Poster #

Antiseizure Medication Treatment Patterns, Reasons for Disruption, and Side Effects for Patients With Dravet Syndrome or Lennox-Gastaut Syndrome: A Retrospective Analysis of US Physician Notes

Mei Lu[1], Dave Iwanyckyj,[2] Sally W. Wade,[3] Pablo Racana,[2] Fernando Otalora,[2] Satish Rao[1]

[1]Takeda Pharmaceuticals USA, Inc., Lexington, MA, USA; [2]Amplity Health, Langhorne, PA, USA; [3]Wade Outcomes Research and Consulting, Salt Lake City, UT, USA

Scan code to receive PDF file of the poster or visit:
www.shirecongressposters.com/256143

Introduction

- Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are 2 rare epileptic syndromes that manifest with unpredictable, frequent seizures and are associated with a wide range of developmental delays[1,2]
- First-line pharmacological treatments for seizure control include broad-spectrum antiseizure medications (ASMs) such as valproate and clobazam[3,4]
- However, generic broad-spectrum ASMs have failed to provide adequate seizure control, leading to the use of heterogeneous adjunct ASMs in the last decade[3,4]
  - As drug-refractory seizures are a hallmark of both epileptic syndromes, patients frequently receive more than 2 ASMs and may experience a high burden of polypharmacy[3,4]
  - Additional challenges arising from polypharmacy include safety monitoring and drug-drug interactions[1–4,7]
  - Treatment becomes further challenging over the patient's lifetime as their comorbidity burden increases[3]
- Considering the treatment-associated challenges in epileptic encephalopathies, there is a need to better characterize current ASM use and related safety concerns

Objective

- To describe real-world treatment patterns for patients with DS or LGS including ASM use (frequency and reasons for ASM treatment disruptions, side effects, and safety monitoring) and non-ASM use

Methods

- This retrospective, qualitative database analysis used Amplity Insights' inpatient and outpatient electronic, unstructured medical transcription records of routine care in the United States (US) from January 2010 to January 2022
- The database included approximately 55 million records from interactions of approximately 25 million patients with 150,000 multispecialty physicians
- Natural language processing (NLP) technology retrospectively analyzed the transcription records in the database to identify patients with confirmed DS or LGS, based on symptoms and/or genetic or electroencephalography findings, and treatment with ≥ 1 ASM
- Patient-level characteristics, ASM use, treatment disruptions, side effects, safety monitoring, and non-ASM therapies are described here

Results

Patient demographics

- A total of 166 patients with DS and 1063 patients with LGS who had received ≥ 1 ASM were identified
- Demographics and patient characteristics are shown in **Table 1**
- Among patients with recorded data at the time of the first captured visit (DS: n = 121; LGS: n = 877):
  - The DS group had higher proportion of pediatric patients (aged < 18 years) compared with the LGS group (83% vs 42%, respectively)
  - The LGS group had a higher proportion of adult patients (aged ≥ 18 years) compared with the DS group (58% vs 17%, respectively)
- Among those with recorded data, patients with DS had a younger mean age at diagnosis (1.1 years) versus patients with LGS (2.1 years)
- Patients with recorded data were predominantly White (DS: 95%; LGS: 90%)

Table 1. Demographics and Characteristics of Patients With DS or LGS

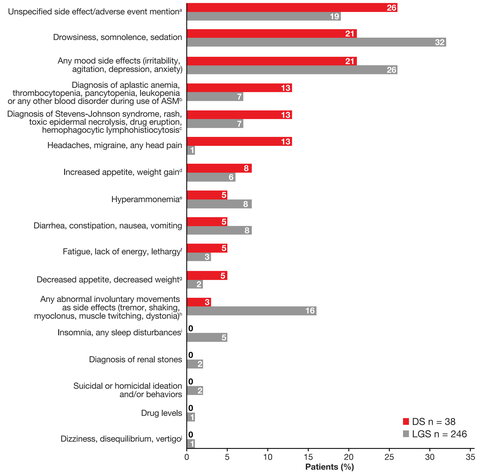
Characteristics	DS	LGS
Total patients, n	166	1063
Age at first visit[a], n	121	877
Mean (median) years	12 (9)	24 (20)
Pediatric (aged 0–17 years), n (%)	101 (83)	370 (42)
Adult (aged 18+ years), n (%)	20 (17)	507 (58)
Age at diagnosis, n	9	53
Mean (median) years	1.1 (0.3)	2.1 (0.9)
Age at diagnosis, min–max years	0.2–6.0	0.2–8.0
Sex, n	162	1050
Female, n (%)	76 (47)	397 (38)
Male, n (%)	86 (53)	653 (62)
Race or ethnicity, n	39	338
White, n (%)	37 (95)	303 (90)
African American or Black, n (%)	1 (3)	25 (7)
Hispanic, n (%)	1 (3)	10 (3)
Asian, n (%)	0 (0)	0 (0)
Other, n (%)	0 (0)	0 (0)
US Census region[b], n	164	1001
South, n (%)	75 (46)	436 (44)
Northeast, n (%)	56 (34)	256 (26)
West, n (%)	29 (18)	190 (19)
Midwest, n (%)	15 (9)	181 (18)
Top 3 specialties of healthcare providers, n	166	1063
Primary care, n (%)	71 (43)	349 (33)
Pediatrics, n (%)	47 (28)	140 (13)
Neurology or epileptology, n (%)	29 (17)	262 (25)

[a]Oldest age given if age is reported on multiple records for a patient in study database. [b]Region where provider is located.
DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; min, minimum; max, maximum; US, United States.

Frequently used ASMs and their safety profile

- Combination ASM therapy was recorded by 67% of patients with DS and 58% of patients with LGS
  - ASMs such as clobazam (DS: 54%; LGS: 49%) and levetiracetam (DS: 53%; LGS: 47%) were used by nearly half of the patients in both disease groups
  - Valproic acid/divalproex was used by 58% of patients with DS and 40% of patients with LGS
  - Other medications used by 20%–40% of patients
    - DS: diazepam (41%, rectal and oral formulations), cannabidiol (35%), topiramate (29%), clonazepam (27%), lorazepam (27%), phenobarbital (26%), midazolam (23%), and zonisamide (23%)
    - LGS: lamotrigine (33%), diazepam (30%, rectal and oral formulations), clonazepam (28%), lorazepam (27%), cannabidiol (26%), lacosamide (25%), rufinamide (22%), topiramate (20%), and zonisamide (20%)
- Rescue medications
  - Up to 58% of patients with DS and 51% of patients with LGS received rescue ASMs such as diazepam, lorazepam, or midazolam
- Side effects
  - Side effects or adverse events were reported by 38 (23%) and 246 (23%) patients with DS or LGS, respectively
  - The most common side effects included (**Figure 1**):
    - Drowsiness, somnolence, sedation: DS: 21%; LGS: 32%
    - Any mood side effects (irritability, agitation, depression, anxiety): DS: 21%; LGS: 26%
    - Unspecified side effects/generic mentions (eg, ASM-caused side effects): DS: 26%; LGS: 19%
    - Any abnormal involuntary movements (tremor, shaking, myoclonus, muscle twitching): DS: 3%; LGS: 16%
    - Aplastic anemia, thrombocytopenia, pancytopenia, leukopenia or any other blood disorder: DS: 13%; LGS: 7%

Figure 1. Side Effects in Patients With DS or LGS Treated With ASMs

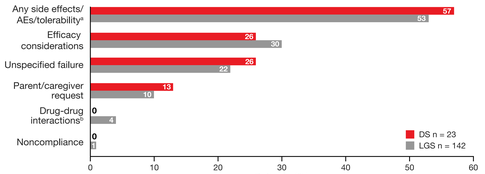


[a]Generic mentions such as "experienced adverse event," "antiseizure medication (ASM) caused side effects," "could not tolerate ASM" etc. [b]Includes thrombocytopenia, leukopenia, pancytopenia, hyperanemia. [c]Includes rash, skin rash, pruritis, dermatitis. [d]Includes mention of terms such as increase/gain/more weight, appetite, hunger, and hungry. [e]Includes elevated/high ammonia. [f]Includes mention of terms such as fatigue, lack of/no energy, lethargy, tired(ness), and listlessness. [g]Includes mention of terms such as decrease/loss/lack of weight, appetite, hunger, and hungry. [h]Includes infantile spasms, tremors, myoclonus, hypsarrhythmia, West syndrome, paroxysmal, kinesigenic dyskinesia syndrome, myoclonic jerks, facial twitching. [i]Includes insomnia and terms related to sleep, including optional qualifying terms such as falling, getting to, apnea, trouble, issue, inability, problem, difficulty, deprivation, delay, deferred, late-onset etc. Also includes terms related to waking/awakening such as early, frequent etc. [j]Includes the terms dizzy, dizziness, disequilibrium, vertigo, lightheaded, and orthostasis.
DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

Treatment disruptions and reasons for treatment disruption

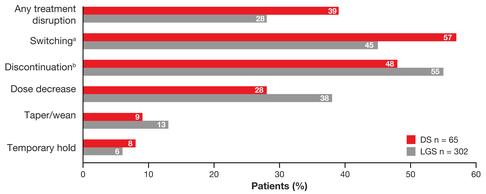
- Overall, 65 patients (39%) with DS and 302 patients (28%) with LGS had at least 1 ASM treatment disruption
  - Of those treatment disruptions with a known reason (DS: n = 23; LGS: n = 142), the most common among patients with DS or LGS was side effects/tolerability (DS: 57%; LGS: 53%) (**Figure 2**)
- In particular, treatment disruptions (**Figure 3**) among patients with DS or LGS were broadly categorized into:
  - Discontinuation (DS: 48%; LGS: 55%)
  - Switching (DS: 57%; LGS: 45%)
  - Dose decreasing (DS: 28%; LGS: 38%)
  - Tapering/weaning (DS: 9%; LGS: 13%)

Figure 3. Treatment Disruptions by Type in Patients With DS or LGS Treated With ASMs



[a]Side effects/adverse effects include all specific symptoms/event in the following list plus any mention of side effects or adverse events without further specification: decreased appetite, decreased weight; increased appetite, weight gain; drowsiness, somnolence, sedation; insomnia, any sleep disturbances; dizziness, disequilibrium, vertigo; diarrhea, constipation, nausea, vomiting; fatigue, lack of energy, lethargy; headaches, migraine, any head pain; blurred vision, double vision, any vision symptoms; swollen gums, changes in gums; hair loss or excessive growth (hirsutism); dyscoordination, ataxia; diagnosis of Stevens-Johnson syndrome, rash, toxic epidermal necrolysis, drug eruption, hemophagocytic lymphohistiocytosis; any mood effects (irritability, agitation, depression, anxiety); suicidal or homicidal ideation and/or behaviors; any abnormal involuntary movements as side effects (tremor, shaking, myoclonus, muscle twitching, dystonia); diagnosis of serotonin syndrome; diagnosis of renal stones; diagnosis of any ocular disorder during ASM use (glaucoma, cataracts, vision loss etc.); diagnosis of aplastic anemia, thrombocytopenia, pancytopenia, leukopenia or any other blood disorder during use of ASM; drug levels; hyperammonemia; lung infection; and any symptom ascribed to ASM use. [b]Includes any drug-drug interactions between ASMs or between ASMs and non-ASMs recorded in the transcriptions, such as fenfluramine needs dose adjustment with stiripentol plus clobazam, caution with serotonergic drugs (ie, serotonin syndrome) or cannabidiol has significant drug-drug interactions with multiple antiseizure and other medications.
AE, adverse event; ASM, antiseizure medication; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

Figure 2. Reasons for Treatment Disruptions in Patients With DS or LGS Treated With ASMs



[a]Switching is defined as the mention of switching from one treatment to another, including symptoms for this action. [b]Discontinuation is defined as mention of discontinuation or other synonyms for stopping a given treatment.
ASM, antiseizure medication; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

Safety and clinical monitoring

- Over half of the patient population with DS or LGS had their blood pressure monitored (DS: 55%; LGS: 56%)
  - Weight checks were conducted in 43% of patients with DS and 33% of patients with LGS
- A similar percentage of patients (DS: 41%; LGS: 40%) in both disease groups reported getting blood-based labs (including liver function tests, complete blood count, and comprehensive metabolic panel)
- ASM drug-level checks were mentioned for 17% of patients with DS and 13% of patients with LGS
- Electroencephalogram (EEG, any type: DS: 47%; LGS: 46%) and radiologic testing (CT, MRI, PET: DS: 33%; LGS: 37%) were the most noted clinical monitoring activities
- Genetic testing was performed on 31% and 11% of patients with DS and LGS, respectively

Non-ASM treatments

- Dietary therapy was most commonly reported (DS: 23%; LGS: 16%), with frequent use of the keto diet (DS: 20%; LGS: 14%)
- Other therapies like occupational, physical, or speech to address developmental delays were used by 16% of patients with DS and 14% of patients with LGS
- Many patients (DS: 10%; LGS: 17%) indicated use of an antipsychotic, antidepressant, or anxiolytic medication for mental health concerns
- Surgical interventions were reported by 1% and 8% of patients with DS or LGS, respectively

Limitations

- Owing to the lack of longitudinal follow-up of the transcription records, there is a possibility of not fully understanding the patient's evolving treatment pattern and medical conditions related to ASM use (such as time to therapy initiation or discontinuation, if and when a new drug was added)
- Under-reporting of ASM/non-ASM and ASM treatment disruptions are possible due to the limited sensitivity of search terms used for NLP queries and/or limited documentation in the transcription notes

Conclusions

- Current treatment options for refractory epileptic conditions DS or LGS with broad-spectrum ASMs, adjunct ASMs, dietary therapies, and surgery, are limited by inadequate seizure control, tolerability, and safety
- Using NLP, this real-world study suggests that patients may benefit from more effective and tolerable ASMs

Disclosures

ML and **SR** are employees of Takeda Pharmaceuticals USA, Inc., and are Takeda shareholders. **DI, PR,** and **FO** are employees of Amplity Health. **SWW** is a partner in Wade Outcomes Research and Consulting, and a consultant to Amplity Health.

Acknowledgments

This research was sponsored by Takeda Pharmaceuticals USA, Inc. Under the direction of the authors, medical writing services were provided by Sangeeta Chakraborty, PhD, of Oxford PharmaGenesis Inc., and were funded by Takeda Pharmaceuticals USA, Inc.

References

1. Anwar A, et al. *Cureus*. 2019;11(6):e5006.
2. Lazaridis D, et al. *PT*. 2019;44(5):255–256.
3. Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2021;35:61–83.
4. Strzelczyk A, Schubert-Bast S. *CNS Drugs*. 2022;36:217–237.
5. Jahngir UM, et al. *Cureus*. 2018;10(8):e3134.
6. Chin RF, et al. *Front Neurol*. 2021;12:734612.
7. Asadi-Pooya A. *Neurol Sci*. 2017;39:403–414.

Content for a healthcare professional audience only

Presented at: American Epilepsy Society (AES) Annual Meeting 2023, Orlando, FL, December 1–5, 2023.