Summit on the Future Treatments in Migraine and Cluster Headaches

Findings from the AMCP Market Insights Program

Meeting Objective

- Understand how AMCP members identify and manage members with migraine and cluster headaches
- Identify how payers establish coverage criteria for new migraine therapies
- Define key information required for payers to aid product differentiation, treatment protocols, and utilization review to ensure optimal outcomes for members
- Define the role of non-pharmaceutical treatment options in patient management

Introduction

Headache is one of the most common symptoms in the general population, but despite its high prevalence and impairment, migraine is often not recognized or effectively treated. Researchers have been working for decades to develop a "targeted" therapies specifically for headaches. Fortunately, with aid from advanced technology and clinical innovations, there are new treatment options available for patients - including CGRP inhibitors and to other therapies headed for Food and Drug Administration (FDA) approval, and a growing class of non-pharmaceutical devices that work via nerve stimulation. As new classes of drugs and non-drug treatments come to market health care providers and payers will need up-to-date evidence and guidance for the use and coverage of novel treatments.

To understand the appropriate and cost effective use of novel treatments, AMCP convened an expert forum of stakeholders. Forum participants included representatives from regional and national health plans, integrated delivery networks, 340b entities and pharmacy benefit managers. (Figure 1). Participants discussed the differentiation of migraine and cluster headaches, treatment and prevention therapies, pipeline pharmaceuticals and devices, and the impact of new treatments on formulary management and the delivery of care.

Differentiation of Headaches

The most common primary headache disorders are tension-type headache, migraine, and cluster headache. Migraine is a chronic neurologic disease characterized by attacks of throbbing, often unilateral pain that are exacerbated by physical activity and associated with photophobia, phonophobia, nausea, vomiting, and, in many patients, cutaneous allodynia.[1] Severe headache and migraine are common in the U.S., with 20% of women and approximately 10% of men aged ≥ 18 years reporting they had at least one in the past 3 months.[2] The burden of illness is often substantial, attacks can significantly impair functional ability at work, school, home, and in social situations.[3,4]

Migraines are often described as recurrent throbbing or pulsating, moderate to severe, and often unilateral pain that lasts 4-72 hours with complete freedom between the attacks (episodic). The headache is associated with nausea, vomiting and/or sensitivity to light, sound or smell.

Cluster headache affects only 0.1% of the population; but patients suffer severe unilateral pain mainly in the first division of the trigeminal nerve, with associated prominent unilateral cranial autonomic symptoms and a sense of agitation and restlessness during the attacks.

Cluster headache is less common, but the most prevalent in the category of headache disorder termed trigeminal autonomic cephalalgia. Cluster headaches are characterized by the short duration, they are strictly unilateral and have accompanying autonomic features of lacrimation, rhinorrhea, conjunctival injection and ptosis.[6] The changing seasons are the most common trigger for cluster headaches, which often occur in the spring or

Figure 1. Market Insights Forum Participant Mix

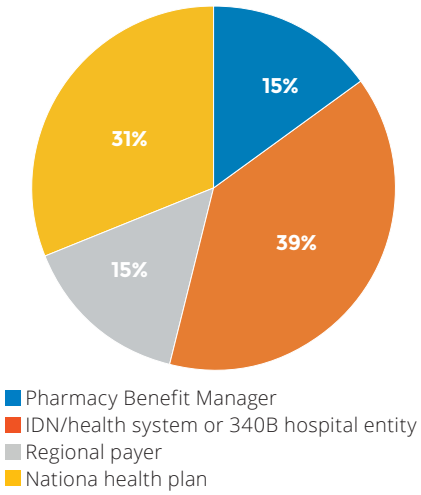

Table 1. ICHD-3 Criteria for Episodic and Chronic Migraine[5]

Episodic migraine	Chronic migraine
A. At least 5 attacks fulfilling criteria B–D	A. Migraine-like or tension-type-like headache on ≥ 15 days/month for > 3 months that fulfill criteria B and C
B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)	B. Occurring in a patient who has had at least 5 attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura
C. Headache has at least 2 of the following 4 characteristics:	C. On ≥ 8 days/month for > 3 months, fulfilling any of the following:
1.Unilateral location	1.Criteria C and D migraine without aura
2.Pulsating quality	2.Criteria B and C for migraine with aura
3.Moderate or severe pain intensity	3.Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
4.Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)	D. Not better accounted for by another diagnosis
D. During headache at least 1 of the following:	
1.Nausea and/or vomiting	
2.Photophobia and phonophobia	
E. Not better accounted for by another diagnosis	

ICHD = International Classification of Headache Disorders.

"I don't think the plan makes a good job of differentiating migraines from cluster headaches. I think they [cluster headaches and migraine] just get lumped in the same category. I would have no way, if I asked my data analyst to pull that out…"

autumn. Due to their seasonal nature, cluster headaches are often mistakenly associated with allergies or sinusitis.

Early acute treatment for both types of headaches is important, and for patients not responding to over-the-counter nonspecific pain medications, the use of specific migraine medications is recommended. The most commonly used migraine specific medication class for acute treatment are "triptans" (5-hydroxytryptamine [5-HT] 1b/1d receptor agonists). Recent developments and the emergence of novel medications, device technologies, and biologics have advanced treatment options for patients with migraine and cluster headaches.

Diagnoses of migraine can be classified based on the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs); patients with fewer than 15 MMDs or MHDs have episodic migraine, and those with at least 15 MHDs, of which at least 8 are MMDs, have chronic migraine (Table 1).[2] About 2 to 3 percent of patients with episodic migraine will transform to having chronic migraine in a given year.

While cluster headaches and migraines are clinically differentiated some managed care organizations are challenged to separate out the headache diagnosis in their pharmacy claims data. Participants noted that the specific type of headache may not always be able to be determined with claims data, and raised the possible limitation of using claims data as there is thought to be general unawareness of the different diagnostic codes for various types of headaches within pharmacy.

Diagnostic delays can limit the ability to administer appropriate acute and preventative treatments. An analysis from the American Migraine Prevalence and Prevention (AMPP) Study showed that the majority of individuals with migraine had not received a correct diagnosis (79.8%) nor specific acute (68.4%) or preventive (60.0%) medications.[7] However, patients consulting a specialist were nearly 1.5 times more likely to receive a chronic migraine diagnosis than those consulting other HCPs.

"I think this access [to the appropriate provider] is probably the single biggest issue that we're facing in looking in some of these therapies and some of these disease states."

The ability to access qualified physician specialists was discussed as a challenge due to the limited number of available headache specialists (approximately 500 UCNS certified headache medicine specialists in the U.S.),[8] neurologists, and geographical locations, e.g. rural vs.

Table 2. Pharmacotherapy with Evidence of Efficacy in Migraine Treatment[8]

Level A	Level B
Triptans	**Anti-emetics:**
DHE Nasal Spray	IV Metoclopramide & Prochlorperazine
NSAIDs:	**Anti-dopamine:**
Diclofenac, aspirin, naproxen, ibuprofen	IV Chlorpromazine & Droperidol IV
Acetaminophen	**Ergots:**
Acetaminophen/aspirin/caffeine 500/500/130 mg	IM/IV DHE
Acetaminophen 1000 mg (for non-incapacitating attacks)	**NSAIDS:**
Butorphanol nasal spray	Ketorolac
	Opioids:
	Codeine/acetaminophen, Tramadol/acetaminophen

Level A = Established as effective for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.) Level B = Probably effective for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)*

urban settings. As a result, patients often seek migraine care from their primary care physician (PCP). While initial evaluation of headache care is appropriate by a non-specialist clinician (e.g. PCP), several payers preferred patients with severe headaches or those resistant to treatment see a specialist who could appropriately evaluate the headache disorder and select subsequent treatments.

To ensure optimal outcomes for their members, payers may implement formulary management programs and drug coverage criteria that require medication prescribing by the appropriate specialist (e.g. headache specialist or neurology) or in consultation with that specialty.

Migraine Treatment

The goals of acute migraine treatment are rapid and consistent relief from pain and associated symptoms without recurrence, restored ability to function, and tolerable treatment side effects.

Many Level A evidence-based acute migraine treatments are available, including triptans, ergotamine derivatives, non-steroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, and analgesic combinations (Table 2).[9] The most commonly used migraine medications are triptans, however, for some patients triptans are not adequately helpful or lose efficacy over time, have intolerable side effects, or cannot be used due to contraindications (e.g., cardiovascular disease). The need for new treatments is demonstrated by the use of rescue medications and recognition that frequent use of acute treatment medications can lead to medication overuse headaches.

Emerging Agents

Emerging agents with novel mechanisms of action that have demonstrated efficacy for the acute treatment of migraine include the small molecule calcitonin gene-related peptide (CGRP) receptor antagonists, ubrogepant and rimegepant, and lasmiditan a selective serotonin (5 -HT1F) receptor agonist (Table 3). Unlike triptans and ergotamine derivatives, these novel treatments do not constrict blood vessels and may have a unique role in patients with cardiovascular contraindications to triptans and they may likely reduce the risk for medication overuse headaches.

Lasmiditan acts on the central nervous system (CNS), and as with other medicines with activity, the FDA is requiring abuse potential studies. There is a risk of driving impairment while taking lasmiditan. People are advised not to drive or operate machinery for at least eight hours after taking lasmiditan, even if they feel well enough to do so. At the time of the meeting the recommended controlled substance classification for lasmiditan was under review by the Drug Enforcement Administration (DEA). It was placed into Schedule V in January 2020.

"The difference between a [controlled schedule] IV and V is a big difference… that is going to restrict access."

Table 3a. Novel Treatments for Migraine

	Lasmiditan	Rimegepant	Ubrogepant	Nerivio
Class	5HT1F agonist (Ditan)	Small Molecule (CGRP) receptor antagonists (Gepant)		Electrical neuromodulation device
Indication	Acute	Acute	Acute	Acute
Formulation	Oral Tablet	Orally Disintegrating Tablet	Oral Tablet	Non-drug, wireless remote electrical neuromodulation device
Dosage	200mg	75 mg	50 mg	Self-applied to the upper-arm for 45 min.
Percent of patients Pain Free at 2 Hours vs. Placebo	38.8% vs. 21.3% [SPARTAN] 32.2% vs. 15.3% [SAMUARI]	19.2% vs. 14.2% [Study 301] 19.6% vs. 12.0% [Study 302]	21.2% vs. 11.8% [Achieve I] 21.8% vs. 14.3% [Achieve II]	37.4% vs 18.6% [Yarnisky et al.]

Eptinezumab-jjmr (Vyepti) was not discussed during the program, but recieved approval from the U.S. Food and Drug Administration in February 2020 as the first IV preventive treatment of migraine in adults.

Additional novel agents are anticipated to be marketed in by mid-2020 and to be more costly to health insurance plans and patients than currently available oral triptans for which generic options are available. Therefore, to achieve cost-effective care while ensuring access for appropriate patients, payers are planning to use standard formulary management strategies (e.g. prior authorization, step therapy, quantity limits) which will likely include requiring trial and failure or contraindication to at least one generic triptan. In addition, they are looking to implement contracting strategies to prefer one or two products in order to gain competitive pricing.

We will evaluate all of the new migraine drugs, then "leverage them against each other for the best possible financial arrangement."

Migraine Prevention

The general recommendations for when to initiate preventive treatment are unchanged. Patients with migraine should be considered for preventive treatment when attacks significantly interfere with daily routines despite acute treatment, there are frequent attacks (≥ 4 MHDs), if there is a contraindication to, failure, or overuse of acute treatments, side-effects from acute treatments, and patient preference.

Preventive treatment plans must be designed to meet the needs of individual patients, and they may involve combining treatments as well as non-pharmaceutical approaches. The use of evidence-based treatments (Table 4) is important to the success of migraine prevention. The goals of migraine prevention are to reduce migraine attack frequency, severity, duration, and disability to improve patient quality-of-life and function and reduce overall cost associated with migraine treatment.

"I find PROs to be extremely helpful. Are you satisfied with the treatment? And then are you more functional? Are you doing more? And that's how we take a measure."

Preventive treatments are an important part of the overall approach for migraine management, and multiple evidence-based guidelines are available.[10-17] Traditional oral treatments were not developed specifically for migraine prevention, and many have moderate efficacy, adverse events, contraindications, or drug-drug interactions that may limit use in select populations.

"The conversation [about starting preventative treatment] is much easier, knowing that there is a migraine-specific treatment."

Table 3b. Novel Agents for Migraine Prevention

	Eptinezumab-jjm r
Class	Small Molecule (CGRP) receptor antagonists (Gepant)
Indication	Prevention
Formulation	Intravenous
Dosage	100 mg every 3 months
Percent of patients vs. Placebo	≥ 50% MMD responders – Months 1-3 49.8% vs 37.4% [Study 1] 57.6% vs 39.3% [Study 2]

Eptinezumab-jjmr (Vyepti) was not discussed during the program, but received approval from the US Food and Drug Administration in February 2020 as the first IV preventive treatment of migraine in adults.

Table 4. Treatments with Evidence of Efficacy in Migraine Prevention[9]

Effective	Probably Effective	Possibly Effective
Divalproex	Amitriptyline	Carbamazepine
Metoprolol	Atenolol	Clonidine
Propranolol	Candesartan	Cyproheptadine
Timolol	Nadolol	Guanfacine
Topiramate	Venlafaxine	Lisinopril
Valproate		Nebivolol
OnabotulinumtoxinA		Pindolol
Erenumab aooe		
Fremanezumab vfrm		
Galcanezumab gnlm		

Injectable Preventative Treatments

Currently, there are several injectable preventive therapies for migraine marketed in the U.S., onabotulinumtoxinA and the newer monoclonal antibodies (mAbs) which act on CGRP (eptinezumab, fremanezumab, galcanezumab) or the CGRP receptor (erenumab). OnabotulinumtoxinA is approved for chronic migraine, and erenumab, fremanezumab, and galcanezumab are approved for episodic and chronic migraine. While the principles of preventive therapy for oral agents generally apply to injectable agents, there are notable points of contrast, including the absence of dose titration/escalation, safety and drug interaction profiles, site-of-care logistics, availability of infusion center chair time for intravenous (IV) products, affordability, pharmacy vs. medical benefit coverage, buy-and-bill decisions, and patient preference around subcutaneous injection or IV therapy.

"And, you know, most plans now tend to want to cover drugs on the pharmacy side, so that we can manage them more effectively than drugs on the medical side."

Cluster Headache Treatment and Prevention

For acute treatment, sumatriptan subcutaneous, zolmitriptan nasal spray, and high flow oxygen remain the treatments for cluster headache with a Level A recommendation.[18] Another acute treatment option is a non-invasive non-drug vasovagal nerve stimulator, which has FDA clearance for acute use during a cluster cycle.

For maintenance and transitional prophylactic therapy, suboccipital steroid injections have emerged as the only treatment to receive a Level A recommendation.[18] However, verapamil is generally regarded first-line preventive therapy for cluster headache, based on expert opinion rather than a high quality of published evidence (Level C). Lithium and warfarin are additional preventative medication options, but are used less frequently due to tolerability and monitoring requirements. High doses of melatonin are commonly used in these patients, at recommended to be started at the beginning of a cluster cycle.

Galcanezumab, which is approved for migraine prevention, is the first agent approved for treatment of episodic cluster headache, but at a higher 300mg dose – which is available in indication-specific prefilled syringe dosage forms. Payers felt having evidence of benefit and FDA approved indications across both migraine and cluster headache was of value due to the challenges with differentiating headache diagnosis in pharmacy claims, the limited access to headache specialists, and for streamlining the formulary treatment options.

Payers may use fewer standard formulary management strategies for novel cluster headache treatments due to the small patient population and limited FDA approved treatment options. An important criteria for coverage will be the appropriate diagnosis of cluster headache which will likely be assessed via documentation of consultation with a qualified physician (e.g. headache specialist or neurologist).

Table 5. Non- Drug Pain Modulation

	Clinical Manifestation	Signaling	Spatial Effect	Duration
CPM	Pain inhibits Pain	Norepinephrine Serotonin	Global	Beyond stimulus exposure
Gate Control Theory	Touch inhibits pain	Gamma aminobutyric acid (GABA)	Local	During stimulus exposure

Neuromodulation Therapy

Several neuromodulator devices have been developed and approved for the treatment of patients with migraine or cluster headache, including a novel remote electrical neuromodulation (REN) prescribed wearable device (Nerivio™), which was FDA approved in May of 2019. In general, these non-drug treatments stimulate the nervous system centrally or peripherally with an electric current or a magnetic field to change pain mechanisms and can be activated by a smartphone. The novel use of neuromodulation is with conditioned pain modulation (CPM), which differs from modulation based on the gate control theory (Table 5). With CPM stimulation information reaches the brainstem through the ascending pain pathway. This information activates the descending pain inhibitory pathway, involving the brainstem pain regulation center, and the release of serotonin and norepinephrine, which inhibit incoming messages of pain in the trigeminal cervical complex that occur during a headache of a migraine attack. Good candidates for non-pharmaceutical treatment options are those patients seeking non-drug therapies, those who have inadequate response or have contraindications to pharmacotherapy, those who need non-oral treatment to do headache related symptoms, or those who are at risk for rebound headaches.

"...this isn't going to cause medication overuse; it's a completely different pathway. In my mind, the patient can use this for every acute attack."

However, in order for a device to be adjudicated and then covered under the pharmacy benefit, the products' national drug codes (NDC) will need to be listed in drug databases (e.g. First Data Bank, Medi-Span). In addition, payers recommended that there is validation of a patient's ability to use the device effectively. Training and patient support programs to ensure appropriate utilization (hub services, provider certifications and patient training) were also highlighted as key factors which would assist product placement and coverage. Currently FDA approved neuromodulation devices are only available via participating clinics or specialty pharmacies, potentially limiting device access for patients.

Potential Impact on Payers

Plans and providers are in need of education on the diagnosis and treatments for migraine and cluster headaches. Payers generally perceive there is undifferentiated clinical evidence between the new agents within their approved indications. Therefore, the newer migraine treatments will likely be met with traditional formulary management and contracting strategies.

The anticipated costs for novel migraine and cluster headache treatments and preventive medications may pose a burden for patients and payers in a disease states that has seen decades of high utilization of generic medications. However, there is some interest in exploring Value-based and Coverage with Evidence Generation arrangements. Outcomes of interest to payers are decreases in ER visits and hospitalizations, decreases in outpatient visits, and medication sparing effects for opioids and triptans. Breakthroughs in non-drug migraine treatment options, which appear similarly effective to medication treatment options based on clinical trial data, will likely lead health plans to reconsider how they evaluate non-pharmaceutical treatments for coverage and formulary placement.

Summary

Advances in the treatment of migraine and cluster headache have the potential to improve outcomes for patients. However, additional education and differentiation in diagnosis and data sets will be valuable to both payers and physicians, to ensure appropriate treatment and coverage criteria. The costs associated with novel treatments are anticipated to be challenging for some patients and payers. To ensure optimal outcomes for their members, payers are likely to implement formulary management programs and drug coverage criteria that require diagnosis and medication prescribing by the appropriate specialist (e.g. headache specialist

or neurology) or in consultation with that specialty. Traditional formulary management strategies will likely be applied across the therapeutic classes as multiple agents within the class are brought to market. Value-based arrangements are of interest to payers, but Coverage with Evidence Generation a may be an important strategy for manufacturers who are bringing innovative non-drug treatments or for those targeting small populations of patients.

Disclosures

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Health plan stakeholders will be considering the following to manage patient needs in an evolving treatment paradigm:

Treatment Access and Quality:

- Payers need to be able to differentiate between cluster and migraine diagnosis.
- Primary care providers need updated education on differential of headache diagnoses.
- Payers and primary care providers need education on evidence based treatment options and guidelines.
- Payers and primary care providers need to understand which treatments are effective for the acute treatment of cluster headaches, and which treatments are effective for reducing the frequency of attacks?
- Formulary and benefit pharmacists will likely need to prepare and engage in evidence reviews and coverage determinations for migraine treatment devices and or digital therapeutics.

Care Management:

- Selecting the right type of migraine patient for the right product.
- Encourage appropriate patients to start on preventative therapy.

Affordability:

- Utilize available independent non-profit research organization (e.g. ICER) reports to improve patient outcomes and understand cost controls.
- Consider standard formulary management strategies (e.g. prior authorization, step therapy, quantity limits) to manage acute migraine treatments.
- Strategies for novel migraine prevention treatments will vary and will largely depend on if the treatment is covered under the pharmacy or medical benefit.
- Few standard formulary management strategies may be needed managing cluster headache treatments due to the small patient population and limited FDA approved treatment options.

Pharmacy Management:

- Assess the availability of neuromodulator devices with contracted specialty pharmacies, as they represent a stakeholder with established ability to aid in providing patient support services and managing costs.

Risk Adjustment and Risk Management:

- Identify and quantify patients who have contraindications to first-line treatments (e.g. cardiovascular, pregnancy), those unable to tolerate the sedative effects of triptans, and those at risk for medication overuse headaches.
- Consider Coverage with Evidence Generation arrangements for novel treatments in small patient populations to generate additional RWE.