MIGRAINES AND THE INTRODUCTION OF CALCITONIN GENE-RELATED PEPTIDE (CGRP) INHIBITORS

BACKGROUND

Migraines impact a significant number of individuals in our nation today with an estimated 39 million people suffering from migraines annually. Of the American population, approximately 18% of women, 6% of men, and 10% of children suffer from migraines. Among those individuals diagnosed with migraines, about 7.8% meet criteria for chronic migraine diagnosis. Prevalence is highest in both men and women between ages 18 and 44 years. Nearly 1 in 4 households has at least 1 migraine sufferer. [1,2,3,4]

Although the exact mechanisms of migraines are not completely understood, they are believed to be the result of a complex series of neural and vascular events originating within the trigeminovascular system. Activation of trigeminal sensory nerves triggers the release of vasoactive neuropeptides (calcitonin gene-related peptide [CGRP], neurokinin A, and substance P) from perivascular axons. These released neuropeptides interact with dural blood vessels to promote vasodilation and dural plasma extravasation, resulting in neurogenic inflammation which produces pain.[5,6]

Migraines are characterized by recurring episodes of throbbing head pain that frequently presents unilaterally, but can present bilaterally. By definition, migraines last 4-72 hours and are moderate to severe in pain intensity. They are aggravated by or cause avoidance of routine physical activity, such as walking or climbing stairs. Migraines are associated with nausea and/or vomiting (N/V), sensitivity to light or sounds, and can be with or without aura.[4,7] Migraines are classified as either episodic or chronic. Episodic migraine (EM) is characterized by 14 or less headache days a month within a 3-month period. Chronic migraine (CM) is classified by 15 or more headache days per month for at least 3 months, of which 8 or more days meet the criteria for migraine.[8] It is important to note that chronic migraine diagnosis does not include medication overuse headache.

Pharmacologic therapies for migraine can be broadly divided into either acute or prophylactic therapy. Typically, acute therapy can consist of a variety of different medication classes such as simple analgesics

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[1] Migraine Research Foundation. 2018. Available from: http://migraineresearchfoundation.org/about-migraine/migraine-facts/. (Accessed August 2018).

[2] Smitherman, TA, et al. The Prevalence, Impact, and Treatment of Migraine and Severe Headaches in the United States: A Review of Statistics from National Surveillance Studies. Headache. 2013 Mar;53(3):427-36. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/head.12074

[3] Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache 2012;52(10):1456-70.

[4] Burch, RC, et al. The Prevalence and Burden of Migraine and Severe Headache in the United States: Updated Statistics From Government Health Surveillance Studies. Headache. 2015 Jan;55(1):21-34. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/head.12482

[5] Minor, D, et al. Pharmacotherapy: A Pathophysiologic Approach [Internet]. 10th ed. New York (NY): McGraw-Hill; c2017. Chapter 61: Headache Disorders.

[6] Bigal, ME, et al. Migraine in the Triptan Era: Lessons from Epidemiology, Pathophysiology, and Clinical Science. Headache. 2009 Feb;49 Suppl 1:S21-33.

[7] Headache Classification Committee of International Headache Society. The International Classification of Headache Disorders, 3rd Edition. Available from: https://www.ichd-3.org/.

[8] Katsarava, Z, et al. Defining the Differences Between Episodic Migraine and Chronic Migraine. Curr Pain Headache Rep. 2012 Feb;16(1):86-92.

(NSAIDs, acetaminophen) or combination analgesic products for mild to moderate attacks. For moderate to severe migraine attacks not associated with vomiting or severe nausea, oral migraine-specific agents are first-line, including oral triptans and the combination of sumatriptan-naproxen. When nausea and/or vomiting accompany the migraine attack, non-oral migraine-specific medications including subcutaneous sumatriptan, nasal sumatriptan and nasal zolmitriptan are used. Antiemetics may also be given to help with N/V. Opioids and barbiturates have been used as treatment and should be reserved as a last resort. There is no high-quality evidence supporting the efficacy of barbiturates for acute migraine treatment. Opioids are generally not as effective as migraine-specific medications for acute migraine treatment. Use of opioids and butalbital is associated with increased risk of for the development of chronic migraine and even medication overuse headache.[9] Prophylactic therapy to decrease the frequency or severity of migraines consists primarily of some beta-blockers, antidepressants, and anticonvulsants, although other classes may also be used.[10] Patients on preventive therapy frequently discontinue or switch treatments due to lack of efficacy or tolerability.[11] Because of a delayed response in many of these therapies, adequate therapeutic trial of preventive therapies may require two to six months of treatment. Without adequate treatment, patients with episodic migraine are more likely to progress to chronic migraine. OnabotulinumtoxinA was the first US Food and Drug Administration (FDA) approved product for chronic migraine prophylaxis.[12]

In May 2018, erenumab (Aimovig™), a fully human monoclonal antibody that binds to the CGRP receptor, was approved by the FDA as a preventive therapy in both episodic and chronic migraine patients.[13] Aimovig is a once monthly, subcutaneous injection that costs up to $6900 (wholesale acquisition costs or WAC pricing) annually.[14] Aimovig's mechanism of action antagonizes CGRP receptor function. The CGRP pathway is important in pain modulation, and CGRP has been observed to increase during a migraine by binding to the CGRP receptor. (FIGURE 1)

[9] ICER report: Pharmacologic Treatment for Episodic Migraine Prevention in Adults (2012)16,113

[10] https://www.uptodate.com/contents/acute-treatment-of-migraine-in-adults

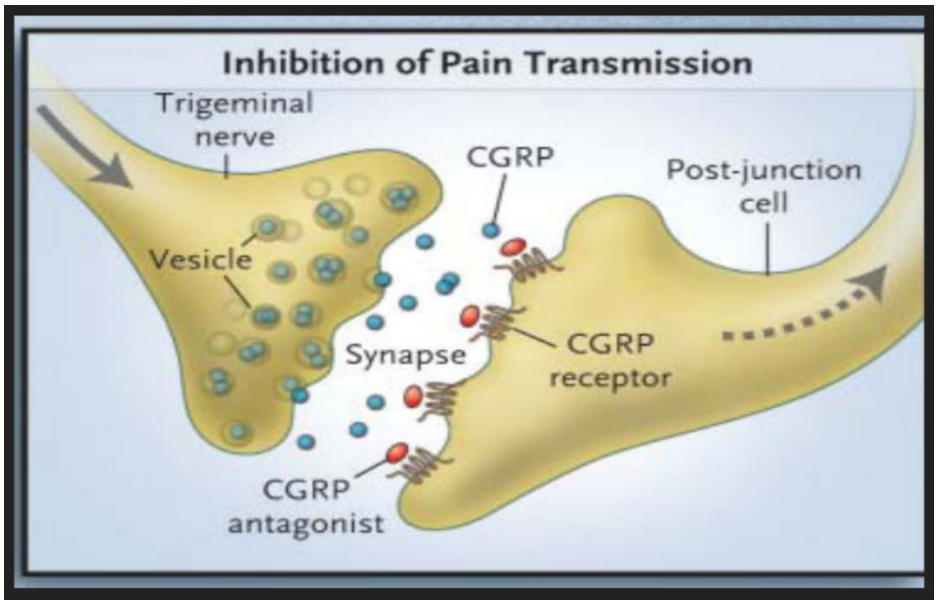
[11] Ford JH, Jackson J, Milligan G, Cotton S, Ahl J, Aurora SK. A Real-World Analysis of Migraine: A Cross-Sectional Study of Disease Burden and Treatment Patterns. Headache. 2017;57(10):1532-1544.

[12] Burch, RC, et al. The Prevalence and Burden of Migraine and Severe Headache in the United States: Updated Statistics From Government Health Surveillance Studies. Headache. 2015 Jan;55(1):21-34. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/head.12482

[13] FDA. FDA approves novel preventive treatment for migraine. May 2018. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm608120.htm. (Accessed August 2018).

[14] Rosenburg, J. FDA Approves Erenumab, First CGRP Inhibitor for Prevention of Migraine. American Journal of Managed Care. 2018 May 18.

FIGURE 1[15]



The effectiveness of Aimovig for the prevention of migraine was evaluated in three clinical trials. Two of the trials included participants with a history of episodic migraine and compared Aimovig to placebo. The third trial included participants with a history of chronic migraine and also compared Aimovig to placebo. In all three studies, Aimovig-treated patients experienced fewer migraine days monthly compared to placebo.[16]

Over the next few years, there is potential for multiple CGRP inhibitors to gain FDA approval and transform the migraine treatment landscape. This new drug class could have major implications on choice of therapy for migraine prophylaxis. In an attempt to gauge the potential impact this new class of medications may have in Mississippi Medicaid, MS-DUR examined the prevalence of Medicaid beneficiaries with a diagnosis of migraine and current treatment patterns for these beneficiaries.

METHODS

A retrospective analysis was conducted using Mississippi Medicaid pharmacy and medical claims from all pharmacy programs for the period from January 2017 to May 2018. Beneficiaries were identified as having migraine headaches if they had two or more medical claims with any ICD-10 code G43.X at least 31 days apart and occurring within one-year. Beneficiaries were classified as having chronic migraines if they had two or more medical claims at least 31 days apart and occurring within one-year that included ICD-10 code G43.7. All prescription claims were extracted for beneficiaries identified as having migraine headaches if the drugs were in a drug class with one or more products having an FDA or compendia supported indication for acute or prophylactic treatment of migraine or headaches. Drugs identified as having FDA medically-approved indications or being identified in any treatment guidelines for migraine are listed in Table 1.

[15]Image Source: http://pharmacologycorner.com/pharmacologic-treatment-migraine -pathophysiology-clinical-features/
[16] Aimovig®{package insert}. California: Amgen, Inc. 2018 (Accessed August 2018).

TABLE 1: Drug Products Identified as Commonly Used For Treatment of Migraine					
	Generic (Brand) Products	**FDA Indications***	**Compendia Supported Indications***	**Strength of Recommendation**	**Efficacy**
Prophylactic Treatment	Divalproex sodium (Depakote)	Migraine Prophylaxis (ppx)		IIb	IIa
	Carvedilol (Coreg)	*not indicated			
	Propranolol (Inderal)	Migraine ppx		IIa	I
	Gabapentin (Neurontin)	*not indicated			
	Pregabalin (Lyrica)	*not indicated			
	Topiramate (Topamax)	Migraine ppx		IIa	I
	Zonisamide (Zonegran)		Refractory Migraine ppx	IIb	IIa
	Amitriptyline (Elavil)		HA Treatment/ppx	IIb	IIa
	Doxepin (Sinequan)	*not indicated			
	Nortriptyline (Allegron)	*not indicated			
	Botox (onabotulinumtoxinA)	Chronic Migraine ppx, HA		IIb	IIa
	Venlafaxine (Effexor)		Tension-Type HA ppx	IIb	IIa
	Timolol (Blocadren)	Migraine ppx		IIa	I
	Metoprolol (Lopressor)		Migraine ppx	IIa	IIa
	Valproic acid (Depakene)	Migraine ppx		IIb	IIa
	Verapamil (Calan)		Migraine ppx	IIb	IIa
	Lisinopril (Zestril)		Migraine ppx	IIb	IIa
Acute Treatment	Sumatriptan (Imitrex)	Acute Migraine		IIa	I
	Eletriptan (Relpax)	Acute Migraine		IIa	I
	Rizatriptan (Maxalt)	Acute Migraine		IIa	I
	Naratriptan (Amerge)	Acute Migraine		IIa	I
	Almotriptan (Axert)	Acute Migraine		IIa	I
	Frovatriptan (Frova)	Acute Migraine		IIa	I
	Zolmitriptan (Zomig)	Acute Migraine		IIa	I
	Diclofenac (Voltaren)		Migraine	IIa	IIa
	Ibuprofen (Motrin)	Migraine		I	I
	Indomethacin (Indocin)	Headache		IIa	IIa
	Ketorolac (Toradol)	Headache		IIa	IIb
	Meloxicam (Mobic)	*not indicated			
	Naproxen (Aleve)	Headache		IIa	I
	Acetaminophen-Codeine (Tylenol #3)	*not indicated			
	Acetaminophen-Hydrocodone (Norco)	*not indicated			
	Acetaminophen-Oxycodone (Percocet)	*not indicated			
	Acetaminophen-Tramadol (Ultracet)	*not indicated			
	Morphine-Naltrexone (Embeda)	*not indicated			
	Oxycodone (Oxycontin)	*not indicated			
	Tramadol (Ultram)	*not indicated			
	Butabital-Aspirin-Caffeine (Fiorinal)	Tension-Type HA		IIb	IIa
	Butabital-Acetaminophen-Caffeine (Fioricet)	Tension-Type/ Muscular HA		IIb	IIa

** Micromedex Solutions (Internet). Truven Health Analytics. Greenwood Village, CO. Accessed 2018 August 8. Available from: www.micromedexsolutions.com*

***Micromedex "Strength of Recommendation" rating of at least IIB and "Efficacy" rating of at least IIA are considered a "medically-accepted indication."*

RESULTS

Table 2 shows the demographic and treatment characteristics for beneficiaries with episodic and chronic migraine diagnoses.

- Overall, 87.9% were diagnosed with only episodic migraine and 12.1% were diagnosed with chronic migraine. These percentages are fairly consistent with the known epidemiology of migraines.
- The majority of migraine patients were female (81.9%) and 21 years of age or older.
- As would be expected, treatment for episodic and chronic migraine patients differed.
- Although chronic migraine patients were more likely than episodic migraine patients to have received prophylactic treatment (88% CM versus 78% EM), the majority of both types of patients received prophylactic treatment.
- Chronic migraine patients were also more likely to have had an office visit with a neurologist (63% CM versus 26% EM) and to have had a prescription written by a neurologist (51% CM versus 24% EM).
- Although chronic migraine patients were more likely to see a neurologist, over a third had not done so during the last 17 months.

TABLE 2: Characteristics of Beneficiaries With Migraine With Medical Claims for Migraine Between January 2017 to May 2018

Demographic Characteristic		Type of Migraine Diagnoses									
		Episodic Migraine Diagnosis Only					Chronic Migraine Diagnosis Present				
		FFS	UHC	MAG	Total		FFS	UHC	MAG	Total		Total	
Age Group	Less than 15 years	80	434	416	930	17.3%	4	15	13	32	4.3%	962	15.7%
	16-20 years	81	347	282	710	13.2%	6	33	20	59	7.9%	769	12.6%
	21-34 years	173	478	545	1,196	22.2%	23	80	93	196	26.4%	1,392	22.7%
	Greater than 35 years	804	742	998	2,544	47.3%	86	184	185	455	61.2%	2,999	49.0%
Gender	Female	858	1,621	1,870	4,349	80.8%	102	277	284	663	89.2%	5,012	81.9%
	Male	280	380	371	1,031	19.2%	17	35	27	79	10.6%	1,110	18.1%
Treatment Type	None	555	130	101	786	14.6%	20	8	1	29	3.9%	815	13.3%
	Acute only	81	151	172	404	7.5%	15	28	17	60	8.1%	464	7.6%
	Prophylactic only	131	420	416	967	18.0%	16	30	21	67	9.0%	1,034	16.9%
	Acute & prophylactic	371	1,300	1,552	3,223	59.9%	69	246	272	587	79.0%	3,810	62.2%
Rx from neurologist		151	533	620	1,304	24.2%	37	176	165	378	50.9%	1,682	27.5%
Office visit with neurologist		187	573	651	1,411	26.2%	63	212	197	472	63.5%	1,883	30.8%
Total Unique Beneficiaries		5,380	87.9%				743	12.1%				6,122	

Table 3 reports information about the use of prophylactic agents by beneficiaries with migraine diagnoses.

- Overall, the most frequently used agents were topiramate, gabapentin and amitriptyline.
- For all of the prophylactic treatment agents, percentage of beneficiaries discontinuing therapy varied considerably by product.
- 23% of beneficiaries discontinued therapy before 60 days and 32% discontinued therapy before 90 days.

TABLE 3: Prophylactic Treatments Used by Beneficiaries With Migraine Diagnoses
(January 1, 2017 - May 31, 2018 -- Includes FFS and CCOs)

Treatment Type / Drug Product		Total Number of RXs	Number of Unique Beneficiaries With 1+ Prescriptions					Number of Unique Beneficiaries With ≥60 Days of Therapy			Number of Unique Beneficiaries With ≥90 Days of Therapy			Percentage of Beneficiaries Stopping Therapy	
			Total	Episodic Only N = 5,380		Chronic N = 743		Total	Episodic Only	Chronic	Total	Episodic Only	Chronic	Before 60 days	Before 90 Days
Prophylactic	**TOTAL WITH PROPHYLACTIC TREATMENT**	**39,737**	**4,274**	**3,627**	**67.4%**	**647**	**87.1%**	**3,290**	**2,912**	**378**	**2,982**	**2,469**	**513**	**23.0%**	**31.9%**
	topiramate*	9,380	1,952	1,782	33.1%	279	37.6%	1,413	1,201	212	1,086	926	160	27.6%	38.5%
	gabapentin	8,368	1,374	1,208	22.5%	244	32.8%	1,040	844	196	876	704	172	24.3%	38.6%
	amitriptyline*	4,968	1,183	1,053	19.6%	202	27.2%	799	656	143	593	486	107	32.5%	44.5%
	propranolol*	2,455	600	525	9.8%	111	14.9%	380	304	76	288	231	57	36.7%	49.3%
	metoprolol*	2,097	400	357	6.6%	73	9.8%	311	253	58	278	222	56	22.3%	36.8%
	pregabalin	2,337	397	345	6.4%	75	10.1%	292	234	58	255	205	50	26.4%	41.1%
	lisinopril*	1,462	368	324	6.0%	57	7.7%	264	230	34	211	188	23	28.3%	37.5%
	divalproex sodium*	1,898	347	305	5.7%	69	9.3%	252	202	50	216	176	40	27.4%	41.8%
	zonisamide*	1,529	295	261	4.9%	59	7.9%	197	155	42	161	128	33	33.2%	47.5%
	venlafaxine*	1,406	254	229	4.3%	41	5.5%	176	147	29	136	113	23	30.7%	42.1%
	nortriptyline	947	253	226	4.2%	41	5.5%	149	120	29	100	81	19	41.1%	52.6%
	onabotulinumtoxinA*	922	234	103	1.9%	161	21.7%	166	26	140	120	12	108	29.1%	88.9%
	carvedilol	708	150	128	2.4%	26	3.5%	114	94	20	95	78	17	24.0%	37.3%
	verapamil*	596	122	104	1.9%	28	3.8%	79	59	20	61	47	14	35.2%	51.6%
	doxepin	594	118	102	1.9%	22	3.0%	79	66	13	63	54	9	33.1%	44.1%
	valproic acid*	50	15	14	0.3%	1	0.1%	9	8	1	7	6	1	40.0%	46.7%
	timolol*	20	3	3	0.1%	0	0.0%	3	3	0	2	2	0	0.0%	0.0%

** Indicates drugs with FDA or compendia supported indication for acute or prophylactic use in treating migraine or headache.*

Table 4 shows the number of different acute and prophylactic medications taken by beneficiaries for ≥60 days and ≥90 days during the 17 month observation period.

- 1,544 beneficiaries had ≥60 days of therapy with 2 or more prophylactic agents, and
- 1,174 beneficiaries had ≥90 days of therapy with 2 or more prophylactic agents.

TABLE 4: Number of Acute and Prophylactic Medications Used by Beneficiaries for 60+ and 90+ Days
(January 1, 2017 - May 31, 2018)

			TOTAL		Pharmacy Program					
					FFS		UHC		MAG	
			Diagnosis		Diagnosis		Diagnosis		Diagnosis	
			Episodic Only	Chronic	Episodic Only	Chronic	Episodic Only	Chronic	Episodic Only	Chronic
Number of Drugs Used for 60+ Days	Acute Treatment	0	3,421	365	909	73	1,227	151	1,285	141
		1	1,298	229	154	25	532	104	612	100
		2	484	100	56	16	186	38	242	46
		3+	177	49	19	6	56	19	102	24
	Phrophylactic Treatment	0	2,468	164	778	47	842	67	848	50
		1	1,713	234	224	36	693	99	796	99
		2	807	197	102	19	325	85	380	93
		3+	392	148	34	18	141	61	217	69
Number of Drugs Used for 90+ Days	Acute Treatment	0	3,978	446	982	84	1,452	179	1,544	183
		1	1,031	211	116	25	420	100	495	86
		2	297	64	32	8	106	25	159	31
		3+	74	22	8	3	23	8	43	11
	Phrophylactic Treatment	0	2,911	230	843	57	1,017	89	1,051	84
		1	1,565	246	201	35	633	108	731	103
		2	660	173	71	14	259	84	330	75
		3+	244	94	23	14	92	31	129	49

CONCLUSIONS AND RECOMMENDATIONS

As of May 2018, there were 4,205 beneficiaries enrolled in Mississippi Medicaid who were age 18 or older and were diagnosed with episodic or chronic migraine. All of these beneficiaries could be potential candidates Aimovig and subsequent CGRP inhibitors.

Board action requested:

DOM and MS-DUR have examined prior authorization criteria being proposed by other state Medicaid agencies and commercial payers for Aimovig®. Some potential criteria are listed below along with comments from the Institute for Clinical and Economic Review (ICER):[17]

- Initial therapy must occur after consult with a neurologist, or must be prescribed by a neurologist.
    - *"Most migraine is cared for by clinicians who are not specialists in neurology or pain management, and access to these specialists can be quite limited in rural areas. Thus, to maximize access to CGRP inhibitors for appropriate patients, should primary care physicians be initially prescribing them? On the other hand, these medications have a new mechanism of action, have very limited safety data, and are given as a self-administered injection, which will require patients to be taught how to properly store and administer the treatment. Is access too limited if only specialists are first allowed to prescribe them?"*
- Failure on X number or more approved prophylactic treatments prior to use of new CGRP targeting products.
    - *"For patients who have no other options for preventive therapy, the ICER CTAF panel voted that there was adequate evidence to demonstrate a positive net health benefit with the CGRP inhibitors in patients with chronic migraine but not in episodic migraine. However, there were some concerns that the patients most likely to receive these agents first were not represented in the clinical trial populations (e.g., those for whom more than three preventive therapies have failed). Patients may also use a CGRP inhibitor in combination with existing prevention rather than as monotherapy, and currently there is no evidence on the benefits and risks comparing these approaches."*
- No presence of comorbid conditions that might be a safety concern for systemic CGRP repression.
    - *"The currently available trials of erenumab and other CGRP's inhibitors in development, such as fremanezumab and galcanezumab, show treatment benefits with few harms. However, these trials assessed outcomes by 12 or 24 weeks, and there remains uncertainty in any durability of effects and AEs from prolonged use. These interventions are the first in the CGRP inhibitor class, and some concerns exist about the long-term effects of continuous blocking of CGRP or its receptor due to*

[17] ICER Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value Final Evidence Report July 3, 2018: Available from: https://icer-review.org/material/cgrp-final-report/

CGRP's cardiovascular protective role. If patients, particularly chronic migraine patients, are expected to take CGRP inhibitors for a long duration (> 1 year), studies with longer follow-up are needed. In its review of erenumab, the FDA specifically requested postmarketing surveillance data for liver toxicity, myocardial infarction, and stroke among patients receiving erenumab."

- Potential limitations on initial length of coverage.
    - *"As with any new mechanism of action, limitations and uncertainties in the evidence base influence decision-making. For the CGRP inhibitors, due to the limitations in terms of populations studied and short-term trial duration described above, clinicians may reasonably exercise restraint in prescribing so as to allow more safety data to unfold. The FDA is requiring additional post-marketing studies of erenumab in pregnant women to identify potential maternal, fetal, and infant serious adverse events. Post-marketing surveillance for liver toxicity, myocardial infarction, and stroke after exposure to erenumab is also requested. In addition, clinicians should have extensive conversations with patients to convey the uncertainties about the new interventions and to understand patient preferences."*

MS-DUR is seeking input from the Board about potential criteria for managing the utilization in this new class.