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Introduction

- Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), and tuberous sclerosis complex (TSC) are severe developmental and epileptic encephalopathies with an onset in infancy or early childhood¹
- Plant-derived, highly purified 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.² Efficacy of CBD in these indications has been established by randomized clinical trials^{3–7}
- In patients with refractory epilepsy, inadequate seizure control or undesirable side effects may result in antiseizure medication (ASM) cycling, polypharmacy, and increased healthcare resource utilization (HCRU)^{8–11}
- Data on the real-world impact of CBD on these outcomes remain limited

Objective

- To assess the real-world effectiveness of CBD on ASM cycling, polypharmacy burden, and HCRU among CBD-naïve adult and pediatric patients with DS, LGS, or TSC

Methods

- This retrospective cohort study used the US Optum® Market Clarity database, which includes integrated claims and electronic health record (EHR) data from 70+ million patients and 150+ US payers
- Adult (aged ≥18 years) and pediatric (aged <18 years) patients who newly initiated CBD between 25 June 2018–30 September 2023 were included
- Lookback period** was defined as the 12 months before CBD initiation (**index event**) and **follow-up** was ≤12 months post-initiation; outcomes were adjusted for patient-observation time to account for variable follow-up
- Interrupted time series analyses were conducted to assess changes in outcomes post–CBD initiation relative to the trend (expected trajectory) prior to CBD initiation (counterfactual scenario; **Supplementary Figure S1**). Data were transformed from natural logarithm to exponentiated values to convey relative reductions in the following outcomes assessed during the 12 months pre- and post-index:
 - ASM cycling:** Mean number of new maintenance ASMs (**Table 1**) per patient per year (PPPY). A maintenance 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 (**Table 1**) per patient per month (PPPM)
 - HCRU:** Seizure-related medical claims or records of hospitalization, emergency department (ED) visits, or physician office visits PPPM
- Results were stratified by epilepsy type and age group
- This study used data on Epidiolex® and the results of this study do not apply to other CBD-containing products

Table 1. List of medications assessed

Medication category	Included medications
Maintenance ASMs	Calcium channel blockers (ethosuximide, gabapentin, methsuximide, pregabalin); cenobamate; clobazam; clonazepam (excluding orally disintegrating tablets); GABAergic drugs (phenobarbital, vigabatrin, tiagabine); agents with multiple targets (excluding cenobamate); felbamate, topiramate, zonisamide, primidone, sodium channel blockers (carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, oxcarbazepine, phenytoin, rifinamide); synaptic vesicle protein 2A modulators (brivaracetam, levetiracetam); valproate (valproate, valproic acid, divalproex sodium); and others (acetazolamide, adrenocorticotrophic hormone, everolimus, ezogabine, fenfluramine, perampanel, stiripentol)
Antipsychotic medications	Antipsychotics (amiprazole, risperidone, olanzapine, haloperidol)
Anxiolytic and antidepressant medications	Barbiturates (amobarbital, pentobarbital, phenobarbital); non-rescue benzodiazepines (alprazolam, chlordiazepoxide, clorazepate, oxazepam, remimazolam, lorazepam, diazepam (excluding rectal, nasal, orally dissolving tablet, and sublingual formulations); non-benzodiazepines (buspirone, meprobamate); SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline); SNRIs (duloxetine, venlafaxine); SARIs (trazodone); and tricyclic antidepressants (amitriptyline, imipramine, nortriptyline, mirtazapine)

ASMs, antiseizure medications; SARIs, serotonin antagonist and reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Results

Baseline demographics and clinical characteristics

Table 2. Baseline characteristics^a of CBD-naïve pediatric and adult patients with DS, LGS, or TSC

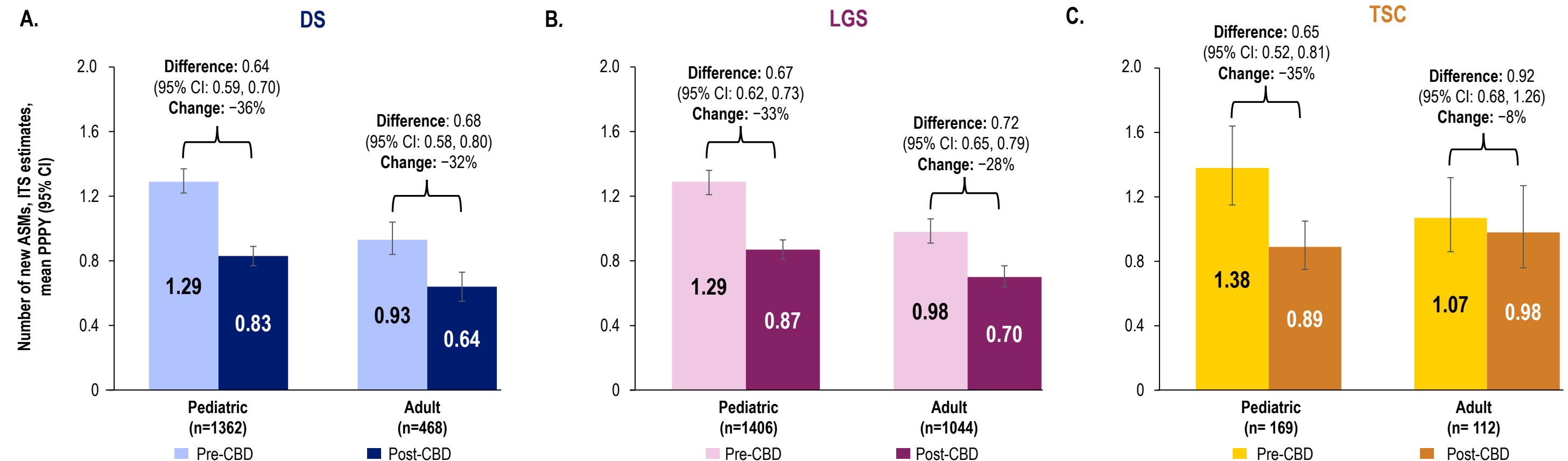
Pediatric (aged <18 years)					Adults (aged ≥18 years)				
Characteristic	Overall (DS, LGS, TSC)	DS	LGS	TSC	Characteristic	Overall (DS, LGS, TSC)	DS	LGS	TSC
Overall N	2937	1362	1406	169	Overall N	1624	468	1044	112
Age group (years), n (%)									
≤1	157 (5)	106 (8)	40 (3)	11 (7)	18–49	1551 (96)	453 (97)	990 (95)	108 (96)
2–5	731 (25)	416 (31)	258 (18)	57 (34)	50–64	68 (4)	13 (3)	51 (5)	4 (4)
6–12	1268 (43)	556 (41)	655 (47)	57 (34)	≥65	5 (0)	2 (0)	3 (0)	0 (0)
13–17	781 (27)	284 (21)	453 (32)	44 (26)					
Sex, n (%)									
Male	1632 (56)	755 (55)	776 (55)	101 (60)	Male	890 (55)	250 (53)	579 (55)	61 (54)
Geographic region, n (%)									
Midwest	1096 (37)	524 (38)	521 (37)	51 (30)	Midwest	674 (42)	211 (45)	417 (40)	46 (41)
Northeast	503 (17)	260 (19)	212 (15)	31 (18)	Northeast	356 (22)	109 (23)	220 (21)	27 (24)
South	878 (30)	352 (26)	471 (33)	55 (33)	South	383 (24)	88 (19)	268 (26)	27 (24)
West	314 (11)	154 (11)	145 (10)	15 (9)	West	142 (9)	37 (8)	97 (9)	8 (7)
Race/ethnicity, n (%)									
Non-Hispanic White	1477 (50)	686 (50)	705 (50)	86 (51)	Non-Hispanic White	971 (60)	287 (61)	614 (59)	70 (63)
Non-Hispanic Black	198 (7)	103 (8)	87 (6)	8 (5)	Non-Hispanic Black	93 (6)	23 (5)	67 (6)	3 (3)
Hispanic/Latino	356 (12)	154 (11)	183 (13)	19 (11)	Hispanic/Latino	126 (8)	43 (9)	74 (7)	9 (8)
Other	60 (2)	27 (2)	28 (2)	5 (3)	Other	24 (1)	7 (1)	14 (1)	3 (3)
Insurance type, n (%)									
Commercial	1201 (41)	540 (40)	582 (41)	79 (47)	Commercial	528 (33)	143 (31)	345 (33)	40 (36)
Medicaid	1180 (40)	500 (37)	613 (44)	67 (40)	Medicaid	532 (33)	123 (26)	374 (36)	35 (31)
Medicare	16 (1)	10 (1)	6 (0)	0 (0)	Medicare	149 (9)	29 (6)	107 (10)	13 (12)
Comorbidities, n (%)									
Intellectual disability/developmental delay	1861 (63)	863 (63)	906 (64)	92 (54)	Intellectual disability/developmental delay	873 (54)	269 (57)	555 (53)	49 (44)
Autism	965 (33)	391 (29)	502 (36)	72 (43)	Autism	483 (30)	136 (29)	316 (30)	31 (28)
Allergies	708 (24)	336 (25)	325 (23)	47 (28)	Allergies	328 (20)	108 (23)	199 (19)	21 (19)
Respiratory disease	601 (20)	279 (20)	292 (21)	30 (18)	Anxiety/depression	278 (17)	74 (16)	179 (17)	25 (22)
ADD/ADHD	460 (16)	165 (12)	257 (18)	38 (22)	ADD/ADHD	203 (13)	48 (10)	140 (13)	15 (13)
Maintenance ASM use, n (%)									
Clobazam	1522 (52)	729 (54)	716 (51)	77 (46)	Clobazam	681 (42)	196 (42)	444 (43)	41 (37)
Sodium channel blockers	1247 (42)	208 (15)	942 (67)	97 (57)	Sodium channel blockers	1077 (66)	147 (31)	848 (81)	82 (73)
Synaptic vesicle protein 2A modulators	1276 (43)	644 (47)	583 (41)	49 (29)	Synaptic vesicle protein 2A modulators	618 (38)	183 (39)	389 (37)	46 (41)
Multiple targets (excluding cenobamate)	985 (34)	474 (35)	461 (33)	50 (30)	Multiple targets (excluding cenobamate)	592 (36)	197 (42)	368 (35)	27 (24)
Valproate	840 (29)	459 (34)	348 (25)	33 (20)	Valproate	480 (30)	167 (36)	283 (27)	30 (27)
Rescue medication use ^a , n (%)									
Any rescue medication use	1554 (53)	666 (49)	792 (56)	96 (57)	Any rescue medication use	640 (39)	181 (39)	418 (40)	41 (37)
Diazepam (rectal gel)	1016 (35)	426 (31)	527 (37)	63 (37)	Diazepam (rectal gel)	250 (15)	65 (14)	168 (16)	17 (15)
Clonazepam (orally dissolving tablet)	565 (19)	250 (18)	288 (20)	27 (16)	Clonazepam (orally dissolving tablet)	119 (7)	27 (6)	78 (7)	14 (13)
Lorazepam (sublingual)	233 (8)	113 (8)	103 (7)	17 (10)	Lorazepam (sublingual)	305 (19)	93 (20)	198 (19)	14 (13)
Diazepam (nasal formulation)	198 (7)	69 (5)	107 (8)	22 (13)	Diazepam (nasal formulation)	37 (2)	14 (3)	21 (2)	2 (2)
Midazolam (nasal formulation)	86 (3)	29 (2)	54 (4)	3 (2)	Midazolam (nasal formulation)	80 (5)	20 (4)	54 (5)	6 (5)
Anxiolytic, antidepressant, and antipsychotic medication use, n (%)									
Non-rescue benzodiazepines	659 (22)	345 (25)	287 (20)	27 (16)	Non-rescue benzodiazepines	380 (23)	117 (25)	242 (23)	21 (19)
Barbiturates	220 (7)	116 (9)	92 (7)	12 (7)	Barbiturates	102 (6)	38 (8)	60 (6)	4 (4)
Antipsychotics	184 (6)	64 (5)	101 (7)	19 (11)	Antipsychotics	165 (10)	56 (12)	97 (9)	12 (11)
SSRIs	109 (4)	38 (3)	59 (4)	12 (7)	SSRIs	194 (12)	42 (9)	128 (12)	24 (21)
SARIs	89 (3)	40 (3)	43 (3)	6 (4)	SARIs	55 (3)	13 (3)	41 (4)	1 (1)

^aPatient demographics such as age and race were derived from the US Optum® Market Clarity database (time point agnostic). Percentages may not sum to 100% due to missing, unknown, or rounded values. The 5 most frequent comorbidities, maintenance ASM use, rescue medication use, and anxiolytic, antidepressant, and antipsychotic medication use in the overall (DS, LGS, TSC) pediatric and adult populations are shown. Comorbidities and medication use were assessed in the fixed 365 days prior to index. ^bMedication use (including rescue medications) is based on prescription or dispensing data from claims/EHR data. ADD/ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; ASM, antiseizure medication; CBD, cannabidiol; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; SARIs, serotonin antagonist and reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TSC, tuberous sclerosis complex.

- A total of 2937 pediatric (DS, n=1362; LGS, n=1406; TSC, n=169) and 1624 adult (DS, n=468; LGS, n=1044; TSC, n=112) patients were included (**Table 2**)
- Most patients were male (56% pediatric; 55% adult), and non-Hispanic White (50%; 60%)
- Intellectual disability or developmental delay (63% pediatric; 54% adult), autism (33%, 30%), and allergies (24%, 20%) were the most prevalent baseline comorbidities
- Overall, 42–52% of patients were taking clobazam, 42–66% were taking sodium channel blockers; and 29–30% were taking valproate

ASM cycling

Figure 1. At 12 months post–CBD initiation^a, reductions were seen in ASM cycling relative to the pre-initiation trend among CBD-naïve pediatric^b and adult patients with (A) DS, (B) LGS, or (C) TSC

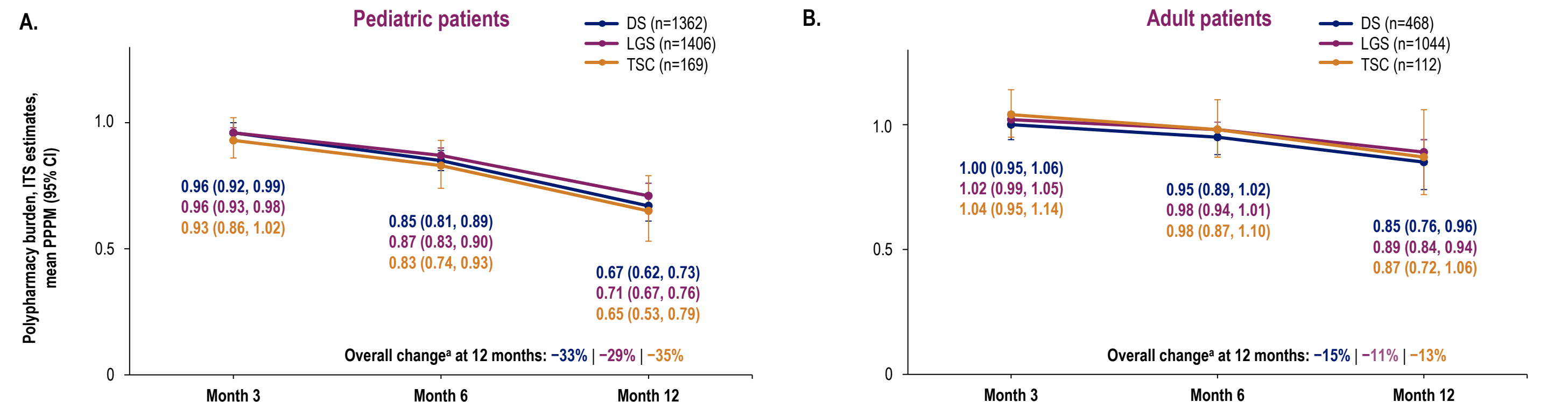


^aOverall changes are modeled estimates post–CBD initiation relative to the expected trajectory if CBD had not been initiated (counterfactual scenario, based on pre-initiation trends) among the same patients. Differences between the observed post-initiation and the predicted counterfactual values are 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 post-initiation to counterfactual estimates. From this ratio of exponentials, overall change is calculated as 1 (null) – exponentiated value estimate × 100 = (%), where a negative sign indicates a percent decrease. ^bIncludes off-label CBD use in pediatric patients <1 year of age. ASM, antiseizure medication; CBD, cannabidiol; DS, Dravet syndrome; ITS, interrupted time series; LGS, Lennox-Gastaut syndrome; LN, natural logarithm; PPPY, per patient per year; TSC, tuberous sclerosis complex.

- At 12 months post–CBD initiation, relative to the pre-initiation trend, reductions in ASM cycling were observed among both pediatric (DS, –36%; LGS, –33%; TSC, –35%) and adult (DS, –32%; LGS, –28%; TSC, –8%) patient groups (**Figure 1**). Reductions were seen at 12 months post–CBD initiation in the overall cohort (DS, LGS, and TSC combined) for both pediatric (–34%) and adults (–28%)

Polypharmacy burden

Figure 2. Post–CBD initiation, trends^a in polypharmacy burden decreased over time relative to the pre-initiation trends among CBD-naïve (A) pediatric^b and (B) adult patients with DS, LGS, or TSC



^aOverall changes are modeled estimates post–CBD initiation relative to the expected trajectory if CBD had not been initiated (counterfactual scenario, based on pre-initiation trends) among the same patients. Differences between the observed post-initiation and the predicted counterfactual 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 post-initiation to counterfactual estimates. From this ratio of exponentials, overall change is calculated as 1 (null) – exponentiated value estimate × 100 = (%), where a negative sign indicates a percent decrease. ^bIncludes off-label CBD use in pediatric patients <1 year of age. CBD, cannabidiol; DS, Dravet syndrome; ITS, interrupted time series; LGS, Lennox-Gastaut syndrome; LN, natural logarithm; PPPM, per patient per month; TSC, tuberous sclerosis complex.

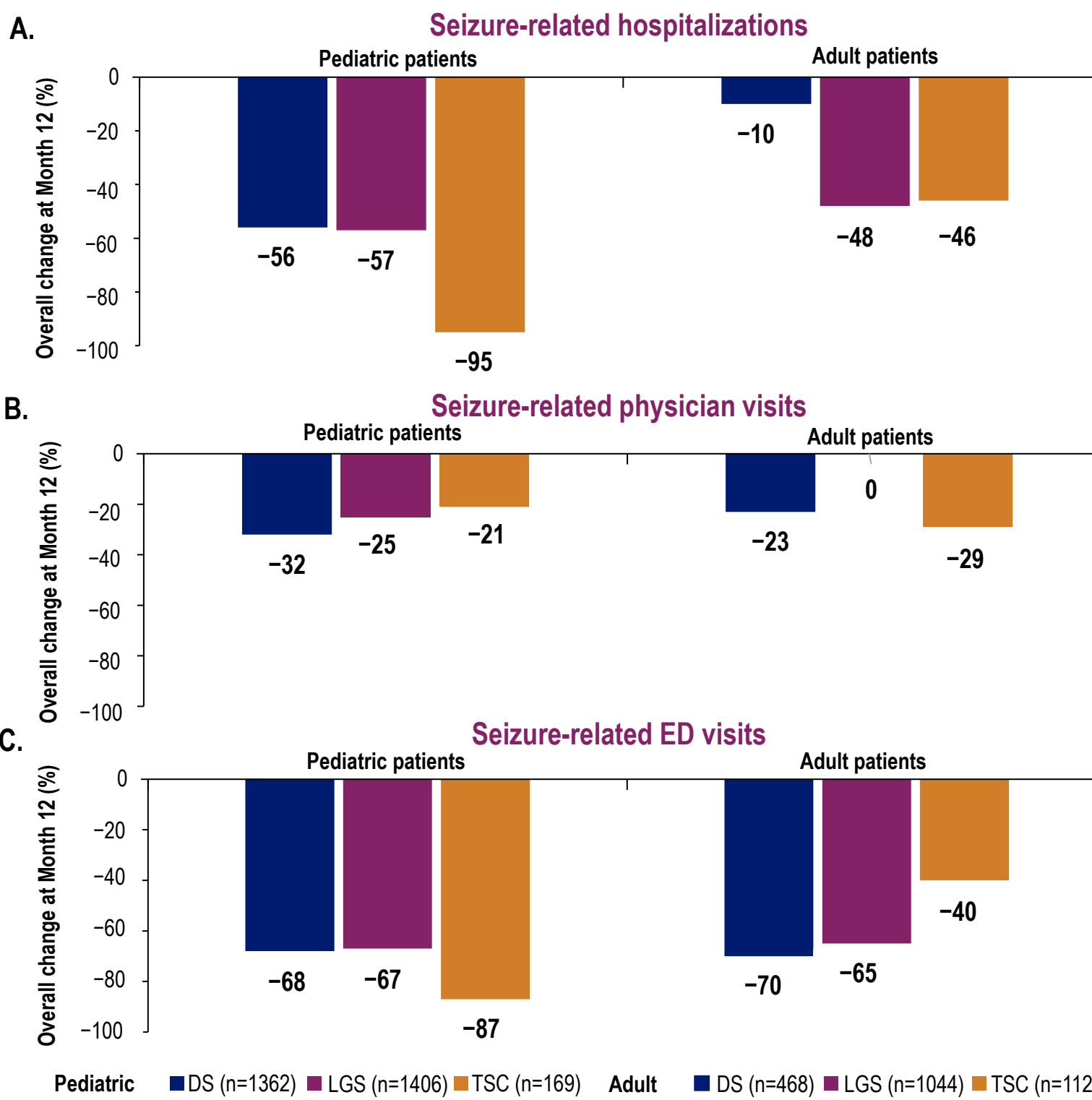
- Progressive reduction in overall polypharmacy burden was observed from 3 to 12 months following CBD initiation, relative to the pre-initiation trend, in the pediatric (DS, –33%; LGS, –29%; TSC, –35%) and adult (DS, –15%; LGS, –11%; TSC, –13%) patient groups (**Figure 2**). Reductions were seen at 12 months post–CBD initiation in the overall cohort (DS, LGS, and TSC combined) for pediatric (–31%) and adults (–12%)

Conclusions

- These real-world insights indicate overall reductions in ASM cycling, polypharmacy burden, and HCRU at 12 months post–CBD initiation in both pediatric and adult patients living with DS, LGS, or TSC
- The findings suggest that CBD may positively impact clinical outcomes and reduce economic burden associated with these conditions in both age groups

HCRU

Figure 3. At 12 months post–CBD initiation^a, reductions were seen in HCRU^{b,c} relative to the pre-initiation trends among CBD-naïve pediatric^d and adult patients with DS, LGS, or TSC



^aOverall changes are modeled estimates post–CBD initiation relative to the expected trajectory if CBD had not been initiated (counterfactual scenario, based on pre-initiation trends) among the same patients. Differences between the observed post-initiation and the predicted counterfactual 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 post-initiation to counterfactual estimates. From this ratio of exponentials, overall change is calculated as 1 (null) – exponentiated value estimate × 100 = (%), where a negative sign indicates a percent decrease. ^bSeizure-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. ^cMean PPPM. ^dIncludes off-label CBD use in pediatric patients <1 year of age. CBD, cannabidiol; DS, Dravet syndrome; ED, emergency department; HCRU, healthcare resource utilization; ICD-10-CM, International Classification of Diseases, Tenth Revision; Clinical Modification; ITS, interrupted time series; LGS, Lennox-Gastaut syndrome; LN, natural logarithm; PPPM, per patient per month; TSC, tuberous sclerosis complex.

- At 12 months post–CBD initiation, relative to the pre-initiation trend, reductions were seen in seizure-related HCRU (hospitalizations, ED visits, and physician visits) in both pediatric and adult patients, across the indications (no change was seen in physician visits among adults with LGS) (**Figure 3**; **Supplementary Table S1**)

Limitations

- Findings are limited to the commercially insured and Medicaid insured US populations represented in the database. The use of a large, longitudinal integrated claims and EHR dataset with standardized coding supports strong internal validity and minimizes selection bias
- This analysis did not include a comparison group, and does not account for potential regression to the mean
- Estimates were unadjusted and therefore could be influenced by confounding factors

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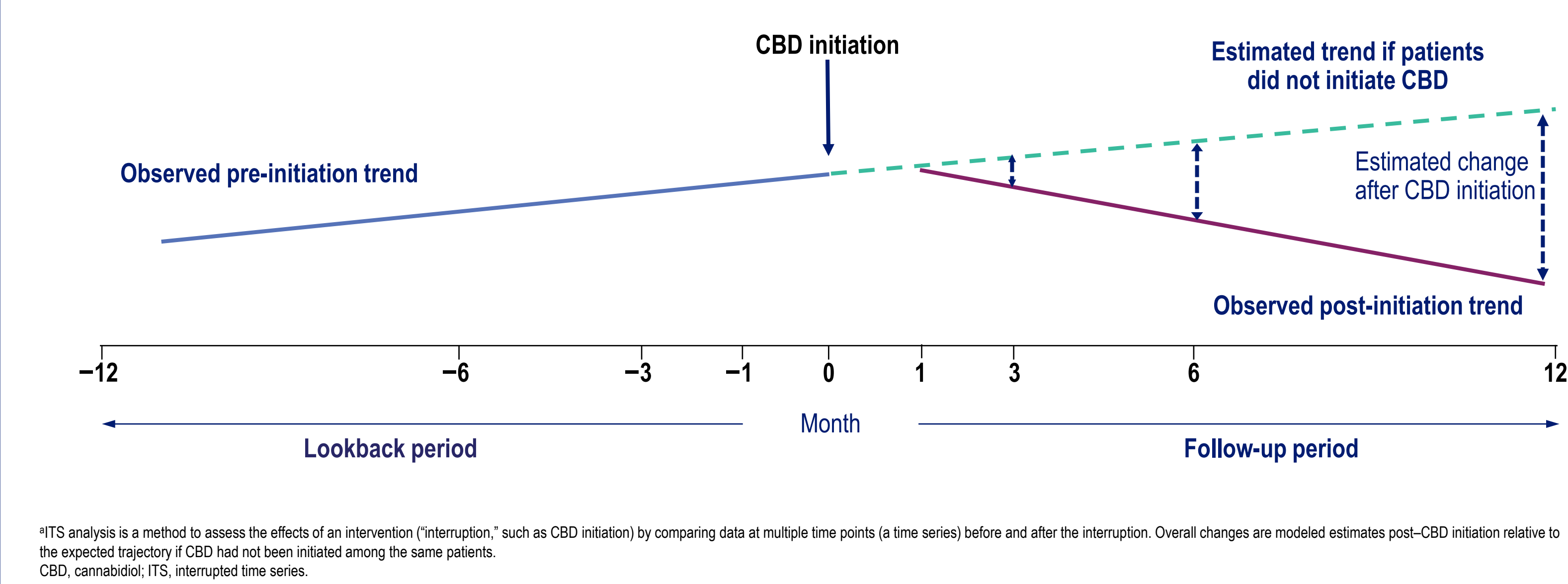
Disclosures: All authors met the ICMJE authorship criteria and had full access to relevant data and information. Neither honoree nor payments were made for authorship. **LB, MF, KR, and AS** are employees of Jazz Pharmaceuticals, Inc., Palo Alto, CA, USA, and hold stock and/or stock options in the company. **MH and VO** are employees of Jazz Pharmaceuticals, UK Ltd., and hold stock and/or stock options in the company. **RF, KB, and DP** have consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc.

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.



Supplementary Material

Figure S1. ITS analysis^a



^aITS 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. Overall changes are modeled estimates post–CBD initiation relative to the expected trajectory if CBD had not been initiated among the same patients.
CBD, cannabidiol; ITS, interrupted time series.

Table S1. Estimated change^a in HCRU^{b,c} at 12 months post–CBD initiation among CBD-naïve pediatric^d and adult patients with DS, LGS, or TSC

Difference in HCRU ^{b,c} PPPM post–CBD initiation: ITS estimates (95% CI)						
Indication	Pediatric Patients (aged <18 years) ^d			Adult Patients (aged ≥18 years)		
	n (Pre-index)	12 months post–CBD initiation Difference/ratio ^e (95% CI)	Reduction ^f at 12 months (%)	n (Pre-index)	12 months post–CBD initiation Difference/ratio ^e (95% CI)	Reduction ^f at 12 months (%)
Seizure-related hospitalizations						
Overall (DS, LGS, TSC)	2937	0.38 (0.26, 0.55)	62	1624	0.60 (0.31, 1.15)	40
DS	1362	0.44 (0.26, 0.74)	56	468	0.90 (0.32, 2.54)	10
LGS	1406	0.43 (0.24, 0.75)	57	1044	0.52 (0.22, 1.21)	48
TSC	169	0.05 (0.01, 0.24)	95	112	0.54 (0.05, 5.82)	46
Seizure-related physician visits						
Overall (DS, LGS, TSC)	2937	0.72 (0.65, 0.81)	28	1624	0.92 (0.74, 1.14)	8
DS	1362	0.68 (0.58, 0.80)	32	468	0.77 (0.54, 1.11)	23
LGS	1406	0.75 (0.64, 0.88)	25	1044	1.00 (0.76, 1.31)	0
TSC	169	0.79 (0.54, 1.14)	21	112	0.71 (0.35, 1.43)	29
Seizure-related ED visits						
Overall (DS, LGS, TSC)	2937	0.31 (0.24, 0.41)	69	1624	0.35 (0.22, 0.54)	65
DS	1362	0.32 (0.22, 0.47)	68	468	0.30 (0.12, 0.77)	70
LGS	1406	0.33 (0.22, 0.49)	67	1044	0.35 (0.21, 0.58)	65
TSC	169	0.13 (0.04, 0.38)	87	112	0.60 (0.07, 5.17)	40

^aOverall changes are modeled estimates post–CBD initiation relative to the expected trajectory if CBD had not been initiated (counterfactual scenario, based on pre-initiation trends) among the same patients. ^bSeizure-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*. ^cMean PPPM. ^dIncludes off-label CBD use in pediatric patients <1 year of age. ^eDifferences between the observed post-initiation and predicted counterfactual values (based on pre-initiation trends) are expressed on the log (LN) scale. Estimates are exponentiated LN values. When exponentiated, a difference on the LN scale is relative change corresponding to the ratio of post-initiation to counterfactual estimates. ^fOverall change = 1 (null) – exponentiated value estimate × 100 = (%). CBD, cannabidiol; DS, Dravet syndrome; ED, emergency department; HCRU, healthcare resource utilization; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; ITS, interrupted time series; LGS, Lennox-Gastaut syndrome; LN, natural logarithm; PPPM, per patient per month; TSC, tuberous sclerosis complex.

