A Retrospective Claims Study Evaluating Mortality in Patients With Lennox-Gastaut or Dravet Syndromes in the United States

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Introduction

- Lennox-Gastaut (LGS) and Dravet syndromes (DS) are rare developmental and epileptic encephalopathies characterized by treatment-resistant seizures and cognitive impairment
- A recent systematic literature review showed that fatality rates in LGS have ranged from 4%-35.3%, with varying cohort sizes and follow-up times; in DS, fatality rates have ranged from 4%-20.8%[1]
- Sudden unexpected death in epilepsy (SUDEP) accounts for 17%-63% of deaths in DS; SUDEP-related mortality data in LGS are limited[1]
- Claims-based mortality studies of large populations of patients with LGS and DS are scarce

Objective

- Here, we used real-world claims data and mortality data from October 01, 2015, to December 31, 2023, to analyze yearly all-cause fatality rates, suspected SUDEP-related fatality rates, and comorbidities associated with mortality for patients with LGS or DS in the US

Methods

- This retrospective claims-based analysis identified patients in the US diagnosed with LGS or DS from October 01, 2015, to December 31, 2023, using the Real Chemistry open claims database, and further classified as living or deceased if present in the Veritas mortality dataset
- Patients were included if they had ≥2 LGS claims (ICD-10: G40.81, G40.811, G40.812, G40.813, and G40.814) or ≥2 DS claims (ICD-10: G40.83, G40.833, G40.834) in the study period; patients with a mortality event were required to have a date of death (DOD) after October 01, 2015, and ≤60 days from their last claim to date of death
  - Because data from 2015-2018 were scarce, and DS ICD-10 codes were not in use until 2020, DS endpoints were analyzed from 2019-2023
- Outcomes in pediatric (<18 years old) and adult (≥18 years old) patients with LGS and DS included annual all-cause case fatality rates (primary), comorbidities in patients with vs. without a mortality event, and SUDEP-related fatality rates
- SUDEP was suspected if no non-SUDEP cause of death related claim was observed in the database within ±60 days of DOD
  - Non-SUDEP causes of death included brain swelling, coagulation defect, coma, COPD, COVID, CV, dementia, gastrointestinal hemorrhage, heart attack, hospice, infection (kidney, liver), neutropenia, other metabolic disorders, pneumonia, respiratory, respiratory failure, sepsis, severe malnutrition, shock, sleep apnea, and stroke
- Annual fatality rates were adjusted to account for incomplete patient capture in claims and mortality datasets
- Standardized mortality ratios (SMRs) and 95% confidence intervals for comorbidities were also reported
  - SMRs compare all-cause fatality rates to the US general population from 2016-2022 for LGS and 2020-2022 for DS

Results

- In total, 29,626 unique patients with LGS and 2259 patients with DS were included; of those, 2509 (8.5%) and 52 (2.3%) had a DOD during the study period (**Table 1**)

Table 1. Patient Characteristics and Payer Channel

	Lennox-Gastaut syndrome		Dravet syndrome	
	Deceased n=2509	Living n=27,117	Deceased n=52	Living n=2207
Median age[a] (IQR), years	22 (34)	16 (18)	10 (18)	10 (12)
Male sex, n (%)	1420 (57)	15,293 (56)	28 (54)	1140 (52)
Payer channel, n (%)				
Medicaid	728 (29)	8775 (32)	16 (31)	715 (32)
Commercial	574 (23)	7650 (28)	20 (38)	844 (38)
Medicare	511 (20)	3010 (11)	5 (10)	70 (3)
Other	141 (6)	1736 (6)	5 (10)	175 (8)

[a]Age at first Lennox-Gastaut or Dravet syndrome claim during study period.
IQR, interquartile range.

Overview

QUESTION

- What are the current real-world annual all-cause Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) all-cause and sudden unexpected death in epilepsy (SUDEP)-related case fatality rates?
- What comorbidities are associated with higher mortality in patients with LGS and DS?

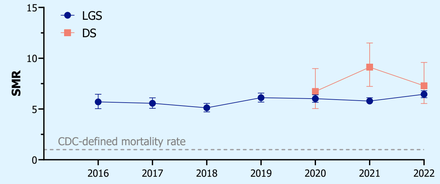
INVESTIGATION

- Using real-world data from Real Chemistry's open claims database and Veritas' mortality database, we examined case fatality rates, standardized mortality ratios (SMRs), and comorbidities associated with mortality in pediatric and adult patients with LGS or DS from October 01, 2015, to December 31, 2023

RESULTS

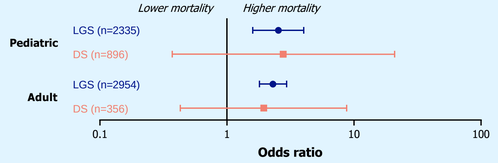
- In total, 29,626 unique patients with LGS and 2259 patients with DS were included; of those, 2509 (8.5%) and 52 (2.3%) had a verified date of death
- The LGS SMR from 2016-2022 ranged from 5.12 (95% CI: 4.72-5.55) to 6.45 (95% CI: 6.11-6.80) times higher than the average person (**Figure A**)
- The DS SMR from 2020-2022 ranged from 6.73 (95% CI: 5.04-8.98) to 9.12 (95% CI: 7.22-11.50) times higher than an average person (**Figure A**)
- Of comorbidities associated with mortality, cardiovascular and respiratory complications were significant in pediatric (Z score, 3.98) and adult patients (Z score, 6.66) with LGS (**Figure B**)

Figure A. Standardized Mortality Ratio in Patients With LGS or DS by Year



Error bars represent 95% confidence intervals.
CDC, Center for Disease Control; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; SMR, standardized mortality ratio.

Figure B. Higher Mortality Rate Associated With Cardiovascular and Respiratory Complications in Pediatric and Adult Patients With LGS (From 2021-2023) and DS (From 2019-2023)



Error bars represent 95% confidence intervals.
DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

CONCLUSIONS

- SMR data show higher mortality in LGS and DS compared with the general population
- An analysis of the association between comorbidities and mortality suggested that cardiovascular and respiratory complications were significant in LGS

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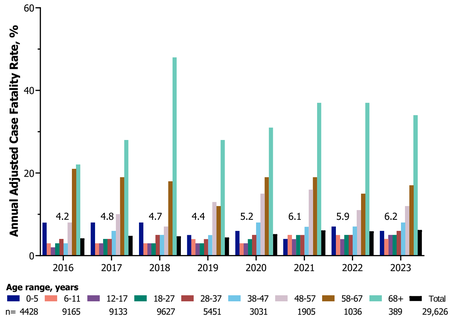
LENNOX-GASTAUT SYNDROME

- The yearly adjusted all-cause case fatality rate for LGS ranged from 4.2% to 6.2% from 2016 to 2023 (**Figure 1**)
  - The suspected SUDEP-related rate for LGS ranged from 1%-2%

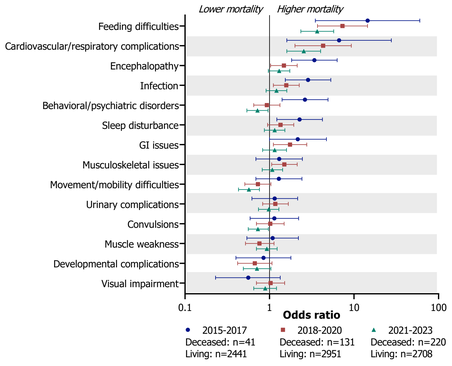
Figure 1. Annual Adjusted LGS All-Cause Case Fatality Rate by Age Group



Numbers on figure indicate total adjusted all-cause case fatality rates per year.
Patient n's are not mutually exclusive; a patient may be included in multiple age ranges over the course of the study.
LGS, Lennox-Gastaut syndrome.

- In pediatric patients with LGS, feeding difficulties and cardiovascular/respiratory complications were most significantly associated with mortality at each 3-year interval examined (**Figure 2**)
  - From 2015-2017, encephalopathy, infection, behavioral/psychiatric disorders, and sleep disturbances were significantly associated with mortality

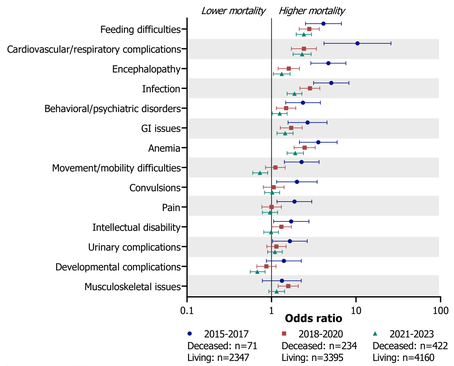
Figure 2. Most Common Comorbidities and Their Association With Mortality in Pediatric Patients With LGS



Error bars represent 95% confidence intervals. A patient may be included in multiple comorbidity groupings.
GI, gastrointestinal; LGS, Lennox-Gastaut syndrome.

- In adult patients with LGS, feeding difficulties, cardiovascular/respiratory complications, encephalopathy, infection, behavioral/psychiatric disorders, GI issues, and anemia were significantly associated with mortality at each 3-year interval examined (**Figure 3**)
  - From 2015-2017, movement/mobility difficulties, convulsions, pain, intellectual disability, and urinary complications were significantly associated with mortality

Figure 3. Most Common Comorbidities and Their Association With Mortality in Adult Patients With LGS

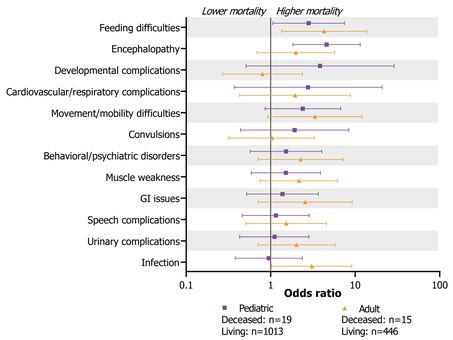


Error bars represent 95% confidence intervals. A patient may be included in multiple comorbidity groupings.
GI, gastrointestinal; LGS, Lennox-Gastaut syndrome.

DRAVET SYNDROME

- In patients with DS, the 5-year adjusted all-cause case fatality rate was 8.6% from 2019-2023, with pediatric and adult fatality rates of 6.6% and 11.6%, respectively
  - The suspected SUDEP-related rate for DS was 2.1%
- From 2019-2023, feeding difficulties were most significantly associated with mortality in pediatric and adult patients with DS (**Figure 4**)
  - In pediatric patients, encephalopathy was also significantly associated with mortality

Figure 4. Most Common Comorbidities and Their Association With Mortality in Pediatric and Adult Patients With DS From 2019-2023



Error bars represent 95% confidence intervals. A patient may be included in multiple comorbidity groupings.
DS, Dravet syndrome; GI, gastrointestinal.

Limitations

- This study was limited by data capture within the database, which required the use of ICD-10 codes
  - This included DS ICD-10 codes that were not in use until 2020
- Coding based on ICD-10 codes for LGS and DS likely has high positive predictive value, but many patients with LGS or DS are coded with more general epilepsy or seizure-related codes
  - Therefore, this represents a high certainty subset of a likely broader population
- SUDEP-related deaths were determined based on listed ICD-10 codes and causes of death, which are related to but differ from the certainty criteria for SUDEP

Conclusions

- Overall, this study shows that all-cause fatality rates in children and adults with LGS or DS are high
- Mortality in pediatric patients with LGS peaks early in life, and again at 48 years and older
- In DS, 5-year fatality rates for adults were higher than for pediatric patients
- Feeding difficulties were associated with mortality at any age in both LGS and DS, whereas cardiovascular and respiratory complications were significantly associated with mortality in LGS only
- Future studies will examine healthcare resource utilization and antiseizure medication use and their association with mortality

References
1. Sullivan J, et al. *Epilepsia*. 2024 May;65(5):1240-1263.

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