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Real-World Polypharmacy and Healthcare Resource Utilization After Early-Line Treatment With Cannabidiol for Lennox-Gastaut Syndrome, Dravet Syndrome, and Tuberous Sclerosis Complex

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Introduction

- Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC) are developmental and epileptic encephalopathies characterized by treatment-resistant epilepsy[1–5]
- A plant-derived, highly purified pharmaceutical formulation of cannabidiol (CBD; Epidiolex®, 100 mg/mL oral solution) is approved in the US for the treatment of seizures associated with DS, LGS, or TSC in patients aged ≥1 year, with efficacy and safety supported by evidence from 5 randomized clinical trials (RCTs)[2–7]
- Individuals with DS, LGS, or TSC who participated in the phase 3 RCTs of CBD were taking a median of 3 antiseizure medications (ASMs) at baseline and had previously discontinued a median of 4–6 ASMs[2–6]
- The effectiveness of CBD when initiated as an early line of therapy has not been well characterized

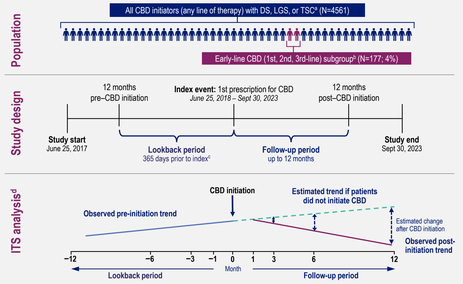
Objective

- To evaluate polypharmacy burden and healthcare resource utilization (HCRU) as surrogate markers of effectiveness in a retrospective cohort study of patients with DS, LGS, or TSC who initiated CBD treatment, including a subset for whom CBD was prescribed as an early-line (first-, second-, or third-line) ASM

Methods

- The US Optum® Market Clarity integrated electronic health record (EHR) and claims database was analyzed, and individuals who met the following criteria were included (**Figure 1**):
  - Initiated CBD use between June 25, 2018, and September 30, 2023, with no documented use in the 12-month lookback period
  - Had a medical record consistent with DS, LGS, or TSC
  - If age ≥1 year at time of initial CBD prescription: ≥365 days of EHR data prior to initial CBD dispensing date (based on earliest EHR activity) with no single gap in activity >180 days
  - If age <1 year at time of initial CBD prescription: no single gap in activity >180 days
  - Had not received another US Food and Drug Administration–approved cannabinoid product (dronabinol, nabilone) during the 12-month lookback period
- Among all included patients, the early-line subgroup was defined as those who initiated CBD as a first, second, or third line of therapy
- The lookback period was defined as the 12 months before CBD initiation (index event), and follow-up was ≤12 months after initiation
- Interrupted time series (ITS) analyses assessed changes in polypharmacy burden (number of concomitant ASMs or anxiolytic, antidepressant, or antipsychotic medications per patient per month [PPPM]) and HCRU (medical claims or records of physician office visits, seizure-related hospitalizations, or emergency department visits, PPPM) before and after CBD initiation
- Reductions in polypharmacy burden and HCRU relative to the trend prior to CBD initiation (lookback period) are reported overall and for the early-line CBD subgroup
- This study included patients prescribed Epidiolex®, and results do not apply to other CBD-containing products

Figure 1. Study schema



[a]Medical record with ≥1 of the following ICD-10-CM diagnosis codes consistent with DS, LGS, or TSC: C71*, F44.5, F70, F71, F72, F73, F78, F79, F80*, F81*, F82*, F84*, F88, F89, G04*, G09*, G11*, G12*, G20, G21*, G22*, G25*, G30*, G31*, G32.81, G35, G40*, G45.9, G80.9, G81.1, G91.2, G92, G93.1, G93.2, G93.5, G93.8, G93.7, G94, Q85.0, I63.50, I67.848, P90, Q01*, Q02, Q03*, Q04.1, Q04.2, Q04.3, Q04.5, Q04.8, Q05*, Q85.1, Q90*, R41.83, and R55*. [b]Treatment with CBD as the first, second, or third ASM following a 365-day lookback period with no ASM use. If a patient initiated CBD at the same time as another maintenance ASM (combination therapy), CBD was considered the earlier line of therapy between the 2 ASMs. [c]For patients ≥1 year of age. If <1 year of age at initial ASM or CBD dispensing date, all available data prior to dispensing date were used. [d]ITS analysis is a method to assess the effects of an intervention ("interruption," such as CBD initiation) by comparing data at multiple time points (a time series) before and after the interruption.

ASM, antiseizure medication; CBD, cannabidiol; DS, Dravet syndrome; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; ITS, interrupted time series; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

Results

Table 1. Baseline demographics of all patients with DS, LGS, or TSC who initiated CBD[a] and the early-line CBD subgroup

Characteristic	All CBD N=4561	Early-line CBD subgroup N=177
Sex, male, n (%)	2522 (55)	98 (55)
Age, median (Q1, Q3), years	13.0 (7.0, 22.0)	4.0 (1.0, 12.0)
Age at baseline, years, n (%)		
<1	42 (1)	34 (19)
1	115 (3)	16 (9)
2–5	731 (16)	48 (27)
6–12	1268 (28)	35 (20)
13–17	781 (17)	16 (9)
18–49	1551 (34)	27 (15)
50–64	68 (2)	1 (1)
≥65	5 (<1)	0 (0)
Epilepsy type, n (%)		
DS	1830 (40)	123 (70)
LGS	2450 (54)	49 (28)
TSC	281 (6)	5 (3)
Insurance type, n (%)		
Commercial	1492 (33)	79 (45)
Medicaid	1689 (37)	59 (33)
Medicare	188 (4)	5 (3)
Unknown	32 (1)	5 (3)
Missing	1160 (25)	29 (16)
Race/ethnicity, n (%)		
Hispanic or Latino	482 (11)	19 (11)
Non-Hispanic Black	291 (6)	15 (9)
Non-Hispanic White	2448 (54)	82 (46)
Other race/ethnicity	84 (2)	3 (2)
Unknown race/ethnicity	1256 (28)	58 (33)
Geographic region, n (%)		
Midwest	1770 (39)	75 (42)
Northeast	859 (19)	27 (15)
South	1261 (28)	46 (26)
West	456 (10)	23 (13)
Unknown region	215 (5)	6 (3)

[a]CBD initiators were defined as having no record of CBD use in the 12-month lookback period prior to index date.

CBD, cannabidiol; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; Q1, first quartile; Q3, third quartile; TSC, tuberous sclerosis complex.

- In total, 4561 patients were identified, of whom 177 (4%) initiated CBD as an early-line therapy (**Table 1**)
- The overall group and the early-line subgroup had a similar sex distribution, racial/ethnic diversity, and geographic location
- The early-line subgroup was **younger**, and included a **higher proportion of patients with DS**, and a **higher proportion with commercial insurance**

Table 2. Baseline comorbidities, maintenance ASM, anxiolytic, antidepressant, antipsychotic, and rescue medication use

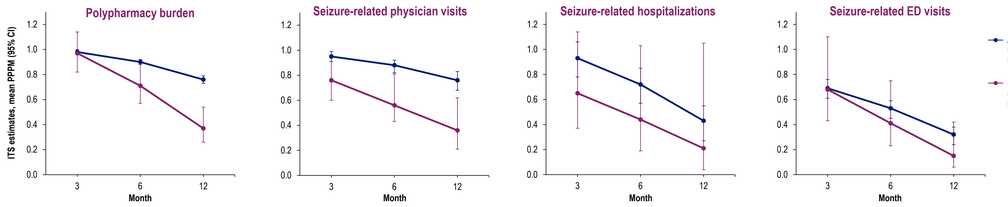
Characteristic	All CBD N=4561	Early-line CBD subgroup N=177
Baseline comorbidities,[a] n (%)		
ADD/ADHD	663 (15)	19 (11)
Allergies	1036 (23)	32 (18)
Anxiety/depression	486 (11)	12 (7)
Autism	1448 (32)	37 (21)
CVD[b]	283 (6)	9 (5)
Diabetes mellitus (type 1 or 2)	86 (2)	2 (1)
Fractures	164 (4)	4 (2)
Hyperlipidemia	214 (5)	4 (2)
Hypertension	271 (6)	8 (5)
Insomnia	371 (8)	9 (5)
Intellectual disability/developmental delay	2734 (60)	91 (51)
Migraine	119 (3)	3 (2)
Neoplasia	385 (8)	12 (7)
Obesity	320 (7)	4 (2)
Respiratory disease	786 (17)	17 (10)
Maintenance ASM use, n (%)		
Calcium channel blockers	227 (5)	3 (2)
Cenobamate	28 (1)	1 (1)
Clobazam	2203 (48)	41 (23)
Clonazepam (excluding ODT)	808 (18)	6 (3)
Everolimus	66 (1)	0 (0)
Fenfluramine	15 (<1)	0 (0)
GABAergic activity, other[c]	576 (13)	14 (8)
Multiple targets (excluding cenobamate)[d]	1577 (35)	14 (8)
Sodium channel blockers	2324 (51)	26 (15)
Synaptic vesicle protein 2A modulators	1894 (42)	64 (36)
Valproate, valproic acid, or divalproex sodium	1320 (29)	17 (10)
Other ASMs[e]	443 (10)	2 (1)
Anxiolytic, antidepressant, or antipsychotic medication use, n (%)		
Antipsychotics	349 (8)	1 (1)
Barbiturates	322 (7)	1 (1)
Non-ASM benzodiazepines	1039 (23)	8 (5)
Nonbenzodiazepines	50 (1)	0 (0)
Selective serotonin reuptake inhibitors	303 (7)	2 (1)
Serotonin and norepinephrine reuptake inhibitors	31 (1)	0 (0)
Serotonin antagonist and reuptake inhibitors	144 (3)	1 (1)
Tricyclic antidepressants	68 (2)	0 (0)
Rescue medication use, n (%)		
Clonazepam (ODT)	684 (15)	2 (1)
Diazepam (nasal formulation)	235 (5)	3 (2)
Diazepam (rectal gel)	1266 (28)	13 (7)
Lorazepam (sublingual)	538 (12)	5 (3)
Midazolam (nasal formulation)	166 (4)	0 (0)

Percentage of patients in cohort: 0 ≥50% 0 ≥50%

[a]Baseline comorbidities were assessed in the 365 days prior to and including index (lookback period). [b]CVD includes atherosclerotic CVD, ischemic heart disease, peripheral vascular disease, and cerebrovascular disease. [c]GABAergic activity, other includes phenobarbital, vigabatrin, tiagabine. [d]Multiple targets include felbamate, topiramate, zonisamide, and primidone. [e]Other ASMs include acetazolamide, ACTH, ezogabine, perampanel, and stiripentol. ACTH, adrenocorticotropic hormone; ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; ASM, antiseizure medication; CBD, cannabidiol; CVD, cardiovascular disease; GABA, gamma-aminobutyric acid; ODT, orally disintegrating tablet.

- Compared with all patients, the early-line subgroup had lower rates of comorbidities and use of other medications (**Table 2**)
  - Autism, intellectual disability, and allergy were the most prevalent comorbidities in both groups; obesity, hyperlipidemia, and respiratory disease had the greatest percentage differences between the groups

Figure 2. After CBD initiation, trends[a] in polypharmacy burden[b] and seizure-related HCRU[c] decreased over time relative to the pre-initiation trends in both the early-line subgroup and the overall population

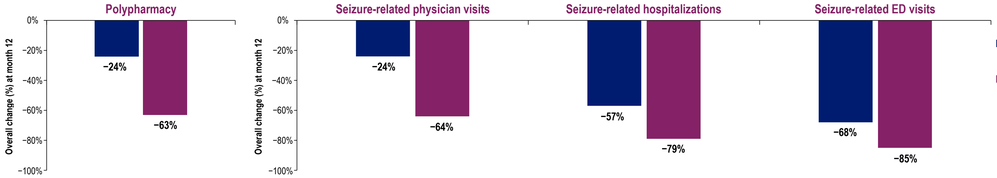


[a]Estimates are difference/ratios modeled from ITS analysis and presented relative to the pre–CBD initiation trends (expected trajectory if CBD had not been initiated among the same patients). ITS estimates shown are exponentiated values from log scale values from ITS model estimates. [b]Polypharmacy burden included concomitant maintenance ASMs and antipsychotic, antidepressant, or anxiolytic medications listed in **Table 2**. Medication use was assessed in the 365 days prior to and at index. CBD was not included as a medication in the polypharmacy count. [c]Seizure-related medical claims or records of hospitalization, ED visits, or physician office visits with a diagnosis code for a seizure, ie, ICD-10-CM G40*, P90, Q85.1, or R56*.

ASM, antiseizure medication; CBD, cannabidiol; ED, emergency department; HCRU, healthcare resource utilization; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; ITS, interrupted time series; PPPM, per patient per month.

- A greater reduction in polypharmacy burden at 12 months was observed in the early-line subgroup relative to the overall population (relative ratio estimate [95% CI], 0.37 [0.26, 0.54] vs 0.76 [0.73, 0.79]) (**Figure 2**)
- A greater reduction in seizure-related physician visits at 12 months was observed in the early-line subgroup relative to the overall population (relative ratio estimate [95% CI], 0.36 [0.21, 0.62] vs 0.76 [0.69, 0.84]) (**Figure 2**)

Figure 3. At 12 months post–CBD initiation[a], reductions were seen in polypharmacy burden and seizure-related HCRU[b,c] relative to the pre-initiation trends in both the early-line subgroup and the overall population



[a]Estimates are modeled from ITS analysis and presented relative to the pre–CBD initiation trends (expected trajectory if CBD had not been initiated among the same patients). Differences between the observed and the predicted post-initiation values are expressed on the log (LN) scale. Estimates are exponentiated LN values. When exponentiated, a difference on the LN scale is a relative change corresponding to the ratio of observed post-initiation values to estimates. From this ratio of exponentials, overall change is calculated as 1 (null) − exponentiated difference/ratio estimate (**Figure 2**) × 100 = (%). Exponentiated percent change value estimates and 95% CIs are shown in **Figure 2**. [b]Mean PPPM. [c]Negative values indicate reductions from pre–CBD initiation to post–CBD initiation.

CBD, cannabidiol; ED, emergency department; HCRU, healthcare resource utilization; ITS, interrupted time series; LN, natural logarithm; PPPM, per patient per month.

- There were greater reductions in polypharmacy and seizure-related physician visits in the early-line cohort (−63% and −64%, respectively) relative to the overall population (both −24%) (**Figure 3**)

Limitations

- The small sample size in the early-line subgroup and differences in baseline characteristics between the early-line subgroup and overall population may limit interpretation of these results
- ITS analyses may not be reflective of real-world patterns because they are projections based on historical trends assuming all else is equal
- Findings may have limited generalizability beyond the insured US populations represented in the database; however, the use of a large, longitudinal integrated claims and EHR dataset with standardized coding supports strong internal validity and minimizes selection bias
- Differences in coding practices and potential errors in diagnostic coding could have impacted the included patient population

Conclusions

- Among patients with DS, LGS, or TSC who initiated CBD treatment, we observed decreases in polypharmacy burden and HCRU compared with trends before initiating CBD
- In the early-line CBD subgroup, further reductions in polypharmacy burden and physician office visits were observed
- Decreased polypharmacy burden and seizure-related HCRU suggest CBD is effective across all lines of therapy, regardless of when initiated, with potentially greater benefit associated with earlier line use

References: **1.** Raga S, et al. *Epileptic Disord.* 2021;23(1):40–52. **2.** Devinsky O, et al. *N Engl J Med.* 2017;376:2011–2020. **3.** Devinsky O, et al. *N Engl J Med.* 2018;378:1888–1897. **4.** Thiele EA, et al. *Lancet.* 2018;391:1085–1096. **5.** Miller I, et al. *JAMA Neurol.* 2020;77:613–621. **6.** Thiele EA, et al. *JAMA Neurol.* 2021;78:285–292. **7.** US Food and Drug Administration. Epidiolex® Prescribing Information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210365s023lbl.pdf. Accessed October 1, 2025.

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Epidiolex® is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.

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