3.287 Change in Antiseizure and Anxiolytic Medications Pre- and Post-Cannabidiol Initiation

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Introduction

- Polypharmacy is common in people with refractory epilepsy who often concurrently take multiple antiseizure medications (ASMs),[1] which may increase the risk of drug–drug interactions and adverse events.[2]
- A plant-derived, highly purified pharmaceutical formulation of cannabidiol (CBD) is approved in the United States for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC).[3]
- The effect of CBD treatment on ASM polypharmacy is unclear.
- In addition to the antiseizure properties of CBD, recent literature suggests a potential beneficial effect of CBD on nonseizure outcomes (eg, anxiety control).[4,5]
- Use of anxiolytics may be a proxy of anxiety control. However, there are scarce data on anxiolytic use following the initiation of CBD.

Objective

- To assess differences in ASM and anxiolytic use before and after CBD initiation among commercially insured and Medicaid patients with LGS, DS, TSC, and other refractory epilepsies.

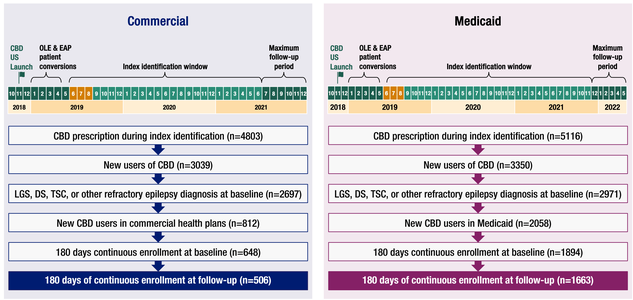
Methods

- This was a retrospective pre–post study of commercially insured and Medicaid patients using the US MarketScan® administrative claims database (**Figure 1**).
- Patients were included if they had LGS, DS, TSC, or other refractory epilepsies, and had initiated the plant-derived highly purified pharmaceutical formulation of CBD (Epidiolex®) between June 2019 and May 2022, with 180 days of continuous enrollment in commercial health plans or Medicaid before and after CBD initiation.
- The numbers of other ASMs and anxiolytics and the numbers of their pharmacological classes per patient per month were assessed and plotted in the 6 months of pre- and post-CBD initiation (lists of medications are available via QR code).
- Segmented regression-based interrupted time-series (ITS) analyses[6–9] were implemented to investigate trends of ASM and anxiolytic use (description of ITS analysis available via QR code).
- Regression coefficients (P<0.05) from the ITS analyses were used to compute annualized changes in other ASM and anxiolytic medication use and their classes after CBD initiation.
  - Analyses were stratified by patient population and health insurance type.
- The study was conducted with Epidiolex® and the results do not apply to other CBD-containing products.

Results

- Of 506 patients enrolled in commercial health plans, 271 had LGS, 15 had DS, 15 had TSC, and 205 had other refractory epilepsies.
- Of 1663 patients on Medicaid, 973 had LGS, 70 had DS, 72 had TSC, and 568 had other refractory epilepsies.
- Patient characteristics are shown in **Table 1**.

Figure 1. Study timeline and sample selection



CBD, cannabidiol; DS, Dravet syndrome; EAP, Expanded Access Program; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; TSC, tuberous sclerosis complex.

Table 1. Patient characteristics

Characteristic	Commercial					Medicaid				
	All[a] (N=506)	LGS (n=271)	DS (n=15)	TSC (n=15)	Other refractory epilepsy (n=209)	All[a] (N=1663)	LGS (n=973)	DS (n=70)	TSC (n=72)	Other refractory epilepsy (n=568)
Age, mean (SD)	15.7 (10.9)	15.0 (9.4)	11.9 (9.2)	12.8 (8.2)	17.2 (12.7)	15.5 (11.0)	14.9 (10.2)	12.1 (8.3)	12.9 (9.5)	17.3 (12.5)
Sex, female, n (%)	249 (49)	121 (45)	6 (40)	11 (73)	111 (54)	727 (44)	403 (41)	35 (50)	27 (38)	270 (48)
Comorbidities, n (%)										
CCI[c]										
0	10 (2)	0	0	1 (7)	9 (4)	49 (3)	0	2 (3)	1 (1)	46 (8)
1–2	272 (54)	133 (49)	9 (60)	10 (67)	120 (59)	722 (43)	381 (39)	50 (71)	48 (67)	255 (45)
3–4	186 (37)	117 (43)	4 (27)	3 (20)	62 (30)	702 (42)	460 (47)	15 (21)	17 (24)	215 (38)
5+	38 (8)	21 (8)	2 (13)	1 (7)	14 (7)	190 (11)	132 (14)	3 (4)	6 (8)	52 (9)
Anxiety	62 (12)	27 (10)	2 (13)	3 (20)	30 (15)	177 (11)	92 (9)	8 (11)	6 (8)	72 (13)
Autism spectrum disorder	96 (19)	69 (25)	7 (47)	5 (33)	15 (17)	356 (21)	237 (24)	25 (36)	29 (40)	76 (13)
Depression	34 (7)	3 (1)	1 (7)	2 (13)	28 (24)	101 (6)	42 (4)	4 (6)	1 (1)	54 (10)
Intellectual disorder(s)	259 (51)	187 (69)	14 (93)	6 (40)	52 (25)	1184 (71)	829 (85)	63 (90)	57 (79)	254 (45)
Learning disabilities	28 (6)	20 (7)	0	0	8 (4)	175 (11)	109 (11)	8 (11)	2 (3)	57 (10)

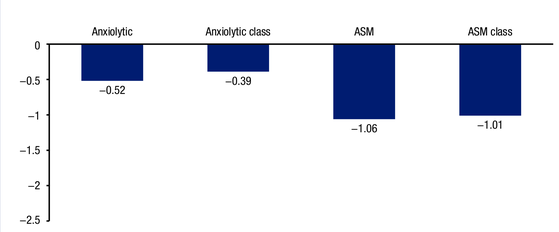
[a]The epilepsy categories are mutually exclusive. Three patients with both LGS and TSC diagnosis at baseline were assigned to TSC only. [b]The LGS, DS, and TSC categories are not mutually exclusive. [c]CCI includes myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, paraplegia and hemiplegia, diabetes, diabetes with complications, renal disease, mild liver disease, moderate/severe liver disease, peptic ulcers, rheumatic disease, human immunodeficiency virus/acquired immunodeficiency syndrome, cancer, and metastatic solid tumor.
CCI, Charlson Comorbidity Index; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; SD, standard deviation; TSC, tuberous sclerosis complex.

ITS analysis

View via QR code

Figure 2. Commercial health plan patients

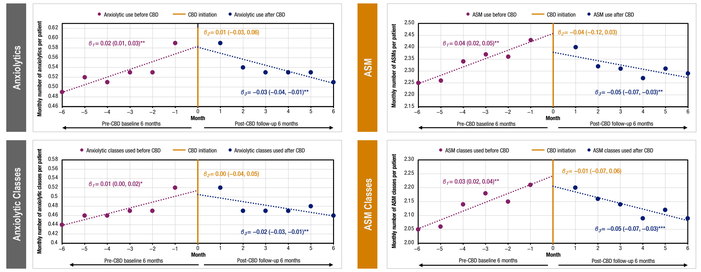
A Annualized changes in the number of anxiolytics and other ASMs and their classes per patient after initiation of CBD



The numbers were computed using ITS estimates with P<0.05. ASM, antiseizure medication; CBD, cannabidiol; ITS, interrupted time series.

- Commercially insured patients used fewer anxiolytics and ASMs post-CBD initiation and their use progressively increased pre-CBD initiation and had a progressively decreasing trend post-CBD initiation.

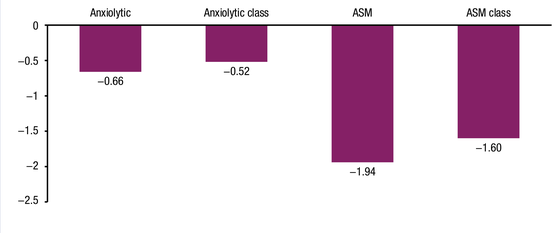
B Trends in the use of anxiolytics and other ASMs pre- and post-CBD initiation



*P<0.05; **P<0.01; ***P<0.001; (95% confidence intervals). ASM, antiseizure medication; CBD, cannabidiol.

Figure 3. Medicaid patients

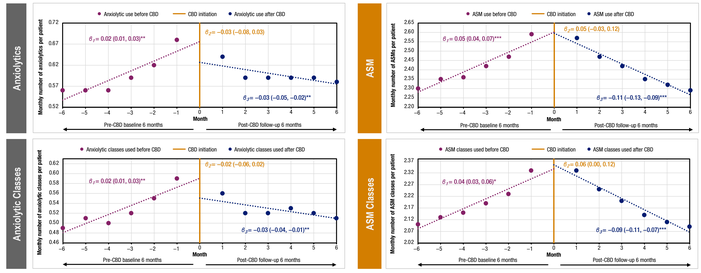
A Annualized changes in the number of anxiolytics and other ASMs and their classes per patient after initiation of CBD



The numbers were computed using ITS estimates with P<0.05. ASM, antiseizure medication; CBD, cannabidiol; ITS, interrupted time series.

- Medicaid patients used fewer anxiolytics and ASMs post-CBD initiation and their use progressively increased pre-CBD initiation and had a progressively decreasing trend post-CBD initiation.

B Trends in the use of anxiolytics and other ASMs pre- and post-CBD initiation



*P<0.05; **P<0.01; ***P<0.001; (95% confidence intervals). ASM, antiseizure medication; CBD, cannabidiol.

Limitations of the study

- Observed effects may not be solely attributed to CBD because there was no control group in the study design.
- Due to the limitation of claims, the intended usage of benzodiazepine and barbiturate prescriptions could not be ascertained for seizure control or anxiety management only, or both.
- The study covered a 6-month period, which may not be long enough to fully observe the impact of CBD on outcomes.

Conclusions

- The number of other ASMs and anxiolytics and their pharmacological classes progressively increased before CBD initiation and progressively decreased after CBD initiation.
- Annualized estimation suggests that initiation of CBD may be associated with a reduction of 1 to 2 ASMs/class per patient and 0.5 anxiolytic/class per patient.
- Future prospective studies are needed to better understand the effect of CBD treatment on concomitant medication use and nonseizure outcomes.

References: 1. Terman SW et al. *Epilepsy Behav.* 2020;111:107261. **2.** Löscher W, Klein P. *CNS Drugs.* 2021;35(9):935-963. **3.** Jazz Pharmaceuticals. Epidiolex® (cannabidiol) oral solution [prescribing information]. 2023. https://www.epidiolex.com/sites/default/files/pdfs/1120/EPX-03645-1120_EPIDIOLEX_(cannabidiol)_USPI.pdf. **4.** Gaston TE et al. *Epilepsy Behav.* 2019;95:10-17. **5.** Berg AT et al. Presented at the AES Annual Meeting; December 3–7, 2021; Chicago, IL, USA. Abstract 3.304. **6.** Wagner AK et al. *J Clin Pharm Ther.* 2002;27:299-309. **7.** Kontopantelis E et al. *BMJ.* 2015;350:h2750. **8.** Jandoc R et al. *J Clin Epidemiol.* 2015;68:950-956. **9.** Hawton K et al. *BMJ.* 2013;346:f403.

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Disclosures: All authors met the ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. **AMM** has consulted for, conducted studies funded by, or received honoraria for services provided to Jazz Pharmaceuticals, Inc. **GF, TG, SMT, TBS,** and **HNV** are employees of Jazz Pharmaceuticals and hold stock and/or stock options in Jazz Pharmaceuticals, plc. 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 years of age.

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Supplementary Materials

Interrupted time series (ITS) analysis[1,2]

Figure S1. ITS analysis to demonstrate trends in outcomes before and after CBD initiation

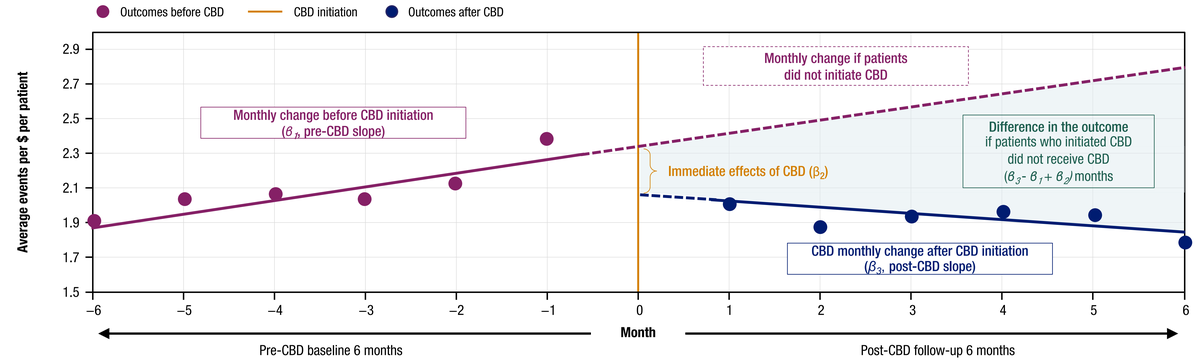


Figure adapted with permission from Fang G, Morse AM, Greco T, Davies KL, Saurer TB, and Viswanathan HN. Presented at International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2023.
CBD, cannabidiol.

- ITS analysis is a quasi-experimental observational study that involves analyzing the time series data or an outcome that is measured over time in a population and comparing the outcome before versus after an intervention.
- ITS segmented regression-based techniques are used to estimate linear trends.

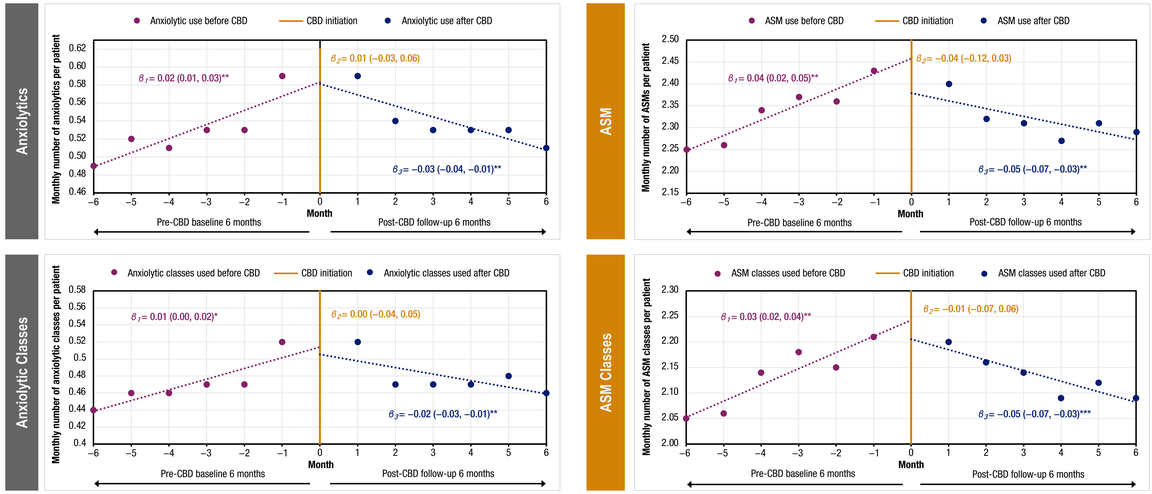
Table S1. Study medications of interest

Antiseizure medication		
Class	**Drug**	
Sodium channel blockers	• carbamazepine • eslicarbazepine acetate • fosphenytoin sodium • lamotrigine	• oxcarbazepine • phenytoin • lacosamide
Calcium channel blockers	• ethosuximide • gabapentin	• methsuximide • pregabalin
Gamma aminobutyric acid (GABA)ergic activity, benzodiazepines	• clobazam • clonazepam	• midazolam
GABAergic activity, other	• vigabatrin • phenobarbital	
Synaptic vesicle protein 2A modulator	• brivaracetam	• levetiracetam
Multiple targets	• ezogabine • felbamate • rufinamide	• topiramate • zonisamide
Other	• acetazolamide • adrenocorticotropic hormone (ACTH) • everolimus • perampanel	• primidone • stiripentol • tiagabine • valproate • valproic acid • divalproex sodium

Anxiolytics		
Class	**Drug**	
Benzodiazepine	• lorazepam • diazepam • alprazolam • clonazepam • remimazolam	• chlordiazepoxide • clorazepate • midazolam • oxazepam
Nonbenzodiazepines	• buspirone	• meprobamate
Barbiturates	• pentobarbital • phenobarbital	• amobarbital
Antidepressants (SSRIs)	• citalopram • escitalopram • fluoxetine	• paroxetine • sertraline
Antidepressants (SNRIs)	• duloxetine	• venlafaxine
Antidepressants (TCAs)	• amitriptyline • imipramine	• nortriptyline • mirtazapine
Antidepressants (SARIs)	• trazodone	

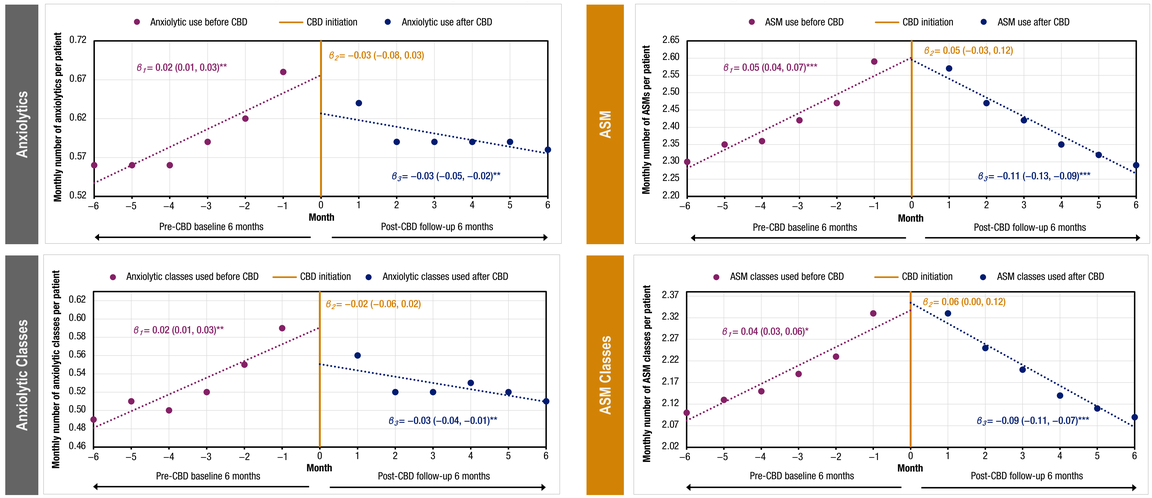
SARIs, serotonin antagonist and reuptake inhibitors; SNRIs, serotonin and norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Figure S2. Trends in the use of anxiolytics and other ASMs pre- and post-CBD initiation among commercially insured patients



*P<0.05; **P<0.01; ***P<0.001; (95% confidence intervals). ASM, antiseizure medication; CBD, cannabidiol.

Figure S3. Trends in the use of anxiolytics and other ASMs pre- and post-CBD initiation among Medicaid patients



*P<0.05; **P<0.01; ***P<0.001; (95% confidence intervals). ASM, antiseizure medication; CBD, cannabidiol.

References: 1. Kontopantelis E et al. *BMJ.* 2015;350:h2750. **2.** Wagner AK et al. *J Clin Pharm Ther.* 2002;27(4):299-309.