Epidiolex Utilization

BACKGROUND

Epidiolex (cannabidiol) was approved by the US Food and Drug Administration (FDA) on June 25, 2018, making it the first and only plant-derived, purified, pharmaceutical-grade, cannabidiol (CBD) prescription medication.[1] CBD is considered a phytocannabinoid, a chemical found within cannabis plants that interacts with cannabinoid receptors throughout the body, from neurons in the brain and peripheral nervous system to the thyroid, liver, gastrointestinal tract, and immune cells.[2,3] While the exact mechanism of action is unknown, CBD has been found to be effective in treatment-resistant epilepsy. Unlike THC, another phytocannabinoid having antiepileptic effects, CBD has no known abuse potential and lacks detectable psychoactive properties, providing patients the benefit of reduction in seizure frequency while experiencing minimal psychoactive side effects.[3]

Epidiolex is available as an oral solution and is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.[4,5] Several phase 3, randomized, placebo-controlled clinical trials have demonstrated that Epidiolex is effective and well tolerated when added to conventional antiepileptic regimens for these indications.[6–9] Dosing of Epidiolex should be initiated at 2.5 mg/kg by mouth twice daily, and titrated up in weekly increments of 2.5 mg/kg twice daily as necessary and tolerated to a maximum dose of 20 mg/kg/day for LGS and DS and 25 mg/kg/day for TSC.[4,5] Common adverse drug effects occurring in greater than 10% of trial participants included somnolence, fatigue, rash, decreased appetite, diarrhea, insomnia, infection, and elevated liver transaminases.[6–9]

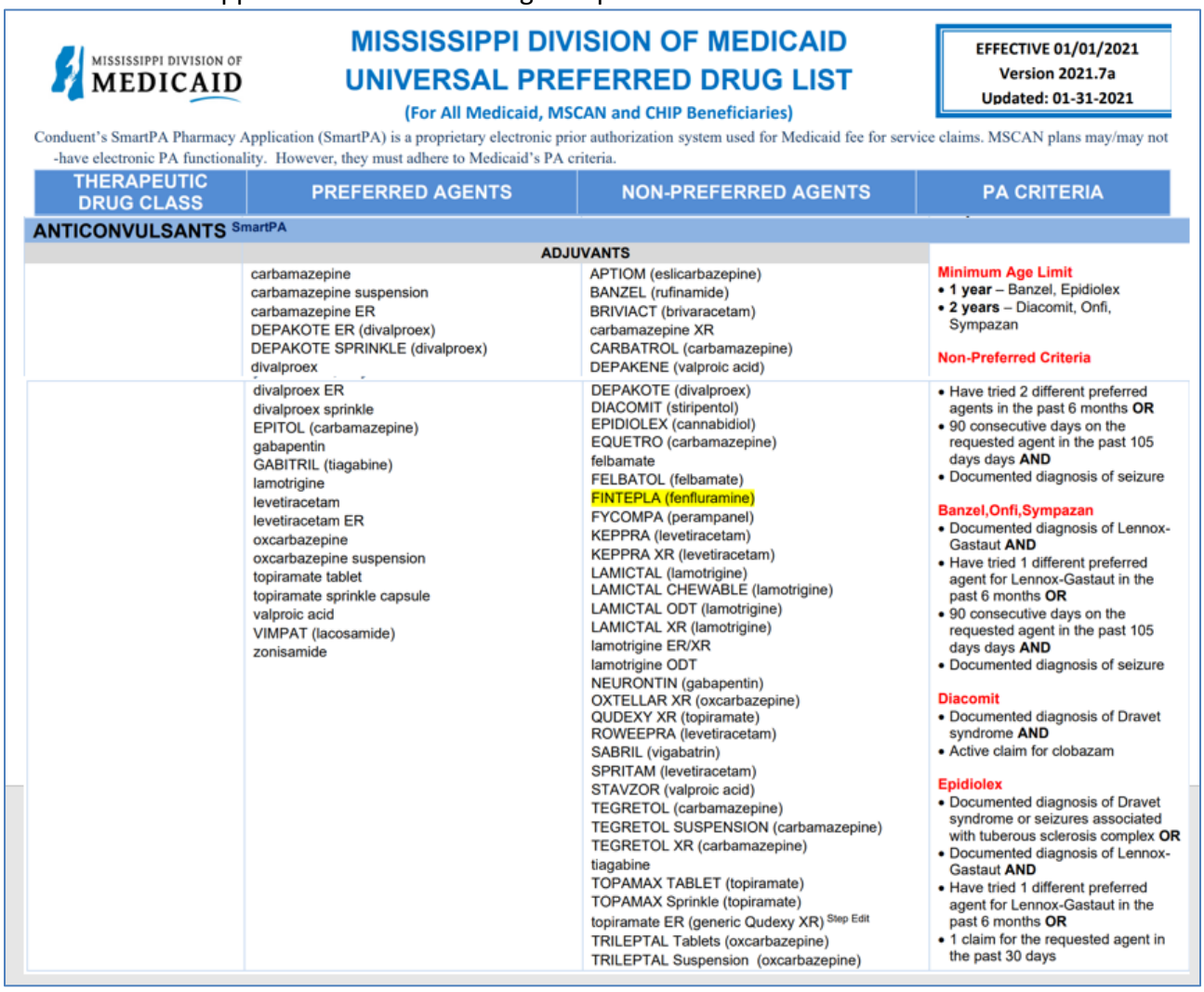
Epidiolex is considered an add-on therapy for treatment-resistant epilepsy, where patients are typically inadequately controlled on at least one antiepileptic drug (AED).[4,5] Valproate is commonly considered first-line treatment for LGS, with clonazepam, topiramate, lamotrigine, felbamate, clobazam, rufinamide, and Epidiolex considered adjunctive treatment options.[10] Clobazam and valproate are common first-line treatment options for DS, with stiripentol, topiramate, clonazepam, levetiracetam, zonisamide, ethosuximide, fenfluramine, and Epidiolex serving as second- and third-line treatment options.[11] There are many AEDs commonly used for the control of seizures associated with TSC and their use depends on several factors including seizure type, affected individual's age, other organ systems impacted, and symptom severity; however the only medications with FDA approved indications for the treatment of seizures associated with tuberous sclerosis are Epidiolex and Afinitor (everolimus).[12,13]

While Epidiolex is the only FDA-approved prescription CBD product, there are other cannabidiol containing products on the market, including hemp oil nationally and medical marijuana and CBD supplements in select states. In Mississippi, Initiative 65, a measure allowing qualified patients with debilitating medical conditions (including epilepsy and other seizures) to use medical marijuana, was passed by voters in November 2020. This amendment allows medical marijuana to

be provided only by licensed treatment centers.[14] Despite their availability, these other products are not federally regulated and either have mixed or are completely lacking efficacy and safety data in relation to seizures.[15]

Epidiolex is nonpreferred on the Universal Preferred Drug List (UPDL) with the following SmartPA requirements: minimum age limit of 1 year, diagnosis requirements, and prior anticonvulsant use requirements for those with a diagnosis of Lennox Gastaut. (Figure 1)

FIGURE 1: Mississippi Medicaid UPDL Listing for Epidiolex



MISSISSIPPI DIVISION OF MEDICAID

MISSISSIPPI DIVISION OF MEDICAID
UNIVERSAL PREFERRED DRUG LIST
(For All Medicaid, MSCAN and CHIP Beneficiaries)

EFFECTIVE 01/01/2021
Version 2021.7a
Updated: 01-31-2021

Conduent's SmartPA Pharmacy Application (SmartPA) is a proprietary electronic prior authorization system used for Medicaid fee for service claims. MSCAN plans may/may not -have electronic PA functionality. However, they must adhere to Medicaid's PA criteria.

THERAPEUTIC DRUG CLASS	PREFERRED AGENTS	NON-PREFERRED AGENTS	PA CRITERIA
ANTICONVULSANTS SmartPA			
	ADJUVANTS		
	carbamazepine carbamazepine suspension carbamazepine ER DEPAKOTE ER (divalproex) DEPAKOTE SPRINKLE (divalproex) divalproex	APTIOM (eslicarbazepine) BANZEL (rufinamide) BRIVIACT (brivaracetam) carbamazepine XR CARBATROL (carbamazepine) DEPAKENE (valproic acid)	**Minimum Age Limit** • **1 year** – Banzel, Epidiolex • **2 years** – Diacomit, Onfi, Sympazan **Non-Preferred Criteria**
	divalproex ER divalproex sprinkle EPITOL (carbamazepine) gabapentin GABITRIL (tiagabine) lamotrigine levetiracetam levetiracetam ER oxcarbazepine oxcarbazepine suspension topiramate tablet topiramate sprinkle capsule valproic acid VIMPAT (lacosamide) zonisamide	DEPAKOTE (divalproex) DIACOMIT (stiripentol) EPIDIOLEX (cannabidiol) EQUETRO (carbamazepine) felbamate FELBATOL (felbamate) FINTEPLA (fenfluramine) FYCOMPA (perampanel) KEPPRA (levetiracetam) KEPPRA XR (levetiracetam) LAMICTAL (lamotrigine) LAMICTAL CHEWABLE (lamotrigine) LAMICTAL ODT (lamotrigine) LAMICTAL XR (lamotrigine) lamotrigine ER/XR lamotrigine ODT NEURONTIN (gabapentin) OXTELLAR XR (oxcarbazepine) QUDEXY XR (topiramate) ROWEEPRA (levetiracetam) SABRIL (vigabatrin) SPRITAM (levetiracetam) STAVZOR (valproic acid) TEGRETOL (carbamazepine) TEGRETOL SUSPENSION (carbamazepine) TEGRETOL XR (carbamazepine) tiagabine TOPAMAX TABLET (topiramate) TOPAMAX Sprinkle (topiramate) topiramate ER (generic Qudexy XR) Step Edit TRILEPTAL Tablets (oxcarbazepine) TRILEPTAL Suspension (oxcarbazepine)	• Have tried 2 different preferred agents in the past 6 months **OR** • 90 consecutive days on the requested agent in the past 105 days days **AND** • Documented diagnosis of seizure **Banzel,Onfi,Sympazan** • Documented diagnosis of Lennox-Gastaut **AND** • Have tried 1 different preferred agent for Lennox-Gastaut in the past 6 months **OR** • 90 consecutive days on the requested agent in the past 105 days days **AND** • Documented diagnosis of seizure **Diacomit** • Documented diagnosis of Dravet syndrome **AND** • Active claim for clobazam **Epidiolex** • Documented diagnosis of Dravet syndrome or seizures associated with tuberous sclerosis complex **OR** • Documented diagnosis of Lennox-Gastaut **AND** • Have tried 1 different preferred agent for Lennox-Gastaut in the past 6 months **OR** • 1 claim for the requested agent in the past 30 days

Since its FDA approval in 2018, Epidiolex use has steadily risen in Mississippi Medicaid. MS-DUR conducted an analysis of Epidiolex utilization trends among Medicaid beneficiaries from June 2018 through December 2020.

METHODS

A retrospective analysis was conducted using Mississippi Medicaid fee-for-service (FFS) and coordinated care organization [CCOs: United Healthcare (UHC), Magnolia (MAG), and Molina (MOL)] claims for the period June 2018 to December 2020 to identify beneficiaries prescribed Epidiolex. Beneficiary age, race, sex, and health plan were identified according to the first claim of Epidiolex (index date) during the study period (Table 1). Target diagnoses were assessed in medical claims data during the period beginning January 2016 until the Epidiolex index date (Table 2). A beneficiary was considered to have a target diagnosis if medical claims data contained an ICD-code for any of the associated diagnoses during the measurement period. Quarterly trends in Epidiolex utilization by number of beneficiaries, pharmacy claims, and associated pharmacy costs were summarized (Tables 3-4, Figure 2). For each Epidiolex claim, characteristics of prescribing providers were also identified (Table 5). Quarterly dosing trends in Epidiolex utilization were evaluated and descriptive statistics were assessed during the study period (Figures 3a-e). Daily Epidiolex dose was calculated by taking the product of the submitted quantity on the claim (ml) and the strength of the product (100mg/ml) divided by the days supply submitted for that claim. Antiepileptic drug utilization in a 90-day period pre and post-Epidiolex utilization was assessed from pharmacy claims data (Tables 6-7). Trends in drug use were summarized by ranking utilization based on number of beneficiaries prescribed the drug and associated costs. Concurrent antiepileptic drug use was also summarized by number of distinct drugs and drug categories used in the pre and post-Epidiolex period.

RESULTS

In Table 1, beneficiary demographic characteristics are presented for those prescribed Epidiolex.

- 70.1% (115/164) of beneficiaries were < 18 years of age;
- 60.4% (99/164) were males;
- 52.4% (86/164) were Caucasian;
- 55% (91/164) were in FFS

Table 1. Demographic Characteristics of Beneficiaries Prescribed Epidiolex (June 2018* - December 2020)									
Variable	**FFS**		**UHC**		**Magnolia**		**Molina**		**Total**
Age Category (yrs)									
0 - 6	15	16.5%	13	43.3%	9	23.7%	1	20.0%	38
7 - 12	24	26.4%	1	3.3%	13	34.2%	1	20.0%	39
13 - 17	28	30.8%	6	20.0%	4	10.5%	0	0.0%	38
18 and above	24	26.4%	10	33.3%	12	31.6%	3	60.0%	49
Total	***91***		***30***		***38***		***5***		***164***
Gender									
Female	33	36.3%	12	40.0%	17	44.7%	3	60.0%	65
Male	58	63.7%	18	60.0%	21	55.3%	2	40.0%	99
Total	***91***		***30***		***38***		***5***		***164***
Race									
Caucasian	56	61.5%	8	26.7%	21	55.3%	1	20.0%	86
African American	23	25.3%	8	26.7%	9	23.7%	2	40.0%	42
Hispanic	2	2.2%	1	3.3%	0	0.0%	0	0.0%	3
Other	10	11.0%	13	43.3%	8	21.1%	2	40.0%	33
Total	***91***		***30***		***38***		***5***		***164***
*Although the study period started from June 2018 when Epidiolex was approved, pharmacy claims were not seen until November 2018.									
NOTE: Age and health plan were assessed at the first Epidiolex claim referred to as the index date.									

Table 2 examines target diagnoses associated with beneficiaries prescribed Epidiolex. Medical claims data was evaluated from January 2016 (> 2 years prior to the first Epidiolex claim) to identify target diagnoses. A beneficiary could have more than one target diagnosis present in claims data. Each target diagnosis identified in claims data was noted in Table 2.

- 22.6% (37/164) of beneficiaries did not have a target diagnosis present in claims data.
    - *Dravet syndrome did not have a specific ICD-10 diagnosis code assigned until late 2020. Other ICD-10 codes commonly utilized for Dravet syndrome (G40.40, G40.41) were also used in identifying beneficiaries with that diagnosis.*
- 18.3% (30/164) of beneficiaries had dual target diagnoses present in claims data.

Table 2: Summary of Target Diagnoses for Beneficiaries Prescribed Epidiolex		
Target Diagnoses*	**Beneficiaries (N=164)**	
	n	**%**
Lennox-Gastaut Syndrome	57	34.8%
Dravet Syndrome	92	56.1%
Tuberous Sclerosis Complex	8	4.9%
No Associated Diagnoses	***37***	***22.6%***
*Target diagnoses were evaluated from January 2016 until Epidiolex index date.		
NOTE: Numbers are not unique across diagnoses, same beneficiary may have multiple diagnoses		

Additional information for Table 2:
A beneficiary was considered to have target diagnoses if they had any claim with ICD-10 code for the said diagnoses during the evaluation period. ICD-10 codes assessed were as follows:
Epilepsy: G40*
Lennox-Gastatut Syndrome: G40.81*
Dravet Syndrome: G40.83*, G40.40*, G40.41* [*ICD-10 code specific for Dravet Syndrome (G40.83*) was not approved until late 2020. 92 benes having a diagnosis of Dravet syndrome is based on ICD-10 codes G40.40* and G40.41*.]*
Tuberous Sclerosis Complex: Q85.1

Of the 164 benes initiating Epidiolex, 37 beneficiaries did not have associated diagnoses. Among the remaining 127 beneficiaries, 30 beneficiaries had dual diagnoses (28 for LGS and DS, 1 for LGS and TSC, and 1 for DS and TSC); therefore, 97/164 (59.1%) unique beneficiaries had a single diagnosis.

Tables 3a/b detail quarterly trends in Epidiolex utilization by number of claims and number of beneficiaries.

- There have been a total of 2,061 claims for Epidiolex with 55.7% (1,148) in FFS.
- The total number of quarterly claims/beneficiaries treated rose consistently through Q2/2020 after which the numbers leveled off.

Table 3a: Trends in Epidiolex Utilization by Pharmacy Claims (November 2018 - December 2020)

Quarter	Plan				Total
	FFS	UHC	Magnolia	Molina	
Q4 2018	8	1	2	0	11
Q1 2019	68	3	25	0	96
Q2 2019	106	16	40	7	169
Q3 2019	128	35	55	11	229
Q4 2019	147	47	57	8	259
Q1 2020	167	59	64	12	302
Q2 2020	189	68	71	6	334
Q3 2020	165	78	73	9	325
Q4 2020	170	73	78	15	336
Total	***1,148***	***380***	***465***	***68***	***2,061***

Table 3b. Trends in Epidiolex Utilization by Beneficiaries (November 2018 - December 2020)

Quarter	Plan				Total
	FFS	UHC	Magnolia	Molina	
Q4 2018	8	1	2	0	11
Q1 2019	65	3	24	0	92
Q2 2019	99	14	38	7	158
Q3 2019	119	35	53	9	216
Q4 2019	137	46	54	8	245
Q1 2020	159	53	59	10	281
Q2 2020	178	60	63	6	307
Q3 2020	153	74	67	8	302
Q4 2020	158	63	68	14	303
Total*	***1,076***	***349***	***428***	***62***	***1,915***

*Does not represent unique beneficiaries.

In Table 4/Figure 2, quarterly trends in costs associated with Epidiolex are shown.

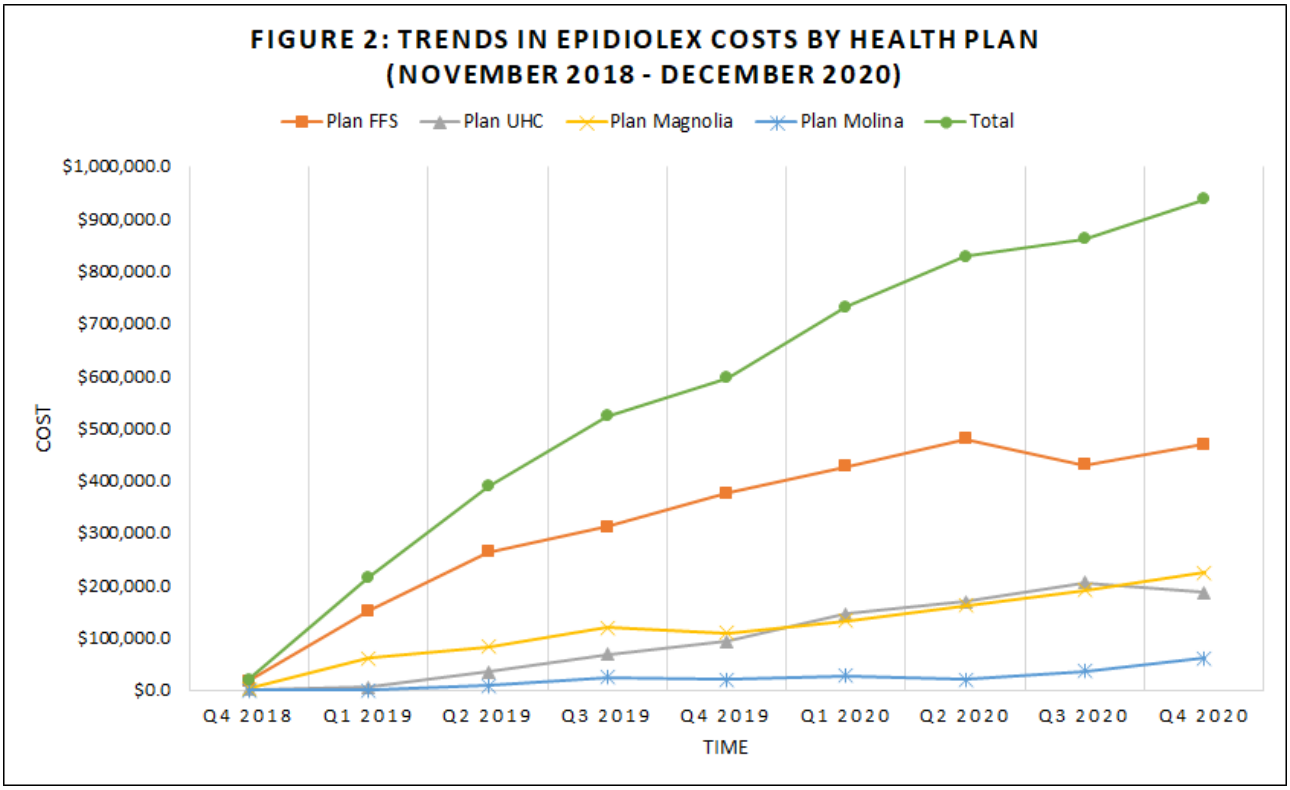
- Total quarterly costs have consistently climbed every quarter although the number of beneficiaries treated quarterly leveled off in Q2/2020.
- The cost/beneficiary treated has risen from $1,775/beneficiary in Q4/2018 to $3,095/beneficiary Q4/2020.

Table 4. Trends in Epidiolex Costs by Beneficiaries (November 2018 - December 2020)

Quarter	Total number of beneficiaries	Plan				Total	Costs per Beneficiary
		FFS	UHC	Magnolia	Molina		
Q4 2018	11	$16,213	$1,320	$1,986	$0	$19,520	$1,775
Q1 2019	92	$150,528	$5,181	$60,115	$0	$215,824	$2,346
Q2 2019	158	$263,917	$34,277	$82,346	$8,159	$388,699	$2,460
Q3 2019	216	$311,547	$67,862	$118,869	$24,778	$523,056	$2,422
Q4 2019	245	$376,104	$92,716	$108,226	$19,045	$596,091	$2,433
Q1 2020	281	$426,605	$145,841	$132,347	$26,440	$731,232	$2,602
Q2 2020	307	$478,606	$169,087	$161,386	$19,083	$828,162	$2,698
Q3 2020	302	$429,005	$205,261	$191,057	$36,020	$861,343	$2,852
Q4 2020	303	$468,530	$185,986	$223,353	$60,036	$937,904	$3,095
Total*	***1,915***	***$2,921,055***	***$907,531***	***$1,079,685***	***$193,561***	***$5,101,832***	

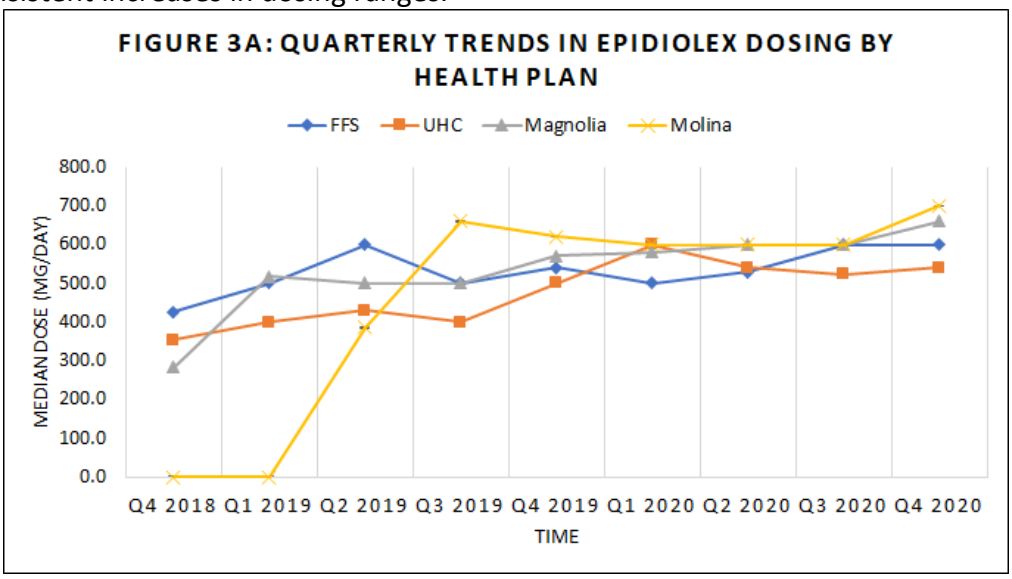
*Does not represent unique beneficiaries.

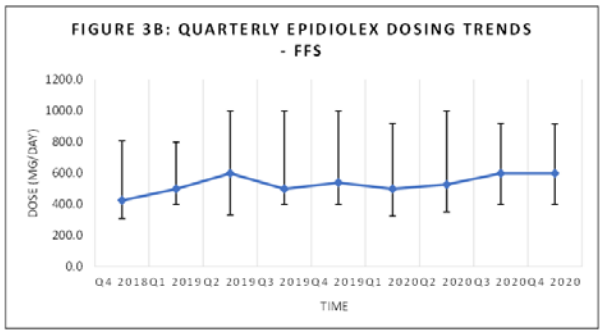
NOTE: This table is based on Table 3b in terms of Epidiolex utilization trends by beneficiaries.

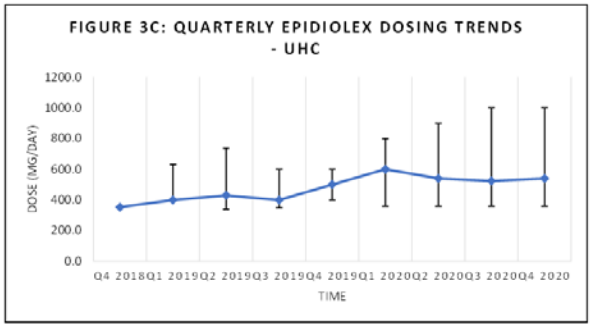


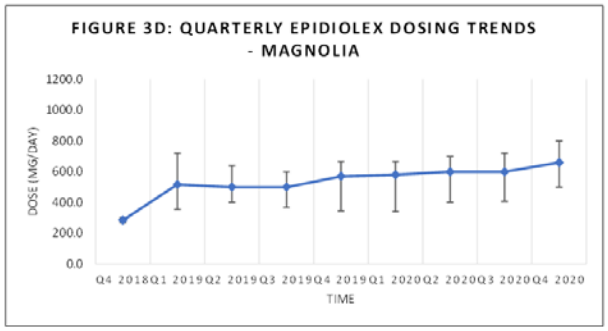
With the number of beneficiaries being treated leveling off in Q2/2020 yet the total costs and costs/beneficiary continuing to rise, MS-DUR assessed Epidiolex dosing trends. Figure 3a details quarterly dosing trends. Figures 3b-e show trends for each plan. Median daily dose point estimates and interquartile ranges are displayed for each quarter.

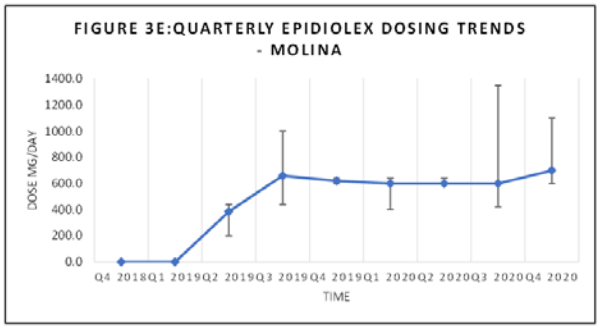
- Generally speaking, median daily dose has steadily risen across all plans with a few peaks occurring throughout the analysis period.
- When examining interquartile ranges, Magnolia and UHC appear to have had the largest consistent increases in dosing ranges.











Upon examining provider characteristics, neurologists and pediatricians made up the majority of prescribers associated with Epidiolex claims. (Table 5)

Table 5: Characteristics of Providers Prescribing Epidiolex (November 2018 - December 2020) (N=164)

Provider type	Number of claims	Number of benes*
MD-Neurology	876	77
MD-Pediatrics	879	75
NP-FM	78	15
Prov-Other	83	9
NP - Other	29	5
MD-Sleep	5	1
Missing	111	14
Total	***2,061***	***196***

*Beneficiary numbers are not additive as one beneficiary can see multiple providers.

Tables 6a/b describe antiepileptic medication utilization during the 90-day period prior to and immediately following Epidiolex initiation.

- Spending on antiepileptic medications, excluding Epidiolex, in beneficiaries prescribed Epidiolex decreased from $1,214,165 prior to initiating Epidiolex to $1,061,593 after initiating Epidiolex. This is a decrease of $152,572.
- The additional spending accounted for by Epidiolex was $993,157

Table 6a: Pre-Epidiolex Utilization Trends of Antiepileptic Drugs Among Beneficiaries Prescribed Epidiolex between November 2018 - December 2020

Drug name	Number of claims	Number of benes*	Total amount paid	Rank based on amount paid	Rank based on # of benes
Vigabatrin	35	11	$448,944	1	16
Clobazam	191	67	$265,718	2	1
Rufinamide	83	30	$203,345	3	7
Lacosamide	146	47	$127,472	4	5
Perampanel	50	18	$49,807	5	12
Diazepam	112	48	$28,760	6	4
Felbamate	25	9	$20,142	7	17
Brivaracetam	15	7	$17,235	8	18
Eslicarbazepine	10	4	$10,245	9	19
Oxcarbazepine	41	14	$6,779	10	14
Levetiracetam	132	51	$5,818	11	2
Topiramate	49	21	$4,957	12	10
Lamotrigine	77	22	$4,420	13	9
Divalproex Sodium	67	24	$3,869	14	8
Zonisamide	143	41	$3,046	15	6
Clonazepam	107	50	$2,929	16	3
Phenobarbital	54	20	$2,875	17	11
Midazolam	4	3	$2,685	18	20
Pregabalin	5	2	$2,670	19	22
Valproic Acid	42	18	$1,017	20	12
Lorazepam	30	14	$434	21	14
Gabapentin	9	3	$382	22	20
Acetazolamide	5	2	$377	23	22
Primidone	5	2	$128	24	22
Phenytoin	4	2	$109	25	22

*Only 158/164 (96.3%) beneficiaries had information on pre-Epidiolex pharmacy utilization in the prior 90-day period.
*beneficiary numbers are not cumulative.

Table 6b: Concurrent Utilization Trends of Antiepileptic Drugs Among Beneficiaries Prescribed Epidiolex between November 2018 - December 2020

Drug name	Number of claims	Number of benes*	Total amount paid	Rank based on amount paid	Rank based on # of benes
Cannabidiol	533	164	$993,157	1	1
Vigabatrin	26	10	$338,594	2	16
Rufinamide	81	30	$214,468	3	8
Clobazam	161	64	$197,506	4	2
Lacosamide	149	48	$139,782	5	3
Perampanel	47	19	$52,508	6	12
Diazepam	98	40	$28,014	7	5
Brivaracetam	19	8	$23,593	8	19
Felbamate	25	9	$16,210	9	18
Oxcarbazepine	38	13	$7,466	10	15
Midazolam	7	4	$5,931	11	20
Topiramate	49	19	$5,681	12	12
Eslicarbazepine	6	2	$5,506	13	22
Pregabalin	8	2	$4,753	14	22
Lamotrigine	68	21	$4,067	15	10
Levetiracetam	124	43	$4,047	16	4
Divalproex Sodium	62	24	$3,404	17	9
Phenobarbital	58	18	$2,742	18	14
Clonazepam	83	39	$2,361	19	6
Zonisamide	113	35	$2,293	20	7
Valproic Acid	54	20	$1,416	21	11
Gabapentin	9	3	$366	22	21
Lorazepam	31	10	$334	23	16
Acetazolamide	4	2	$278	24	22
Phenytoin	5	2	$133	25	22
Ethosuximide	1	1	$93	26	26
Primidone	2	1	$47	27	26

*beneficiary numbers are not cumulative.

NOTE for Tables 6a and 6ab: Drug utilization trends were assessed in a 90-day period prior to and following Epidiolex initiation. Benzodiazepines included in this evaluation are based on current MS-UPDL v2021.7a (diazepman, clobazam, and midazolam) or if they were classified under 'anticovulsants-benzodiazepine convulsants' in the main NDC file (lorazepam, diazepam, and clonazepam).

Table 7. Summary of Antiepileptic Medication Usage in Pre- and Post-Epidiolex Initiation

Number of drugs	Pre-Epidiolex		Post-Epidiolex*	
	# of benes	%	# of benes	%
1 - 2	41	25.9%	55	34.6%
3 - 4	87	55.1%	85	53.5%
5 or more	30	19.0%	19	11.9%
Total	***158***		***159***	

Number of distinct drug categories	Pre-Epidiolex		Post-Epidiolex*	
	# of benes	%	# of benes	%
1 - 2	55	34.8%	65	40.9%
3 - 4	86	54.4%	80	50.3%
5 or more	17	10.8%	14	8.8%
Total	***158***		***159***	

NOTE: Drug utilization trends were assessed in a 90-day period pre- and post-Epidiolex initiation. Only 158/164 (96.3%) beneficiaries had information on pre-Epidiolex pharmacy utilization.
*For evaluation of concurrent medication usage following Epidiolex initiation, Epidiolex was excluded in the assessment of number of drugs. In post-Epidiolex column, 5/164 beneficiaries were only on Epidiolex, and thus, excluded giving a total of 159.

Table 7 shows a summary of the number of concurrent medications prescribed pre- and post-Epidiolex initiation.

- Compared to pre-Epidiolex figures, the number of beneficiaries receiving 1-2 additional medications increased while the number of beneficiaries taking 5 or more additional medications decreased during post-Epidiolex initiation.

CONCLUSIONS

Epidiolex is the first cannabidiol (CBD) prescription medication approved for use by the FDA as add-on therapy for certain types of treatment-resistant epilepsy. Since its introduction in 2018, utilization of Epidiolex in Mississippi Medicaid has steadily increased. Analyses indicated that while the number of beneficiaries being treated with Epidiolex appeared to stabilize beginning Q2/2020, costs associated with its use continued to climb. Increased costs could be associated with an increase in dosage ranges prescribed for beneficiaries.

RECOMMENDATION

1. In light of the apparent increase in the dosage ranges being prescribed, DOM should establish dosing limits based on the labeled maximum dose recommendations. Such limits would allow for clinical review through prior authorization for doses exceeding these limits.

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