P495

Effect of Cannabidiol on Antiseizure Medication Cycling, Polypharmacy, and Healthcare Resource Utilisation in Patients With Dravet Syndrome, Lennox-Gastaut Syndrome, or Tuberous Sclerosis Complex: Real-World Data from a US Claims Analysis

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Introduction

- Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC) are all associated with treatment-resistant seizures that often begin in early childhood and persist into adulthood, along with substantial neurodevelopmental deficits[1–4]
- Inadequate seizure control, side effects, or drug interactions frequently result in antiseizure medication (ASM) cycling (switching or adding ASMs), polypharmacy, and increased healthcare resource utilisation (HCRU)[5–7]
- In the EU and UK, cannabidiol (CBD; Epidyolex® [EU], 100 mg/mL oral solution) is approved for use as adjunctive therapy of seizures associated with TSC in patients aged ≥2 years, or in conjunction with clobazam (CLB) for patients aged ≥2 years with DS or LGS[8,9]
- Real-world data on the impact of CBD on ASM cycling, polypharmacy burden, and HCRU remain limited

Objective

- To evaluate the effectiveness of CBD in patients with DS, LGS, or TSC in terms of ASM cycling, polypharmacy, and HCRU
- This specific analysis was in patients aged ≥2 years, newly receiving CBD and, for those with DS and LGS, in patients who had received CLB within 12 months of CBD initiation[9]

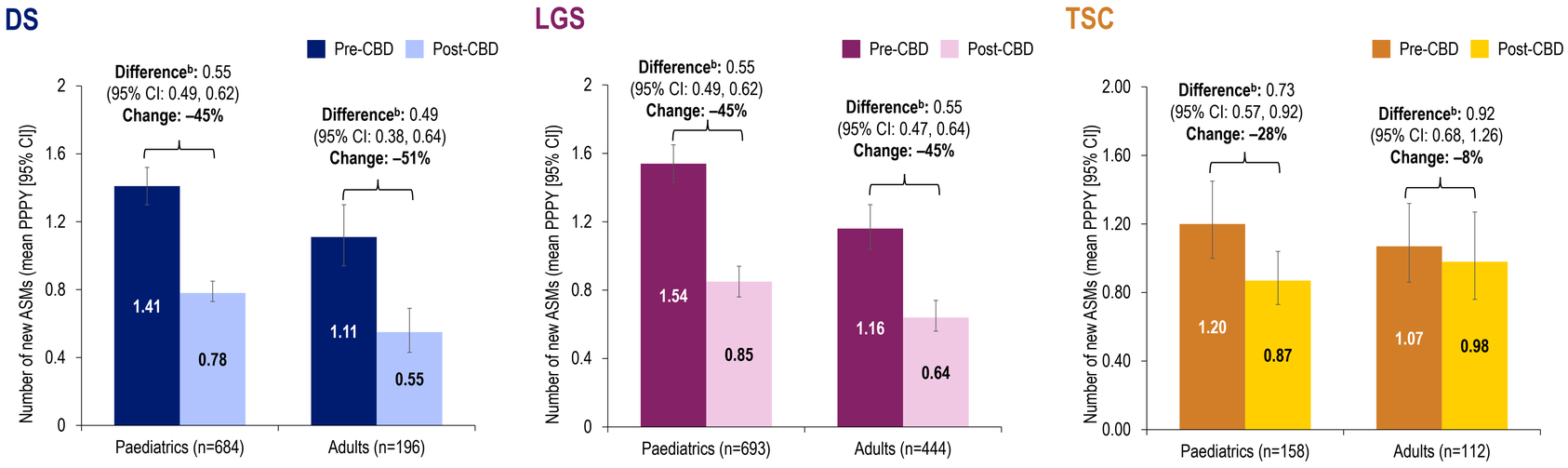
Methods

- This retrospective cohort analysis of claims and electronic health record (EHR) data included patients
  - ≥2 years old
  - with ICD-10 diagnostic codes for DS, LGS, or TSC
  - newly initiated on CBD between June 2018 and September 2023 (index date)
  - ≥12 months of EHR activity prior to initial ASM
  - continuous (without a single gap) EHR activity for >180 days
  - for those with DS or LGS, received CLB within 12 months prior to or at index (CBD initiation)
- **Baseline:** 12 months before index date
- **Follow-up:** all patients had variable follow up periods of ≤12 months of EHR activity following the index date
- **Outcomes:**
  - **ASM cycling** number of new maintenance ASMs used in the 12 months before and after CBD initiation; an ASM was considered 'new' if it had not been prescribed in the 90 days prior to its initiation
  - **Polypharmacy burden:** number of concomitant maintenance ASMs, antipsychotics, or antidepressant and anxiolytic medications taken during the 12 months before and after the CBD index date
  - **HCRU:** seizure-related physician office visits, hospitalisations, and emergency room (ER) visits during the 12 months before and after the CBD initiation
- Results were stratified by paediatric (2 to <18 years) and adult (≥18 years) patients, and by epilepsy type
- Interrupted time series (ITS) analyses were conducted to assess changes in outcomes versus the counterfactual scenario; i.e. expected trajectory had CBD not been initiated
  - Data were modelled on the natural log scale and exponentiated to represent relative difference ratios scale
- This study examined the use of Epidiolex® (US), and results do not apply to other CBD-containing products

Results

- Overall, 1535 paediatric and 752 adult patients were included
- Most were male (55.7% in both populations), and non-Hispanic White (paediatrics: 51.1%; adults: 58.2%)
- Intellectual disability was prevalent at baseline across the DS, LGS, and TSC populations (paediatrics: 62.3%, 68.1%, and 55.1%; adults: 58.7%, 55.2%, and 43.8%, respectively)
- The most used maintenance ASMs were sodium channel blockers among patients with LGS (paediatrics: 72.3%; adults: 87.2%) and TSC (paediatrics: 57.0%; adults: 73.2%)
  - The most used ASMs in patients with DS were synaptic vesicle protein 2A modulators (paediatrics: 46.1%; adults: 40.8%) and multiple-target ASMs (excluding cenobamate; paediatrics: 38.7%; adults: 48.0%)
- The most commonly prescribed rescue medication among paediatric patients was diazepam (rectal gel, 33.9–38.8%); among adults, it was lorazepam (sublingual, 12.5–22.7%)
- Details of baseline characteristics, including ASM and rescue medication use, can be viewed in the **Supplementary Material** via the QR code

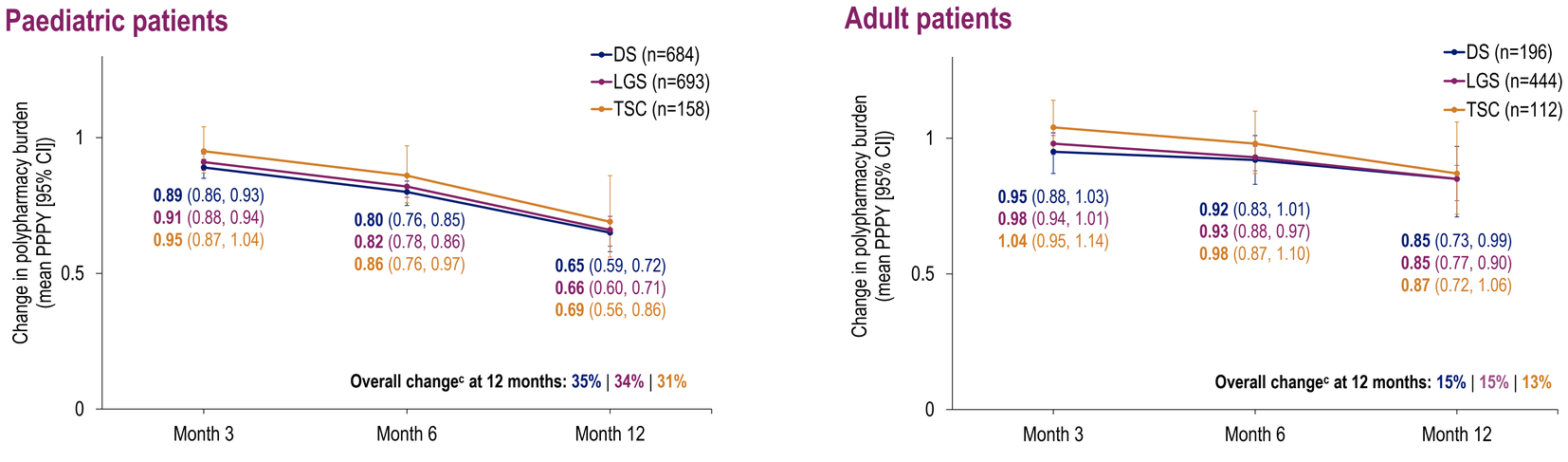
Figure 1. ASM cycling in the year before and after CBD initiation (ITS estimates[a])



- At 12 months post-CBD initiation, reductions in overall ASM cycling in paediatric patients with DS, LGS, and TSC were estimated at 45%, 45%, and 28%, respectively, and 51%, 45%, and 8% in adults, respectively, compared with counterfactual[b] (**Figure 1**)

[a]Data were modelled on the natural log scale and back-transformed to represent relative differences on a ratio scale; [b]Differences in pre- and post-CBD estimates represent after CBD initiation, compared with expected trajectory had CBD not been initiated (counterfactual).
ASM, antiseizure medication; CBD, cannabidiol; CI, confidence interval; DS, Dravet syndrome; ITS, interrupted time series; LGS, Lennox-Gastaut syndrome; PPPY, per patient per year; TSC, tuberous sclerosis complex.

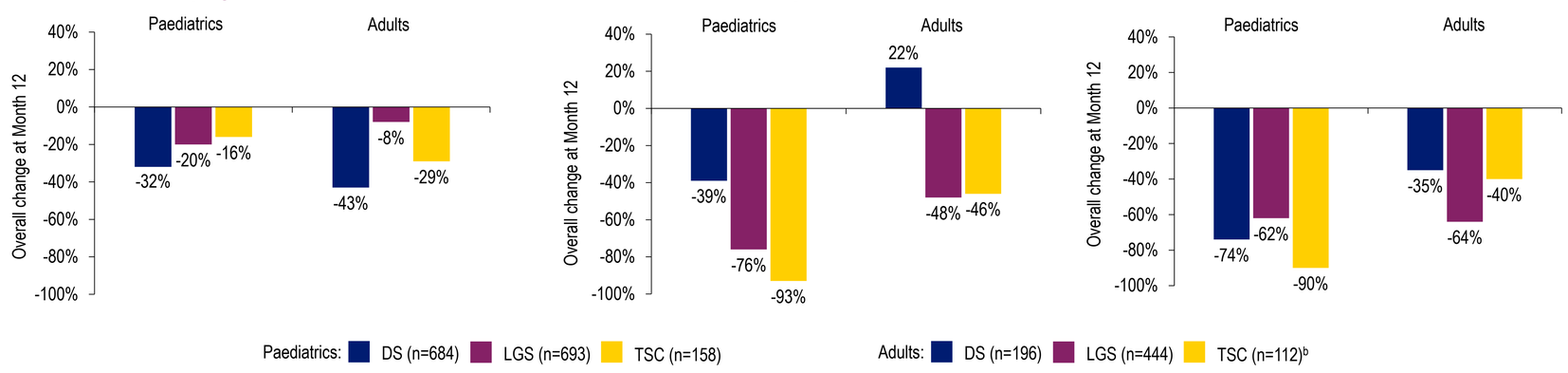
Figure 2. Estimated change[a,b] in polypharmacy burden during the year following CBD initiation (ITS estimates, 95% CIs)



- A progressive reduction in overall polypharmacy burden, including the use of maintenance ASMs, antipsychotics, antidepressants, and anxiolytic medications, was observed from 3 to 12 months following CBD initiation in both paediatric and adult patients with DS, LGS, or TSC (**Figure 2**)
  - Decreasing trends indicate a reduction in the number of medications taken per patient per year following CBD initiation

[a]Differences in pre- and post-CBD estimates represent after CBD initiation, compared with expected trajectory had CBD not been initiated (counterfactual); [b]Estimated change = 1 (null) – exponentiated value estimate; [c]Overall change = 1 (null) – exponentiated value estimate x 100.
CBD, cannabidiol; CI, confidence interval; DS, Dravet syndrome; ITS, interrupted time series; LGS, Lennox-Gastaut syndrome; PPPY, per patient per year; TSC, tuberous sclerosis complex.

Figure 3. Overall change[a] in HCRU at Month 12 post-CBD initiation (ITS estimates, %)



- Overall, decreases were seen in seizure-related physician office visits, hospitalisations, and ER visits following CBD treatment in both paediatric and adult patients across the indications, except for seizure-related hospitalisations in adults with DS (**Figure 3**)
  - **Example interpretation:** Among paediatric patients with DS, after initiating CBD, mean seizure-related physician office visits observed was 32% less than expected (based on trajectory had patients not initiated CBD) at 12 months. In other words, paediatric patients with DS observed a smaller number of monthly seizure-related physician office visits by 0.68 [(1-0.68)=0.32*100(%)=32%] on the exponentiated scale than if patients had continued their initial trajectory

[a]Overall change = 1 (null, i.e. expected trajectory had CBD not been initiated [counterfactual], measured through ITS modeling) – exponentiated value estimate x 100; [b]n=41 patients for seizure-related physician office visits.
CBD, cannabidiol; DS, Dravet syndrome; ER, emergency room; HCRU, healthcare resource utilisation; ITS, interrupted time series; LGS, Lennox-Gastaut syndrome; TSC, tuberous sclerosis complex.

Conclusions

- These real-world insights indicate overall reductions in mean ASM cycling, polypharmacy, and seizure-related physician and ER visits 12 months after CBD initiation in both paediatric and adult patients with DS, LGS, or TSC
- Limitations inherent to observational studies using claims and EHR data apply for this study; the estimates were unadjusted and may be influenced by confounding factors, and the use of a US database may limit generalisability to the EU population
- Despite the limitations, these real-world findings show seemingly comparable reductions in HCRU across both paediatric and adult populations, and indicate that CBD may help reduce the clinical and economic burden of disease in both age groups

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Clinical trial ID: Not applicable.

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P495

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Supplementary Material

Table S1. Baseline characteristics of paediatric and adult patients with DS, LGS, or TSC who were naïve to CBD

		Paediatric population			Adult population		
		DS (N=684)	LGS (N=693)	TSC (N=158)	DS (N=196)	LGS (N=444)	TSC (N=112)
Age group (years)	2–5 (vs 18–49)	33.5%	22.7%	36.1%	96.9%	94.6%	96.4%
	6–12 (vs 50–64)	44.9%	45.0%	36.1%	3.1%	5.4%	3.6%
	13–17 (vs >65)	21.6%	32.3%	27.8%	0.0%	0.0%	0.0%
Sex	Male	55.1%	55.3%	60.1%	50.0%	58.6%	54.5%
Race/Ethnicity	Non-Hispanic White	53.4%	49.1%	50.0%	61.7%	55.6%	62.5%
	Non-Hispanic Black	7.9%	5.5%	5.1%	4.1%	6.5%	2.7%
	Hispanic/Latino	10.1%	13.6%	12.0%	10.7%	7.9%	8.0%
	Others	1.9%	2.6%	3.2%	1.5%	1.8%	2.7%
	Unknown	26.8%	29.3%	29.7%	21.9%	28.2%	24.1%
Comorbidities	ADD/ADHD	15.5%	18.5%	24.1%	11.7%	15.1%	13.4%
	Allergies	26.3%	24.7%	26.6%	21.4%	21.6%	18.8%
	Anxiety/depression	5.8%	6.6%	6.3%	14.8%	15.8%	22.3%
	Autism	34.1%	37.2%	45.6%	29.6%	32.9%	27.7%
	Cardiovascular disease	5.6%	6.5%	4.4%	6.1%	6.1%	3.6%
	Diabetes mellitus	1.2%	1.2%	0.6%	2.0%	4.3%	4.5%
	Fractures	2.8%	3.5%	3.2%	5.6%	5.6%	5.4%
	Hyperlipidaemia	1.0%	1.3%	2.5%	8.2%	9.7%	16.1%
	Hypertension	3.5%	4.0%	5.1%	6.6%	8.1%	19.6%
	Insomnia	8.3%	8.8%	8.9%	6.1%	9.5%	2.7%
	Intellectual disability/developmental delay	62.3%	68.1%	55.1%	58.7%	55.2%	43.8%
	Migraine	1.8%	1.6%	1.3%	1.5%	3.6%	2.7%
	Neoplasia	4.4%	4.8%	53.2%	6.6%	6.3%	46.4%
	Obesity	5.0%	4.0%	8.2%	6.1%	14.4%	12.5%
	Respiratory disease	21.6%	24.7%	19.0%	10.7%	11.9%	8.0%
Maintenance ASM use	Calcium channel blockers	5.3%	5.3%	2.5%	5.1%	2.9%	7.1%
	Cenobamate	0.1%	0.0%	0.6%	0.5%	2.0%	0.0%
	Clobazam[a]	100.0%	100.0%	44.3%	100.0%	100.0%	36.6%
	Clonazepam (excluding orally dissolving tablet)	16.4%	16.2%	8.2%	20.9%	22.1%	21.4%
	Everolimus	0.0%	0.0%	25.3%	0.0%	0.0%	20.5%
	Fenfluramine	0.9%	0.1%	0.0%	1.5%	0.0%	0.0%
	GABAergic activity, other	11.4%	10.7%	35.4%	9.7%	3.8%	18.8%
	Multiple targets (excluding cenobamate)	38.7%	34.8%	28.5%	48.0%	40.3%	24.1%
	Sodium channel blockers	16.2%	72.3%	57.0%	34.7%	87.2%	73.2%
	Synaptic vesicle protein 2A modulators	46.1%	42.0%	26.6%	40.8%	39.0%	41.1%
	Valproate	38.7%	29.7%	20.9%	39.3%	26.6%	26.8%
	Other	7.3%	9.5%	7.0%	12.2%	13.7%	8.9%
Any rescue medication prescribed		51.8%	59.3%	56.3%	38.3%	45.7%	36.6%
Rescue medications	Clonazepam (orally dissolving tablet)	20.5%	22.9%	15.2%	6.6%	8.1%	12.5%
	Diazepam (nasal formulation)	5.6%	8.7%	12.0%	3.1%	2.9%	1.8%
	Diazepam (rectal gel)	33.9%	38.8%	37.3%	14.3%	16.9%	15.2%
	Lorazepam (sublingual)	9.1%	7.5%	9.5%	18.4%	22.7%	12.5%
	Midazolam (nasal formulation)	2.2%	4.5%	1.9%	6.1%	6.8%	5.4%
Anxiolytic, antidepressant, antipsychotic medication use	Antipsychotics	5.4%	7.4%	12.0%	11.7%	10.1%	10.7%
	Barbiturates	7.6%	6.5%	6.3%	6.6%	3.8%	3.6%
	Non-rescue benzodiazepines	26.5%	21.5%	17.1%	26.5%	21.6%	18.8%
	Non-benzodiazepines	0.6%	0.4%	1.3%	1.0%	1.8%	2.7%
	SSRIs	3.1%	3.9%	7.6%	10.2%	13.1%	21.4%
	SARIs[b]	3.8%	3.0%	3.8%	3.1%	5.0%	0.9%
	SNRIs	0.1%	0.1%	0.0%	1.0%	2.5%	0.0%
	Tricyclic antidepressants	0.4%	1.3%	0.6%	2.6%	2.7%	0.9%

[a]Patients with DS or LGS in this study were selected based on clobazam use, in line with EMA indication; not all patients with TSC received clobazam, as coadministration of CLB with CBD is not required for TSC; [b]SARIs, such as trazodone, nefazodone etc.
ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder; ASM, antiseizure medication; CBD, cannabidiol; CLB, clobazam; DS, Dravet syndrome; EMA, European Medicines Agency; GABA, gamma-aminobutyric acid; LGS, Lennox-Gastaut syndrome; SARI, serotonin antagonist and reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TSC, tuberous sclerosis complex.