.7)
	Maintenance Period	37	4.8 (5.1)	4.0 (0.0–8.0)
	Maintenance Period (Week 1 to 4)*	37	5.2 (6.1)	3.2 (1.0–8.0)
	Maintenance Period (Week 5 to 8)*	37	4.9 (6.0)	3.0 (1.0–7.0)
	Maintenance Period (Week 9 to 12)*	37	4.9 (5.8)	3.0 (1.0–7.7)

Footnotes: GWPCARE1B and GWPCARE2, Intention-To-Treat Analysis Set, Placebo subjects. *Patients with at least 7 days of seizure data within the period. **Abbreviations:** IQR, interquartile range; SD, standard deviation.

Table 1. Current seizures during the treatment period of the study (placebo-treated patients), by age group and overall

Type of seizure*	2–5 years Number of patients (%) (N=35)	6–12 years Number of patients (%) (N=52)	13–18 years Number of patients (%) (N=37)	Overall Number of patients (%) (N=124)
Hemiclonic	7 (20.0)	6 (11.5)	6 (16.2)	19 (15.3)
Complex partial seizures (focal dyscognitive)	18 (51.4)	25 (48.1)	9 (24.3)	52 (41.9)
Secondarily generalized tonic-clonic	6 (17.1)	8 (15.4)	9 (24.3)	23 (18.5)
Generalized tonic-clonic	30 (85.7)	42 (80.8)	27 (73.0)	99 (79.8)
Absence (any type)	12 (34.3)	22 (42.3)	15 (40.5)	49 (39.5)
Myoclonic	18 (51.4)	26 (50.0)	18 (48.6)	62 (50.0)
Tonic	9 (25.7)	14 (26.9)	8 (21.6)	31 (25.0)
Atonic	10 (28.6)	9 (17.3)	4 (10.8)	23 (18.5)
Clonic	6 (17.1)	9 (17.3)	3 (8.1)	18 (14.5)
Tonic/atonic (cannot differentiate)	3 (8.6)	1 (1.9)	1 (2.7)	5 (4.0)
Infantile spasms (if <3 years of age)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epileptic spasms (if ≥3 years of age)	NR	1 (1.9)	NR	1 (0.8)**
Non-convulsive status (>30 min)	2 (5.7)	5 (9.6)	1 (2.7)	8 (6.5)
Convulsive status (>30 min)	7 (20.0)	8 (15.4)	3 (8.1)	18 (14.5)
Other	1 (2.9)	3 (5.8)	3 (8.1)	7 (5.6)

Footnotes: *Not all patients had every type of seizure; some patients had more than one type of seizure. **Calculated for relevant patient population. **Abbreviations:** NR, not reported.

Table 2. Multivariate stepwise selection log-transformed ANCOVA analysis of convulsive seizure cluster frequency

Parameter	Parameter estimate (log ratio)	95% CI	P-value
Seizure cluster defined as ≥3 convulsive seizures in 24 hours*			
log (baseline seizure clusters per 28 days)	0.838	(0.75, 0.92)	<.0001
Age	0.036	(0.01, 0.06)	0.0027
BMI	-0.029	(-0.05, -0.00)	0.0261

Footnotes: GWPCARE1B and GWPCARE2, Intention-To-Treat Analysis Set. Convulsive seizures include tonic, clonic, tonic-clonic and atonic seizures. *A convulsive seizure cluster was defined as ≥3 convulsive seizures in a 24-hour period. Treatment period was defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit. A value of 1 was added to the seizure cluster frequency for all subjects prior to log-transformation. Log-transformed baseline seizure rate was forced into the model. **Abbreviations:** ANCOVA, analysis of covariance; CI, confidence interval.

CONCLUSIONS

- This study identified a potential link between age, BMI and seizure cluster frequency.
- Our results suggested that seizure cluster frequency is relatively stable during the maintenance period of placebo therapy. Thus, it may be a valuable outcome measure in future trials, particularly given its link to morbidity, reduced quality of life, and premature mortality.
- Further research to assess the natural history of DS, ideally with larger cohorts and objective measures, is needed to confirm our findings.

References

1. Dravet C. The Core Dravet Syndrome Phenotype. Epilepsia. 2011;52(2):3–9 **2.** Ohki T, Watanabe K, Negoro T, et al. Severe Myoclonic Epilepsy in Infancy: Evolution of Seizures, Seizure. 1997;6(219–224) **3.** Baumann K, Devinsky O. Seizure Clusters: Morbidity and Mortality. Front Neurol. 2021;12:636045 **4.** Devinsky O, Cross JH, Wright S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med 2017;377:699–700 **5.** Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS et al. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol 2020;77:613–21.

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