CONNECTICUT MEDICAL ASSISTANCE PROGRAM DEPARTMENT OF SOCIAL SERVICES & HEALTH INFORMATION DESIGNS

Connecticut Medical Assistance Program Quarterly Newsletter

Migraine is a leading cause of disability in the US and worldwide, affecting approximately 20% of women and 10% of men.[1] 9,042 patients enrolled in the Connecticut Medical Assistance Program received at least 1 diagnosis of migraine during 3rd quarter 2020. Migraine typically occurs in patients 15-64 years of age, peaking between 35-45 years of age, and declining in the 6th and 7th decades of life.[2-4] Patients who suffer from migraine can experience occupational, social, educational, and financial burdens as well as a decrease in quality of life associated with this recurrent disorder. Patients with migraine have higher instances of other comorbid disease states such as depression and anxiety and migraine prevalence has been reported highest in those living below the poverty level. [2,3,5]

Hallmarks of migraine include moderate to severe headache lasting 4-72 hours, unilateral and pulsating pain, worsened by physical activity, and can be accompanied by nausea & vomiting, and photophobia & phonophobia.[6] Approximately 15% of patients with migraine experience aura, which can present as visual, sensory, or speech disturbance.[7] Migraine with aura is associated with a higher prevalence of comorbid psychiatric disorders. Aura typically occurs prior to the onset of headache but can last through the headache and even continue after the headache has stopped.[2] Premonitory phase of migraine, different from aura, can occur up to 48 hours prior to the headache phase and can include symptoms such as irritability, mood changes, difficulty in concentrating, congestion, food cravings, and increased thirst.[8] Postdrome phases, or the period after the headache, can last hours to days and can include additional symptoms such as fatigue and lethargy.[8]

Common migraine triggers include missed meals, menstruation, stress, weather changes, food and alcohol (chocolate, soft cheeses, red wine), and certain odors. Modifiable risk factors for migraine include medication overuse, obesity, caffeine intake.[7] Non-modifiable risk factors include age, female gender, comorbid depression, and socioeconomic status.[7] Migraines are also thought to have a 50% genetic component.[9]

It is theorized that migraine involves both the central and peripheral nervous systems, originating in the trigeminovascular system. Activation of the neurovascular system allows for release of vasoactive peptides such as calcitonin gene-related peptide (CGRP), substance P, and pituitary adenylyl cyclase activating peptide-38 (PACAP-38), which cause vasodilation and neurogenic inflammation.[2,10] When vasoactive peptides are released by the trigeminal neurons, they cause pain in the trigeminal vascular system, essentially causing a migraine to occur.[11]

Treatment of migraine can be classified as acute treatment or preventative therapy. Patients who experience episodic migraine (EM), defined as migraine < 15 days per month, often receive acute treatment.[12] The goal of acute migraine treatment is to stop the attack without recurrence. Secondary goals include restoring patient functioning while minimizing side effects.[13] Acute treatment is more effective when administered at the onset of attack versus once symptoms occur.[7] Non steroidal anti-inflammatory drugs (NSAIDs) and triptans are considered first line agents in the acute treatment of migraine; however, newer classes of medications such as gepants and ditans are also viable options. 4 devices have FDA approval for the treatment of migraine and are available by prescription but will not be discussed here.[14]

Acute migraine treatment with evidence supporting clinical efficacy include:[15]

- Ergot alkaloids
- NSAIDs
- Triptans (Serotonin 5-HT_{1B-1D} agonists)
- Ditans ($5HT_{1F}$ receptor agonists)
- Gepants (Small molecule CGRP receptor antagonists)

Ergot alkaloids are no longer commonly used as a first line approach; however, they do remain an option for acute treatment of migraine. Dihydroergotamine mesylate was developed in 1943 to replace the tartrate formulation for better vascular safety profile. The main mechanism of action of this medication is targeting $5HT_{1B,1D}$. Treatment causes significant nausea and vomiting, and titration is recommended. Dihydroergotamine mesylate may be useful in treating refractory migraines today. Ergotamine, which has been in use since 1963, targets multiple receptors including 5HT. It may be a useful option in treating patients with migraine attacks lasting > 48 hours. Ergotamine causes significant vasoconstriction as well as nausea and vomiting.[8]

NSAIDs, such as ibuprofen and naproxen, are commonly used as acute migraine treatment and are considered a first line agents.

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NSAIDs are contraindicated in patients with a history of GI bleed or peptic ulcer disease and should be used with caution in patients with cardiovascular disease.

Triptans bind to $5HT_{1B}$ and $5HT_{1D}$. $5HT_{1B}$ is found in the vascular smooth muscle causing vasoconstrictive effects when triptans are administered.[16] Triptans inhibit the release of CGRP in addition to being 5HT $_{1B-1D}$ agonists. All triptans come in tablet formulation but some also come as subcutaneous injection (sumatriptan), nasal spray (sumatriptan and zolmitriptan), and melt tablets (rizatriptan and zolmitriptan). All triptans are contraindicated in uncontrolled hypertension, coronary artery disease, Prinzmetal angina, ischemic bowel, and pregnancy. Patients with recurring headaches after initial administration of a triptan may benefit from a longer acting formulation to help prevent the reoccurrence of the headache. Head to head trials show triptans to be as effective at treating acute migraine attacks as NSAIDs. Additionally, if a patient fails one triptan, that does not mean they will fail them all. It is recommended to limit triptan intake to < 10 days per month to avoid medication overuse headache (MOH).[8] A lack of efficacy and migraine recurrence can be seen in up to 50% of patients treated with triptans.[17] Up to 24% of patients taking oral triptans and 40% of patients taking injectable formulations may experience side effects such as chest tightness, throat discomfort, tingling, numbness or heaviness in the chest, throat and arms.[18]

Available triptans include:

- Sumatriptan (also sumatriptan/naproxen combination)
- Naratriptan – longer acting
- Rizatriptan
- Zolmitriptan
- Eletriptan
- Almotriptan
- Frovatriptan – longer acting

Ditans are $5HT_{1F}$ receptor agonists and work to decrease the release of CGRP within the trigeminal vascular system. The blockage of 5HT blocks the activation of the trigeminal neurons and their ability to release vasoactive neuropeptides such as CGRP.[2] Ditans bind to different serotonin receptors than triptans circumventing the vasoconstrictive effects seen with the triptans, therefore, they are not contraindicated in patients with cardiovascular issues.

Lasmiditan, currently the only FDA approved centrally acting a $5HT_{1F}$ receptor agonist, is a class V controlled substance. It is orally administered at the onset of a migraine for acute treatment. Mild side effects identified include dizziness, fatigue, lethargy, nausea, and somnolence. The occurrence of cardiovascular side effects were found to be low with no vasoconstricting side effects such as angina, cerebral infarction, hypertensive stroke, or ischemic stroke.[16] This medication may be a good option for patients who are in need of acute migraine treatment but have preexisting cardiovascular disease.

Small molecule CGRP medications (gepants)

- Ubrogepant – orally administered for acute treatment of migraine, 25-100 mg
- Rimegepant – orally administered for acute treatment of migraine, 75 mg

Gepants are small molecule CGRP receptor antagonists which block CGRP receptors centrally and peripherally, inhibiting vasodilation and neurogenic inflammation, decreasing the activity of the trigeminal vascular system.[9] Effectiveness of the gepant class has been shown to be similar to triptans when treating acute migraine attack. Results from the phase III trials with ubrogepant and rimegepant found that approximately 20% of patients experienced resolution of headache and were considered pain free 2 hours post administration of either medication.[19] Ubrogepant and rimegepant have a longer duration of action compared to the triptans and are not contraindicated in cardiovascular disease.[9] Additionally, the gepants on the market today show no evidence of causing hepatotoxicity.

While NSAIDs, triptans, ergotamines, ditans, and gepants are all viable options for acute treatment, some migraine patients may benefit from preventative treatment. Patients who experience frequent attacks, severe or debilitating effects, disability, or when acute treatment is no longer working, may be candidates for preventative therapy. Recognition of psychiatric and neurological disorders is important, especially when selecting a prophylactic treatment for migraines as some options may treat multiple disorders. It is recommended that both chronic migraine (CM) patients, and EM patients experiencing four or more migraines per month, should receive prophylactic therapy.[18]

CM, which has been shown to affect 2% of the population[20], is defined as headache ≥ 15 days per month of which ≥ 8 are migraine headache days (MHDs) for at least 3 months.[12] CM is less common than EM but is associated with greater disease burden and higher rates of comorbid conditions.[21] Approximately 3% of EM patients will progress to CM annually, however, patients can fluctuate between EM and CM depending on the number of headaches and MHDs they experience per month.[21] Risk factors for progressing to CM include: frequency of headaches, ineffective acute treatment, stress, obesity, and overuse of acute migraine therapy.[21]

Medication overuse is a risk factor for migraine attacks and can cause medication overuse headaches (MOH). MOH in EM

Table 1. Connecticut Medical Assistance Program Noteworthy Migraine Medication Utilization by Class 3rd Quarter 2020

Medication Class	Unique Recipients to fill a prescription	Number of Prescriptions filled
Triptans	5,202	9,598
Ditans	10	11
Gepants	506	856
CGRP mAb	1,110	2,524

patients can often be misinterpreted as CM. MOH is defined as taking more than 14 days of aspirin, acetaminophen, or NSAIDs in a 30 day period, or taking more than 9 days of opioids, triptans, or ergotamine in a 30 day period for migraine relief.[6] Once medication overuse is stopped, approximately 50% of people who were thought to have CM revert back to EM.[6] Opioids, barbiturates, and combination analgesics containing these drugs have been shown to increase the development of MOH.[8] It is important to rule out MOH when considering prophylactic treatment of migraine patients. It is recommended that patients use a headache diary to track their symptoms, especially when attempting to differentiate between MOH and CM.

Preventative therapy for both EM and CM include many medications; however, certain beta blockers, antiepileptics, and antidepressants have evidence in the literature to support efficacy. (Table 2) OnabotulinumtoxinA has evidence supporting prevention of chronic migraine only and was the first drug specifically approved for prevention of CM.[12,21-23]

Some FDA approved migraine prevention medications include propranolol, timolol, divalproex sodium, and topiramate. Other medications may be used but either have not gained FDA approval and/or lack efficacy. With regard to the beta blockers for the prevention of episodic migraine, propranolol has the most evidence of effectiveness in migraine prophylaxis. Next is metoprolol, followed by timolol and then atenolol and nadolol.[24] With regard to the anticonvulsants for the prevention of episodic migraine, topiramate (for EM and CM) and divalproex have efficacy data to support use.[24] With regard to the antidepressants for the prevention of episodic migraine, amitriptyline has the most data showing efficacy, venlafaxine is thought to have probable effectiveness.[24]

CGRP monoclonal antibodies (mAbs) are a new class of medications approved for the prevention of migraine in adults. mAbs have long ½ lives which require less frequent dosing compared to other medications, which may have an effect on adherence. They are considered highly specific for their target making them effective at reaching receptors. They are large molecules which do not cross the blood brain barrier, so their effect is peripheral, specifically at the trigeminal nerve endings.[10] They are not metabolized by the liver. It should be cautioned that while having minimal short-term side effects, there is much that is unknown regarding the long-term use of these medications. Careful watching and monitoring is recommended. Approximately 32% of patients had complete migraine freedom after drug administration, in short term trials of up to 6 months. More long term trials are needed to prove safety and efficacy beyond 6 months and to rule out the potential for cardiovascular side effects.[10] There are cardiovascular risks associated with blocking the CGRP pathway (ischemia, blockage of vasodilation) and long term use of these products needs to be studied and evaluated over time. It should be noted that other oral prophylactic therapies to prevent migraine have similar or comparable efficacy to the mAbs.[10]

- Eptinezumab (Vyepti) - IgG1 CGRP ligand antagonist administered IV. Binds directly to CGRP. Produced using yeast. Administered IV 100 mg every 3 months.
- Fremanezumab (Ajovy) - Humanized IgG2 CGRP ligand antagonist. Bind directly to CGRP. Administered SC 225 mg monthly or 675 mg every 3 months.
- Galcanezumab (Emgality) – IgG4 CGRP ligand antagonist. Bind directly to CGRP. Administered SC 240 mg loading dose followed by 120 mg monthly.
- Erenumab (Aimovig) –IgG2 CGRP receptor antagonist. The only mAb that binds directly to the CGRP receptor, rather than to CGRP itself. Recommended dose is 70 mg SC monthly.

Migraine is a debilitating disease that can interfere with many aspects of a patient's life. While there are many available acute and preventative migraine treatments, only 50% of patients respond to either type of therapy.[9] Personalized medicine is key in treating this disease as each patient brings unique considerations, comorbidities, and contraindications into the equation. Other variables such as cost of treatment options and history of medication adherence are important, especially when selecting a preventative treatment. Modifiable risk factors should be addressed and nonpharmacological options for managing acute attacks considered.

Table 2. Preventative Medications for Episodic Migraine[22]

First Line Agents Medications with established efficacy	Second Line Agents (Medications with probable efficacy)
Antiepileptic drugs Divalproex sodium Sodium valproate Topiramate	**Antidepressants** Amitriptyline Venlafaxine
β-Blockers Metoprolol Propranolol Timolol	**β-Blockers** Atenolol Nadolol
Triptans Frovatriptan*	**Triptans** Naratriptan* Zolmitriptan*

*For menstrual associated migraines

1. Percentage of adults who had a severe headache or migraine in the past 3 months, by sex and age group – national health interview survey, United States, 2018. MMWR Morb Mortal Wkly Rep 2020; 69:359.
2. Peters G. Migraine overview and summary of current treatment options. *Am J Managed Care*. 2019;25:S23-34.
3. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. *Headache*. 2018;58(4):496-505.
4. MacGregor EA. Migraine. *Ann Intern Med*. 2017;166(7):49-64.
5. Dresler T, Caratozzole, Guldolf K, et al. Understanding the nature of psychiatric comorbidity in migraine: a systematic review focused on interactions and treatment implications. *J Headache Pain*. 2019; 20:51.
6. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalagia*. 2018; 38: 1-211.
7. Uritis I, Clark G, An D, et al. An evidence based review of fremanezumab for the treatment of migraine. *Pain Ther*. 2020;9:195-215.
8. Ong JJ, Felice M. Migraine treatment: current and acute medications and their potential mechanisms of action. *Neurotherapeutics*. 2018; 15:275-290.
9. Pomes LM, Guglielmetti M, Bertamino E, et al. Optimising migraine treatment: from drug-drug interactions to personalized medicine. *J Head Pain*. 2019; 20(56): 1-12.
10. Raffaelli B, Reuter U. The biology of monoclonal antibodies: focus on calcitonin gene-related peptide for prophylactic migraine therapy. *Neurotherapeutics*. 2018; 15:324-335.
11. Dodick D, Lipton RB, Ailani J, et al. Ubrogepant for the treatment of migraine. N Engl J Med. 2019; 381(23): 2230-2241.
12. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59(1):1–18.
13. Hutchinson S, Lipton RB, Ailani J, et al. Characterization of acute prescription migraine medication use: results from the CaMEO study. *Mayo Clin Proc*. 2020; 95(4):709-718.
14. Digre K. What's new in the treatment of migraine? *J Neuro-Opthalmol*. 2019;39:352-359.
15. Lipton RB, Munjal S, Buse DC, et al. Unmet acute treatment needs from the 2017 migraine in America symptoms and treatment study. *Headache*. 2019; 59: 1310-1323.
16. Krege JH, Rizzoli PB, Liffick E, et al. Safety findings from phase 3 lasmiditan studies for the acute treatment of migraine: results from SAMURAI and SPARTAN. *Cephalalgia*. 2019;39(8):957-966.
17. Puledda F, Messina R, Goadsby PJ. An update on migraine: current understanding and future directions. *J Neurol*. 2017(264): 2031-2039.
18. Negro A, Koverech A, Martelletti P. Serotonin receptor agonists in the acute treatment of migraine: a review on their therapeutic potential. *J Pain Research*. 2018;11:515-526.
19. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: a phase 3 randomized study. Neurology. 2018;91:e2222-e2232.
20. Su M, Yu S. Chronic migraine: a process of dysmodulation and sensitization. Mol Pain. 2017;14:1-10.
21. Agostoni EC, Barbanti P, Calabresi P, et al. Current and emerging evidence-based treatment options in chronic migraine: a narrative review. *J Head Pain*. 2019;20(92):1-9.
22. Silberstein SD, Holland S, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78(17): 1337–45.
23. Starling AJ, Vargas BB. A narrative review of evidence-based preventive options for chronic migraine. *Curr Pain Headache Rep*. 2015;19(10):49.
24. Ha H, Gonzalez A. Migraine headache prophylaxis. *Am Fam Physician*. 2019;99(1):17-24.
25. Lassen LH, Haderslev PA, et al. CGRP may play a causative role in migraine. *Cephalalgia*. 2002;22(1): 54–61.
26. Gao B, Yang Y, Wang Z, et al. Efficacy and safety of rimegepant for the acute treatment of migraine: evidence from randomized controlled trials. *Front Pharmacol*. 2019;10(1577):1-10.
27. Szperka CL, Ailani J, Barmherzig R, et al. Migraine care in the era of COVID-19: clinical pearls and plea to insurers. *Headache*. 2020;60:833-842.
28. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med*. 2019;381:142-9.
29. Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: new drugs, new hope? *J Headache Pain*. 2019;20 (37):1-13.
30. Sprenger T, Viana M, Tassorelli C. Current prophylactic medications for migraine and their potential mechanisms of action. *Neurotherapeutics*. 2018;15:313-323.

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