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Cannabidiol prescribing in the United States: An analysis of real-world data

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HIGHLIGHTS

- Patterns of Epidiolex® (cannabidiol) prescribing are not well characterized in the US.
- Using administrative data, we analyzed 4127 people who were prescribed Epidiolex®.
- Epidiolex® recipients often do not have FDA-approved diagnostic indications for cannabidiol.
- Co-prescription of medications with known interactions with Epidiolex® is common.

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ABSTRACT

Background: Off-label prescribing of Epidiolex® (pharmaceutical cannabidiol) comes with both potential benefits and risks for patients. The aims of this study were to: (1) identify the percentage of people prescribed Epidiolex® who do not have diagnostic indications for Epidiolex® (Lennox Gastaut Syndrome [LGS], Dravet Syndrome [DS], and Tuberous Sclerosis Complex [TSC]) and (2) examine potential co-prescribing of medications that may interact with Epidiolex®.

Method: Using TriNetX analytics, a web-based database of de-identified electronic health records spanning >110 million people in the United States, we analyzed 4214 people receiving Epidiolex® in 2022. We computed the number of people prescribed Epidiolex® who did not have diagnoses for LGS, DS, or TSC. We evaluated the prevalence of co-occurring prescriptions that are known to interact with cannabidiol following each individual's first Epidiolex® prescription.

Results: Among individuals receiving Epidiolex®, 40 % did not have FDA-approved diagnostic indications (LGS/DS/TSC) in the medical record. In the overall sample, co-occurring psychotropic prescribing was prevalent, including medications with known interactions with cannabidiol (Clobazam=47.2 %; Diazepam=47.4 %; Clonazepam=40.7 %). Among individuals without LGS/DS/TSC who received Epidiolex®, the most common diagnoses received following the index prescription were unspecified epileptic syndromes (53.8 %), sleep disorders (25.7 %), anxiety disorders (25.9 %), mood disorders (18.6 %) and autism spectrum disorders (10.8 %).

Conclusion: Off-label prescribing and co-prescription of medications with known interactions with cannabidiol is prevalent. Further research is needed to elucidate longitudinal outcomes associated with off-label Epidiolex® prescribing.

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1. Introduction

Epidiolex® (pharmaceutical cannabidiol [CBD]) is a non-intoxicating cannabinoid that is approved by the United States (US) Food and Drug Administration (FDA) for the treatment of seizures associated with three epilepsy syndromes: Lennox Gastaut syndrome [LGS], Dravet syndrome [DS] and Tuberous Sclerosis Complex [TSC] (Wechsler et al., 2024; Xu et al., 2024). While synthetic versions of tetrahydrocannabinol have previously been approved by the FDA, Epidiolex® represented the first time a cannabis plant-derived compound was deemed acceptable for medical use in the US (Britch et al., 2021; Yang and Szaflarski, 2019). In the United Kingdom and European Union, pharmaceutical cannabidiol (spelled as Epidyolex®) has also been approved for the treatment of LGS, DS, and TSC (Wechsler et al., 2024).

These recent approvals worldwide raise questions about whether pharmaceutical cannabidiol may experience an uptick in off-label prescribing for medical and psychiatric conditions beyond LGS, DS, and TSC (Rubin, 2019; Yang and Szaflarski, 2019). For instance, pharmaceutical cannabidiol is emerging as a promising off-label treatment for insomnia (Bhagavan et al., 2020), anxiety (Wright et al., 2020), and non-LGS/DS/TSC genetic epilepsy syndromes such as CDKL5, Aicardi, Dup15q, and Doose syndromes (Abu-Sawwa et al., 2020; Devinsky et al., 2018). Yet, off-label prescribing comes with both benefits and risks, as concern has been raised about drug-drug interactions, suboptimal dosing, and safety monitoring challenges for Epidiolex® (Wechsler et al., 2024). To date, population-level data on the potential off-label indications for pharmaceutical cannabidiol are not well-characterized.

Real-world clinical evidence, defined as the use of routinely-collected health care data such as electronic health records, insurance claims, and government registries, may be useful in monitoring the uptake of pharmaceutical cannabidiol. We used electronic health records data spanning over 110 million people in the US, to compute the rates of Epidiolex® prescribing in 2022, as well as co-occurring diagnoses and prescriptions. This information can help evaluate the extent to which Epidiolex® is being utilized off-label. Further, understanding prescribing practices for Epidiolex® and common co-prescriptions may provide essential preliminary data to help optimize the safety of cannabidiol prescribing (Smith et al., 2024).

2. Methods

This study was a secondary analysis of the TriNetX Network (Palchuk et al., 2023), a comprehensive electronic health records-based dataset. Details of the TriNetX data have been described in our prior work (Brown et al., 2024). In brief, the TriNetX Network includes inpatient clinical data, ambulatory clinical data, and linked prescriptions for over 100 million people in the US. The data also encompass multiple electronic health record types, including Epic Systems (encompassing over one-third of the market share of US hospitals) and the Veterans Affairs electronic health record systems in the US. On average, the TriNetX databases capture over ten years of data across each healthcare organization, with over 50 % of patients having over five years of continuous data. Most healthcare organizations refresh their TriNetX data at least monthly, with some updating as frequently as daily. Each individual has a unique identifier that links individuals across years, health care systems, and file types (i.e., prescription data, admissions data, and healthcare organization visit data). Methods for the validation of TriNetX data have been previously described (Palchuk et al., 2023). Due to the de-identified nature of our secondary data, the study was determined to be non-human subjects research by the Carilion Clinic Institutional Review Board.

In the present study, individuals were required to have continuous health care enrollment between the first date of Epidiolex® receipt in 2022 ("*index date*") and 10/27/2024 ("*date of query*"). We identified people receiving two or more Epidiolex® prescriptions, ascertained via RxNorm code between 1/1/2022–12/31/2022, a year that corresponded to increases in sales of Epidiolex® (JazzPharmaceuticals, 2023). We required a second prescription required in order to reduce misclassification and increase the likelihood that individuals were consuming their medication (Asamoah-Boaheng et al., 2021). If the diagnoses of LGS, DS, and/or TSC were present, we inferred that Epidiolex® was prescribed for those conditions. To assess potential off-label prescribing of Epidiolex®, we conducted a secondary analysis among individuals *without* diagnoses for LGS, DS, or TSC at any time point in the medical record.

The outcome variables of interest were: 1) diagnoses (i.e., mood disorders, anxiety disorders, insomnia) and 2) psychotropic prescriptions prescribed between the index date and date of query. To examine overlap of over non-cannabidiol prescriptions and Epidiolex® at the time of the first script, we conducted secondary analyses assessing the medications that were prescribed in the 1-, 3- and 6-months immediately following the date of the first Epidiolex® prescription. Diagnoses were delineated by International Classification of Diseases-10 Clinical Modification (ICD-10-CM) codes (see Supplement). Recognizing that Epidiolex® may interact with other medications via the CYP450 pathways (Smith et al., 2024), co-occurring psychiatric medications (i.e., antidepressants, antipsychotics, benzodiazepines, psychotropic medications) (Balachandran et al., 2021) with known interactions with cannabidiol were ascertained via RxNorm and Anatomical Therapeutic Chemical codes. For more details on the study design and STROBE/RECORD-PE reporting guidelines, see Supplement. Per TriNetX's adherence to HIPAA, cells with fewer than ten observations were rounded to "<10."

3. Results

Our sample consisted of 4214 individuals with two or more prescriptions for Epidiolex® in 2022 (Table 1). The mean age was 22.2 years (SD=18.1), with 47.5 % identified as female and 73.7 % White. Overall, 40 % of the sample did not have an FDA-approved diagnostic indication for Epidiolex® in the medical record (n=1713) at any point in time. Between the first (index) Epidiolex® prescription and the date of query, 46.3 % had at least one claim for LGS, 4.7 % for DS, and 3.6 % for TSC. (Table 1); nearly one-third had a diagnosis for sleep disorders (29.2 %) following the index date, and 15.5 % had a diagnosis for autism spectrum disorder.

With regards to co-occurring prescriptions, nearly 50 % of the sample received at least one prescription for clobazam and diazepam between the index date and the date of query (10/27/2024). Approximately one-third of the sample had at least one script for antidepressants and one-fifth of the sample had at least one script for opioids following the index Epidiolex® prescription. As shown in eTable 2, the majority of Epidiolex® recipients who were co-prescribed clobazam (47.2 %) between the index date and date of query had received clobazam in the 90 days following the index date (37.9 %). Likewise, the majority of Epidiolex® recipients who were co-prescribed other antiseizure medications (i.e., diazepam, clonazepam, carbamazepine) after the index date received the non-cannabidiol antiseizure medications in the 90 days following the initial Epidiolex prescription.

To assess potential off-label prescribing, we conducted a subgroup analysis by limiting our sample to individuals without LGS/DS/TSC who received Epidiolex® (n=1713). Among these individuals without LGS/DS/TSC, the most common seizure disorder was "Epilepsy, unspecified" (53.8 %), followed by complex partial seizures (27 %), simple partial seizures (22.4 %), other epileptic syndromes (17.6 %), and generalized idiopathic epilepsy (16.7 %). Among people without LGS/DS/TSC, the most common non-seizure-related diagnoses received following the index date were sleep disorders (25.7 %), anxiety disorders (25.9 %), mood disorders (18.6 %) and autism spectrum disorders (10.8 %). Over one-fifth of individuals receiving Epidiolex ® off-label also received medications with known interactions with cannabidiol such as diazepam (36.0 %), clonazepam (32.9 %), clobazam (32.8 %), and lorazepam

Table 1
Characteristics of the analytic sample.

	Among all people w/ ≥2 Epidiolex® fills in 2022, n=4214		Limited to people without# LGS, DS, or TSC, w/ ≥2 Epidiolex ® fills in 2022, n=1713	
Mean Age at Index, years (+/- SD)	22.2 +/- 18.1		29.7 +/- 22.0	
Female Gender	2002	47.5	913	2002
Ethnicity				
Non-Hispanic	3106	73.7	1331	3106
Hispanic or Latino	644	15.3	197	644
Race (not mutually exclusive with ethnicity)				
White	3015	71.5	1287	3015
Black or African American	428	10.2	140	428
Other Race	206	4.9	72	206
Asian	131	3.1	47	131
Medications Prescribed Between First Epidiolex® Prescription and Date of Query				
Antidepressants	4214	100 %	1713	100 %
Selective serotonin reuptake inhibitors	966	22.9 %	533	31.1 %
Amitriptyline**	479	11.4 %	270	15.8 %
Nortriptyline	52	1.2 %	30	1.8 %
Antipsychotics	834	19.8 %	334	19.5 %
Opioids	1600	38.0 %	644	37.6 %
Oxycodone	715	17.0 %	321	18.7 %
Hydromorphone	578	13.7 %	261	15.2 %
Morphine**	546	13.0 %	201	11.7 %
Antiseizure Medication				
Diazepam**	1999	47.4 %	616	36.0 %
Clonazepam**	1714	40.7 %	564	32.9 %
Lorazepam**	1492	35.4 %	516	30.1 %
Clobazam**	1987	47.2 %	562	32.8 %
Levetiracetam**	1675	39.7 %	543	31.7 %
Lacosamide**	1013	24.0 %	421	24.6 %
Valproate**	1068	25.3 %	288	16.8 %
Lamotrigine**	880	20.9 %	360	21.0 %
Carbamazepine**	111	2.6 %	60	3.5 %
Oxcarbazepine**	363	8.6 %	177	10.3 %
Phenobarbital**	437	10.4 %	131	7.6 %
Phenytoin**	130	3.1 %	46	2.7 %
Fosphenytoin**	245	5.8 %	63	3.7 %
Chlordiazepoxide**	10	<1.0 %	10	<1.0 %
Ethosuximide**	110	2.6 %	55	3.2 %
Gabapentin**	509	12.1 %	270	15.8 %
Co-Occurring Diagnoses Received Between First Epidiolex® prescription and Date of Query				
Mood [affective] disorders	456	10.8 %	319	18.6 %
Anxiety disorders	736	17.5 %	444	25.9 %
Psychotic disorders	39	<1.0 %	16	<1.0 %
Substance-related disorders	195	4.6 %	133	7.8 %
Chronic pain, not elsewhere classified	215	5.1 %	143	8.3 %
Acute pain, not elsewhere classified	196	4.7 %	87	5.1 %
Sleep disorders	1261	29.9 %	441	25.7 %
Autism-spectrum disorder	655	15.5 %	185	10.8 %
Attention-deficit hyperactivity disorder	320	7.6 %	111	6.5 %
Cancers or neoplasms	463	11.0 %	238	13.9 %
Lennox-Gastaut syndrome (FDA indication for Epidiolex®)	1950	46.3 %	0	0.0 %
Dravet syndrome (FDA indication for Epidiolex®)	198	4.7 %	0	0.0 %
Tuberous sclerosis (FDA indication for Epidiolex®)	152	3.6 %	0	0.0 %
Other seizure disorders				
Seizures of localized onset	423	10.0 %	212	12.4 %
Simple partial seizures	789	18.7 %	384	22.4 %
Complex partial seizures	1034	24.5 %	462	27.0 %
Generalized idiopathic epilepsy	912	21.6 %	286	16.7 %
Absence epileptic syndrome	213	5.1 %	66	3.9 %
Juvenile myoclonic epilepsy	44	1.0 %	25	1.5 %
Lafora progressive myoclonus epilepsy	10	<1.0 %	10	<1.0 %
Other epileptic syndromes	1087	25.8 %	302	17.6 %
Seizures related to external causes	72	1.7 %	32	1.9 %
Epileptic spasms	335	7.9 %	69	4.0 %
Other seizures	231	5.5 %	58	3.4 %
CDKL 5 Deficiency Disorder	15	<1.0 %	10	<1.0 %
Epilepsy, unspecified	2737	65.0 %	921	53.8 %

ˆ=FDA indication for Epidiolex®
**= Medications with potential cannabidiol interactions (Balachandran et al., 2021)
#=Exclusion of n=2501 without a claim for LGS, DS, or TSC at **any point** during insurance enrollment (not limited to time between date of first Epidiolex ® prescription and date of query)

(30.1 %) following the index Epidiolex® prescription.

4. Discussion

To our knowledge, there are no observational studies providing descriptive statistics on the real-world prevalence of Epidiolex® prescriptions in the US. While the majority of individuals receiving Epidiolex® had diagnoses for seizure disorders, they often did not have FDA-approved diagnostic indications in the medical record (LGS, DS, and TSC). Upon excluding individuals receiving Epidiolex® with any of these three diagnoses, we learned that the most common off-label indications may include sleep disorders, anxiety disorders, and non-LGS/DS/TSC epilepsy syndromes.

Placebo-controlled studies of cannabidiol's efficacy are lacking across all types of epilepsy, but there is a considerable amount of open-label data to support the use of the drug in various forms of refractory epilepsy (de Carvalho Reis et al., 2020; Talwar et al., 2023). While many individuals derive clinically meaningful benefits from off-label cannabidiol (Abu-Sawwa et al., 2020; Devinsky et al., 2018), such benefits should also be weighed alongside the potential risks posed by drug-drug interactions. We found that many recipients of Epidiolex® had overlapping scripts for medications that may interact with cannabidiol. This has important clinical implications, particularly in light of July 2024 consensus recommendations identifying a "critical" need for data illuminating the potential of drug-drug interactions among recipients of pharmaceutical cannabidiol (Wechsler et al., 2024). Prior studies illustrated the potential for pharmacokinetic and pharmacodynamic interactions between cannabidiol and commonly prescribed anti-seizure (Gilmartin et al., 2021) and antidepressant (Vaughn et al., 2021) medications, primarily due to the CYP2C19 enzyme in the liver. Of note, somnolence, diarrhea, and lethargy, particularly when Epidiolex is consumed with clobazam, are the most common drug-drug interactions seen among individuals consuming Epidiolex® (Dos Santos et al., 2020; Patel et al., 2022). Cases of pneumonia in the setting of altered mental status and persistent diarrhea requiring hospitalization have been reported in the context of cannabidiol-clobazam interactions (Dos Santos et al., 2020; Patel et al., 2022). While somnolence and diarrhea are not typically life-threatening, they can contribute to significant quality of life disruptions that predict antiseizure medication discontinuation (Anderson et al., 2021; Fazlollahi et al., 2023). Such consequences of drug-drug interactions are not reliably captured in the present dataset, and future studies with more refined datasets (i.e., CMS claims, Merative MarketScan) may help to elucidate longitudinal outcomes of people

receiving Epidiolex®

There are several limitations to consider. While we have a listing of individuals' diagnoses, the TriNetX data does not specify the condition Epidiolex® was used to treat, and we do not have detailed data on physicians' rationale for prescribing Epidiolex®. More than half of individuals without LGS, DS, and TSC received diagnoses of "Epilepsy, unspecified," and we are unable to verify the off-label use of Epidiolex® for other epilepsy syndromes such as Aicardi, Dup15q, and Doose syndromes (Abu-Sawwa et al., 2020; Devinsky et al., 2018; Gofshteyn et al., 2017; Sexton et al., 2021) that are not reliably captured via ICD codes. While the prevalence of sleep disorders (nearly one-third of the sample) may suggest that some individuals were prescribed Epidiolex® for insomnia, sleep-related conditions can also co-occur with LGS, DS, and TSC. Due to the limitations of the TriNetX platform's built-in analytic tools, we are unable to calculate precisely how many individuals with sleep disorders using Epidiolex® were receiving the cannabidiol prescription off-label, as opposed to having comorbid LGS, DS, and TSC. The sizeable prevalence of autism spectrum disorders in the sample may reflect autism spectrum disorder's comorbidity with LGS, DS, and TSC, although preliminary studies have suggested that cannabidiol may have anxiolytic benefits for some children with autism spectrum disorders who do not have LGS, DS, and TSC (Hacohen et al., 2022). In addition, emerging literature has highlighted the potential of cannabidiol in treating anxiety (Berger et al., 2022)- and cancer-related symptoms (Sexton et al., 2021).

These results may undercount the true prevalence of cannabidiol consumption, as Epidiolex® can be expensive and limited by insurance barriers (Kerr et al., 2019). As a result, many individuals may elect to use artisanal cannabidiol products procured from commercial dispensaries, which is not captured by this data (Kerr et al., 2019). In fact, various non-prescription, hemp-derived cannabidiol products are widely available and frequently utilized throughout the US (Wilson-Poe et al., 2023), and there is concern that patients and clinicians may struggle to differentiate between Epidiolex® and non-FDA-approved cannabidiol products(Wechsler et al., 2024). Because artisanal hemp-derived cannabidiol products have significant heterogeneity in their composition, partly due to a lack of regulatory oversight (Miller et al., 2022), research is needed to evaluate health outcomes among those receiving non-FDA-approved cannabidiol products (Wechsler et al., 2024). Additionally, many individuals using cannabidiol may not disclose cannabis consumption to their physicians (Li et al., 2023) and learn about cannabis from non-medical sources including internet, social media, friends, and family. In fact, some individuals consuming non-medical cannabis report unsuccessful trials of clinician-prescribed Epidiolex® (Zhu et al., 2022).

5. Conclusion

Our study provides descriptive statistics suggesting that as many as two fifths of all Epidiolex® recipients may not have FDA-approved diagnostic indications for pharmaceutical cannabidiol in the electronic health record. We also illustrate that recipients of Epidiolex® may also be receiving prescriptions with the potential for drug-drug interactions. As noted in recent consensus-based guidance on the optimization of Epidiolex® for the treatment of LGS, DS, and TSC (Wechsler et al., 2024), more research is needed to evaluate longitudinal health outcomes among recipients of Epidiolex®.

Ethics statement

Due to the de-identified nature of our secondary data, the study was determined to be non-human subjects research by the Carilion Clinic Institutional Review Board.

Role of the sponsor

The funding sources had no role in the study design, implementation, or interpretation of results.

Role of the Funding Source

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Financial disclosures

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Data sharing agreement

Analyses were conducted via TriNetX's built-in analytic interface, and thus no programming code was utilized. Data can be obtained via written request: https://trinetx.com/data-sets-analytics/

CRediT authorship contribution statement

Yifan Li: Writing – review & editing, Writing – original draft, Validation. **Binx Yezhe Lin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Kevin Young Xu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Fabio Nascimento:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization. **Jacob Borodovsky:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Jacob Steinle:** Writing – review & editing, Writing – original draft, Validation. **Pallawi Jyotsana:** Writing – review & editing, Writing – original draft, Validation. **Ruth Ling:** Writing – review & editing, Writing – original draft, Validation. **Lisa Gong:** Writing – review & editing, Writing – original draft, Validation. **Chloe Lessard:** Writing – review & editing, Writing – original draft, Validation.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI was used by the author

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Kevin Xu reports financial support was provided by National Institute on Drug Abuse. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Dissemination Declaration

Dissemination to study participants and patient organizations is not possible or applicable due to the de-identified nature of our data.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dadr.2024.100303.

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