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## Drug Class Update: Headache Treatment and Prevention

**Date of Review:** April 2025

**Date of Last Review:**

CGRP Inhibitors – August 2023

Serotonin Agonists – August 2020

Non-opioid combination analgesics (no prior review)

**Dates of Literature Search:**

CGRP Inhibitors - 06/01/2023 - 11/27/2024

Serotonin Agonists – 06/01/2023 – 11/27/2024

Non-opioid combination analgesics- 01/01/2023-02/03/2025

**Current Status of PDL Class:**

See **Appendix 1**.

**Purpose for Class Update:**

This update will review current evidence for headache treatment and prevention for the following drug classes: calcitonin gene-related peptide (CGRP) inhibitors, serotonin agonists, and non-opioid combination analgesics. The literature will also be evaluated for guidance on tension headache treatment, a diagnosis which is currently not funded under the prioritized list which is being re-evaluated by the Health Evidence Review Commission (HERC).

**Plain Language Summary:**

- The purpose of this review is to look at drugs used to treat and prevent headaches. This includes migraine, tension-type headaches (TTH) and others.
- For treating symptoms of migraine, guidelines recommend nonsteroidal anti-inflammatories, like ibuprofen, or drugs called serotonin agonists or triptans.
- People who experience 15 or more headaches per month find treatment to prevent migraines helpful. Guidelines recommend drugs such as propranolol and amitriptyline to be tried first for prevention. Other options for migraine prevention are called calcitonin gene-related peptide (CGRP) inhibitors.
- For people who have TTH, drugs such as ibuprofen and acetaminophen can help to reduce pain and headache duration.
- Guidelines recommend against the use of drugs that contain butalbital and opioids because of risk of dependency and chance of making headaches worse due to using it too often.

**Research Questions:**

1. What is the new comparative evidence for efficacy and effectiveness for the CGRP inhibitors, serotonin agonists and non-opioid combination analgesics for preventative and acute migraine and headache treatment for the outcomes of headache frequency, reduction in the number of migraines, and quality of life?
2. What is the evidence for safety associated with CGRP inhibitors, serotonin agonists and non-opioid combination analgesics for preventative and acute migraine and headache treatment (e.g., withdrawals due to adverse events or severe adverse events)?

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3. Are there subpopulations in which CGRP inhibitors, serotonin agonists and non-opioid combination analgesics for preventative and acute migraine and headache treatment are associated with more benefit or more harm?

### Conclusions:

- In this drug class update, there were 6 new systematic reviews and meta-analyses, 6 new high-quality guidelines, one new formulation and one new safety alert identified for inclusion.

#### Acute Migraine Treatment:

- Guidelines and systematic reviews recommend nonsteroidal anti-inflammatories (NSAIDs) or serotonin agonists (i.e., triptans) first-line treatment for migraine attacks based on high-quality evidence.<sup>1-4</sup>
- American Academy of Neurology (AAN) recommends ibuprofen, sumatriptan, zolmitriptan, rizatriptan and almotriptan for the acute treatment of migraine in children and adolescents based on moderate-quality evidence.<sup>5</sup>
- A Cochrane review found moderate-quality evidence that triptans were more effective than placebo in children and adolescents based on the outcome of pain freedom at 2 hours for the acute treatment of migraine, relative risk (RR) 1.67 (95% confidence interval [CI], 1.06 to 2.62) and RR 1.32 (95% CI, 1.19 to 1.47).<sup>6</sup>

#### Preventative Migraine Treatment:

- High quality guidelines recommend propranolol, amitriptyline, and CGRP receptor antagonists for the prevention of migraine based on moderate- to high-quality evidence.<sup>1,3,4</sup> Propranolol is recommended first line (low-quality evidence) and CGRP receptor antagonists are recommended after failure of other preventative treatments.<sup>1,4</sup> Candesartan and telmisartan are recommended for the prevention of episodic migraines based on moderate-quality evidence.<sup>3</sup>
- The Scottish Intercollegiate Guidelines Network (SIGN) and the International Classification of Headache Disorders, 3<sup>rd</sup> edition (ICHD-3) classify chronic migraines as patients with 15 or more headaches per month and the National Institute for Health and Care Excellence (NICE) recommends treatment in those that have 4 or more migraines per month.<sup>1,7,8</sup>

#### Tension-Type Headaches:

- The Veterans Administration (VA)/Department of Defense (DoD) recommends ibuprofen and acetaminophen for acute treatment of tension-type headaches (TTH) and amitriptyline for preventative treatment, based on low-quality evidence.<sup>3</sup>
- A Cochrane review found evidence that acetaminophen 1000 mg was more effective than placebo for the treatment of frequent episodic tension-type headaches based on high-quality evidence. Lower doses of acetaminophen, 500 mg to 650 mg, were not found to be more effective than placebo (low-quality evidence).<sup>9</sup>
- A 2015 Cochrane review found moderate-quality evidence that the use of ibuprofen 400 mg was more effective than placebo for the outcome of pain freedom at 2 hours in adults with TTH.<sup>10</sup>
- Aspirin 1000 mg was found to be more effective than placebo based on a review done by Cochrane for patients with TTH in 2017 (low-quality evidence). Aspirin use was found to be associated with a lower use of rescue medication compared to placebo in adults with TTH, 14% versus 31% (very low-quality evidence).<sup>11</sup>

#### Cluster Headache:

- The VA/DoD recommendation for cluster headache prevention is neither for or against the use of verapamil.<sup>3</sup> There is weak evidence to support the use of galcanezumab. NICE recommends verapamil be considered for cluster headache prevention but offers no other treatment recommendations.<sup>4</sup>
- Guidelines recommend avoiding butalbital use due to an increased risk of medication overuse headaches and dependence.<sup>2</sup>

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### Headache in Pregnancy:

- Multiple guidelines recommend that pregnant people with headache should receive acute headache treatment with acetaminophen based on low-quality evidence. If additional pain relief is required then NSAIDs or triptans may be considered.<sup>1,4,12</sup>

### Adverse Events:

- Adverse events associated with migraine and headache treatments vary depending on drug class. NSAIDs are gastrointestinal irritants and may cause nausea, vomiting and photophobia.<sup>1</sup> Triptans are associated with only mild to moderate adverse events but should be avoided in patients with uncontrolled hypertension and symptomatic cerebrovascular and cardiovascular disease. The use of aspirin is not recommended for people that are pregnant and should not be used in the third trimester of pregnancy.<sup>1</sup> In general, the use of CGRP inhibitors are well tolerated, with injection site reactions being the most common adverse event. Lasmiditan has been associated with gastrointestinal and neurological adverse reactions.<sup>2</sup>
- The use of opioids and butalbital-containing medications have a two-fold higher risk of medication overuse headache (MOH) compared to triptans, NSAIDs, and acetaminophen.<sup>2</sup> The VA/DoD recommends no more than 5 days of butalbital containing products to avoid the occurrence of MOH.<sup>3</sup>

### Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the evidence. After review of costs in executive session, make rizatriptan tablets, rizatriptan rapid tablets, and eletriptan tablets preferred.
- Recommend updating the PA criteria for CGRP inhibitors and serotonin agonists with clerical updates and new drug additions.
- Recommend removing uncontrolled hypertension warning for erenumab from the PA criteria, as the FDA has recently applied this warning to the entire CGRP class.
- Recommend PA criteria for butalbital containing products.

### Summary of Prior Reviews and Current Policy:

- The CGRP inhibitor class was last reviewed in June of 2023 and there were no changes made to the PDL at that time. Current policy for PA approval requires documentation of at least 4 migraines per month, failure of FDA-approved migraine prophylactic therapies (beta-blockers, anticonvulsants, and tricyclic antidepressants) and a specialist consult for approval (**see Appendix 5**). Erenumab and fremanezumab are currently preferred therapy options in the CGRP inhibitor PDL class (**see Appendix 1**).
- The serotonin agonist class was last reviewed in August of 2020. Lasmiditan was reviewed as a new drug and maintained as non-preferred on the PDL and added to the PA criteria. After executive session, Tosymra (sumatriptan nasal spray) was made non-preferred. All triptans have quantity limits to ensure appropriate use. Non-preferred drugs will deny on initiation and preferred drugs will deny only when maximum dose is exceeded.

### Background:

Headache is a frequently diagnosed condition occurring at a lifetime prevalence of 66%.<sup>3</sup> Headache disorders account for more disability-adjusted life years than all other neurologic disorders combined.<sup>3</sup> Primary headache disorders are tension-type headache, migraine headache and cluster headache. Secondary headaches are MOH, posttraumatic headache (PTH) and cervicogenic headache (e.g., disorders of the bony, intervertebral disc or in the muscular or other soft tissue elements of the neck and is usually associated with neck pain).<sup>3</sup>

### Migraine:

Migraine is a common headache ailment characterized by debilitating headache pain, nausea, and/or light and sound sensitivity. Migraine or severe headaches have been reported in 40 million adults in the United States (US).<sup>13</sup> Women experience migraine more often than men.<sup>14</sup> Migraine severity can range from mild to severe and is known to impact quality of life, including missed work days and interference in personal relationships. Diagnosis of migraine is based on patient reported symptoms and there is a lack of objective testing options to definitively diagnose migraine. Criteria has been developed by the International Classification of Headache Disorder to help classify migraine (**Table 1**).<sup>7</sup> Migraine is commonly characterized as either episodic or chronic, based on migraine frequency.<sup>15</sup> Episodic migraine is defined as patients with fewer than 15 migraine or headache days per month and chronic migraine sufferers have more than 15 monthly headache days and at least 8 are monthly migraine days.<sup>1,15</sup> Migraine may be associated with an aura, referring to the onset of sensory or motor symptoms occurring before or after headache onset.<sup>13</sup> Early treatment of migraine, in particular those with aura, is correlated with improved efficacy of treatment. Some factors that may dispose individuals to migraine include: emotional stress, menstruation, visual stimuli, weather changes, and certain foods or activities.<sup>14</sup> Patients with frequent attacks should be considered for preventative treatment to minimize the risk of medication overuse headaches which can occur when acute migraine medications are used more than 10 days per month or more than 15 days per month for aspirin, acetaminophen and NSAIDs. The need for ongoing preventative therapy should be accessed after 6 to 12 months.<sup>1</sup>

**Table 1. International Classification of Headache Disorders, 3<sup>rd</sup> edition (ICHD-3)<sup>7</sup>**

Criteria for Migraine without Aura	Criteria for Migraine with Aura
<p>A. At least 5 attacks fulfilling criteria B through D</p> <p>B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)</p> <p>C. Headache has at least 2 of the following characteristics:</p> <ul style="list-style-type: none"> <li>• Unilateral location</li> <li>• Pulsating quality</li> <li>• Moderate to severe pain intensity</li> <li>• Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)</li> </ul> <p>D. During headache at least on the following:</p> <ul style="list-style-type: none"> <li>• Nausea, vomiting, or both</li> <li>• Photophobia and phonophobia</li> </ul> <p>E. Not better accounted for by another ICHD-3 diagnosis</p>	<p>A. At least 2 attacks fulfilling criterion B and C</p> <p>B. One or more of the following fully reversible aura symptoms:</p> <ul style="list-style-type: none"> <li>• Visual</li> <li>• Sensory</li> <li>• Speech and/or language</li> <li>• Motor</li> <li>• Brainstem</li> <li>• Retinal</li> </ul> <p>C. At least three of the following six characteristics:</p> <ul style="list-style-type: none"> <li>• At least one aura symptom spreads gradually over <math>\geq 5</math> minutes</li> <li>• Two or more symptoms occur in succession</li> <li>• Each individual aura symptom lasts 5 to 60 minutes</li> <li>• At least one aura symptom is unilateral</li> <li>• At least one aura symptom is positive</li> <li>• The aura is accompanied, or followed within 60 minutes, by headache</li> </ul> <p>D. Not better accounted for by another ICHD-3 diagnosis</p>

Treatment of migraine is divided into 2 types: acute (abortive) and preventative. Acute therapy is most effective when given as soon as symptoms appear. Common treatment options are NSAIDs, acetaminophen, triptans, antiemetics and dihydroergotamines.<sup>14</sup> Treatments can have an onset of action of approximately 10 minutes to 30 minutes, depending on drug and route of administration. Triptans, NSAIDs, and acetaminophen are recommended first line for migraine.<sup>2,16</sup> Patients that experience severe nausea or vomiting may be candidates for an oral or rectal antiemetic. Oral triptans or triptan/naproxen combination products are recommended for patients with moderate to severe migraine attacks and are the most commonly used migraine treatment.<sup>13</sup> These recommendations are supported by guidelines, including NICE, which recommends triptans in combination with aspirin or acetaminophen first-line, starting with the most cost-effective treatment.<sup>17,2</sup> Triptan products also have the advantage of availability in oral, nasal and subcutaneous formulations. Treatment

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recommendations for children and adolescents with migraine include ibuprofen and triptans.<sup>6</sup> Adverse events were found to be similar between the triptans, when used by adult patients, by the Canadian Agency for Drugs and Technology in Health (CADTH).<sup>18</sup>

CGRP inhibitors are migraine therapies used to block CGRP, which is thought to play a role in migraine prevention, acute migraine treatment and cluster headache. FDA-approved CGRP inhibitors for migraine prevention are: atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab and rimegepant. The CGRP inhibitors used for acute treatment are: rimegepant, ubrogepant, and zavegepant. Galcanezumab is the only treatment used for cluster headache treatment. CGRPs are usually prescribed after trial and failure of more commonly used, cost-effective therapies such as propranolol or amitriptyline.

Ditans are a new type of triptan medication for migraine that works on the 5-HT<sub>1F</sub> receptor, void of vasoconstriction properties prompting cardiovascular (CV) warnings associated with triptan products that work as 5-HT<sub>1</sub> agonists. Lasmiditan is the only FDA approved ditan. Lasmiditan has demonstrated efficacy in improving migraine symptoms at 2 hours, 1 day and at 1 week.<sup>2</sup>

For patients who do not tolerate other acute migraine treatments, ergotamine preparations are an option; however, adverse events (i.e., numbness and muscle pain) and limited efficacy have resulted in low utilization.<sup>13</sup> Patients who experience a moderate to severe attack associated with vomiting or severe nausea, may benefit from SC sumatriptan, nasal sumatriptan or zolmitriptan, non-oral antiemetics and parenteral dihydroergotamine.<sup>14</sup> The American Headache Society recommends against the use of opioids and butalbital-containing products first-line for migraine and other headache disorders, due to increased risk of MOH.<sup>2</sup>

The most commonly studied intermediate outcomes related to the acute treatment of migraine headache, and other types of headaches, include headache pain improvement, headache pain freedom (ranging from 30 minutes to 2 hours), relief of most bothersome symptom (e.g., photophobia, phonophobia, nausea, or vomiting) and need for rescue medication. Disability, health-related quality of life, employment-related outcomes, and Patient Global Impression of Change (PGIC) are important health outcomes related to migraine therapy. The PGIC is a scale ranging from 1-7 (very much worse to very much better) to assess the patients' rating of overall improvement. The Migraine Disability Assessment Test (MIDAS) is used to quantify headache disability based on a 7-item questionnaire. The score is based off of activity limitations ranging from little or no disability to severe disability.<sup>13</sup> Scores of 0-5 are indicative of little or no disability, 6-10 mild disability, 11-20 moderate disability, and 21 or greater as severe disability.<sup>13</sup>

#### Medication Overuse Headache:

Medication overuse headache, also referred to as rebound headache, is a common headache condition resulting from excessive use medications to treat acute headache conditions.<sup>3</sup> Medication-overuse headache is a common condition that is defined as headache for 15 or more days a month corresponding with frequent use of acute medications for more than 3 months.<sup>1,3</sup> Usually, MOH is associated with individuals that have a history of migraine. Butalbital, opioids, triptans, ergotamine and non-opioid analgesics have all been known to cause MOH.<sup>3</sup> Drug classes associated with MOH include triptans, opioids, and combination analgesics when used 10 or more days per month. Over the counter (OTC) analgesics (e.g., ibuprofen, aspirin, and acetaminophen) have been linked to MOH when used for 15 days or more per month.<sup>1,3</sup> The VA/DoD advises that MOH can occur with opioid use of 8 days or more per month for >3 months.<sup>3</sup> Medication overuse headaches are linked with butalbital use and can occur with 5 or more days of use for greater than 3 months.<sup>3</sup> The use of butalbital-containing products is especially problematic due to a high association with MOH and abruptly stopping therapy can precipitate withdrawal seizures.<sup>3</sup> Risk factors for the development of MOH are: headache frequency, migraine diagnosis, other excessive medication use for headache, history of anxiety or depression, physical inactivity, sick leave of greater than 2 weeks in the last year, self-reported whiplash, and smoking.<sup>3</sup>

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### Cluster Headache:

Cluster headache is a debilitating headache condition which is 4 times more likely to affect men compared to women.<sup>19</sup> The frequency of attacks for individuals with cluster headache ranges from 1 every other day to 8 per day. Treatment for patients with cluster headache include acute treatment and prevention. The Subcutaneous sumatriptan, zolmitriptan nasal spray, galcanezumab and high flow oxygen are weakly recommended as treatment options.<sup>3</sup>

Preventative therapy is a key component of cluster headache treatment, since acute therapy is useful for aborting the individual attack but has no effect on recurrent attacks.<sup>20</sup> Preventative therapy should be initiated immediately once the cluster headache attacks begin. Guidelines recommend verapamil first line for chronic headache.<sup>20</sup> Suboccipital steroid injections have good evidence for use as preventative therapy for cluster headache.<sup>16</sup> The regimen consisted of single injection of a short or long-acting betamethasone. Galcanezumab is also considered an effective second-line preventative therapy. Combination therapy or monotherapy with prednisone, topiramate or lithium, can be considered for patients who lack symptom improvement or do not tolerate first-line monotherapy.<sup>20</sup> Additional preventative therapies with positive evidence for use but based on low-quality evidence are: lithium, warfarin, and melatonin.<sup>16</sup> There is insufficient evidence to recommend frovatriptan, capsaicin nasal spray, nitrate tolerance (i.e., decreased sensitivity to nitrates with continued use), and prednisone. There is negative evidence (evidence against use) for the use of sodium valproate, sumatriptan, deep brain stimulation, cimetidine/chlorpheniramine, misoprostol, oxygen and candesartan as preventative therapy.<sup>16</sup>

### Tension Type Headache:

Tension-type headaches (TTH) occur at variable frequencies and last 30 minutes to 7 days. Classification of TTH by the International Classification of Headache Disorders (ICHD-3 beta) divided TTH into episodic and chronic.<sup>9</sup> Chronic TTH is defined by the presence of headache on 15 or more days per month on average, for 3 months or more. All other types of TTH are considered episodic.<sup>10</sup> Tension headaches are often mild to moderate in pain severity. Tension headaches are not usually associated with nausea or vomiting and are not aggravated by routine activities. Treatment with analgesics, such as ibuprofen or acetaminophen, are often used for TTH.

The CGRP inhibitors have low utilization with just 34 claims in quarter 3 of 2024 but are associated with significant costs. The triptans had 253 claims in quarter 3 of 2024 but account for a small budgetary impact to the Oregon Health Authority (OHA).

### **Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

## **New Systematic Reviews:**

### Cochrane – Drugs for the Acute Treatment of Migraine in Children and Adolescents

A 2016 systematic review and meta-analysis evaluated therapies for the acute treatment of migraine in those up to 17 years of age.<sup>6</sup> Migraine affects 3% to 10% of children and adolescents. Children were defined as those under the age of 12 years and adolescents 12 to 17 years of age. The mean age was 12.9 years with a mean range of ages of 8.2 to 14.7 years.<sup>6</sup> Literature was searched up till February 2016. Twenty-seven RCTs evaluating migraine treatments met inclusion criteria. Drugs included in the review were: almotriptan, naratriptan, rizatriptan, sumatriptan + naproxen, zolmitriptan, acetaminophen, ibuprofen, and dihydroergotamine (DHE).<sup>6</sup>

The included studies were low- to moderate-quality, downgraded due to imprecision and inconsistency. Low-quality evidence demonstrated that ibuprofen was more effective for treating acute migraine in children based on the outcome of pain freedom at 2 hours (RR 1.87; 95% CI, 1.15 to 3.04).<sup>6</sup> Triptans were also found to be more effective than placebo in children based on pain freedom at 2 hours (RR 1.67; 95% CI, 1.06 to 2.62; moderate-quality evidence). Triptans were studied in adolescents and found to be more effective than placebo for pain freedom at 2 hours (RR 1.32; 95% CI, 1.19 to 1.47; number needed to benefit [NNTB] = 6) based on moderate-quality evidence.<sup>6</sup> One trial studied the combination of sumatriptan/naproxen compared to placebo in adolescents and found the combination more effective than placebo for pain freedom at 2 hours (RR 2.66; 95% CI, 1.57 to 4.51; moderate-quality evidence).<sup>6</sup> Acetaminophen and dihydroergotamine (DHE) were both studied in small separate studies in children and were not found to be superior to placebo for the treatment of migraine.<sup>6</sup>

No serious adverse events were reported with the use of triptans in adolescents but there were more minor adverse events with triptans compared to placebo (number needed to harm [NNTH] 8).<sup>6</sup> Adverse events were not significantly increased with triptans when compared to placebo in any studies involving children.

### Cochrane – Acetaminophen for Acute Treatment of Episodic Tension-type Headache in Adults

A 2016 Cochrane review evaluated the efficacy of oral acetaminophen use in adult patients with episodic TTH.<sup>9</sup> Twenty-three studies (n=8079) evaluating frequent episodic type headaches were included. Frequent episodic tension-type headaches were defined as two to 14 headaches every month.

Most studies did not report details of study methodology and were determined to be high risk of bias by the authors. Acetaminophen 1000 mg was found to be more effective than placebo in for pain freedom at 2 hours for the treatment of episodic TTH based on 8 studies (RR 1.3; 95% CI, 1.1 to 1.4; number needed to treat [NNT 22]) (high quality of evidence).<sup>9</sup> There is moderate quality of evidence that pain freedom at 1 hour was found to be superior with acetaminophen 1000 mg compared to placebo (RR 1.2; 95% CI, 0.90 to 1.5; 4 studies). At 4 hours pain freedom was higher with acetaminophen 1000 mg compared to placebo based on moderate quality evidence (RR 1.2; 95% CI, 1.16 to 1.3; NNT 8.2).<sup>9</sup> Use of rescue medication was lower in patients treated with acetaminophen 1000 mg compared to placebo with a NNT of 7.76 based on moderate quality of evidence (RR 0.58; 95% CI, 0.50 to 0.69).<sup>9</sup> There were more adverse events in people treated with acetaminophen compared to placebo, but results were not statistically significant (RR 1.1; 95% CI, 0.94 to 1.3; moderate quality evidence).

Acetaminophen 500 mg to 650 mg was compared to placebo for episodic TTH and was not found to be more effective based on the outcome of use of rescue medication based on 2 studies (low-quality evidence).<sup>9</sup> The outcomes of pain freedom at 2 hours were not studied. Low-quality evidence found acetaminophen 1000 mg was not more effective than ketoprofen 25 mg or ibuprofen 400 mg.

### Cochrane - Ibuprofen for Acute Treatment of Episodic Tension-type Headache in Adults

A 2015 systematic review and meta-analysis done by Cochrane evaluated the use of ibuprofen for acute TTH in adults.<sup>10</sup> Twelve studies were included. Ibuprofen doses studied were 200 mg (2 studies), 400 mg (9 studies) and fast-acting 200 mg (1 study). All patients had moderate to severe pain and frequent TTH (1 to 14 headaches per month).<sup>10</sup> The average headache frequency was not often reported.

Evidence for the use of ibuprofen 400 mg doses were analyzed together in the meta Pain freedom at 2 hours was higher with ibuprofen 400 mg compared to placebo based on 4 studies (RR 1.5; 95 % CI, 1.2 to 2.0; NNT 14; moderate-quality evidence).<sup>10</sup> Pain freedom at 1 hour was not statistically significantly different between groups. Low-quality evidence found the use of rescue medication to be lower with ibuprofen 400 mg than with placebo (RR 0.6; 95% CI, 0.4 to 0.8) based on 2 studies.<sup>10</sup> Adverse events were similar between ibuprofen and placebo, 4.1% and 3.8%, respectively. Data from one study comparing ibuprofen 200 mg to placebo did not provide any usable efficacy data.

#### Cochrane – Aspirin for Acute Treatment of Episodic Tension-type Headache in Adults

The use of aspirin for acute symptoms in adults with TTH was evaluated in a 2017 Cochrane review.<sup>11</sup> There were 5 studies identified comparing aspirin to placebo. The preferred primary outcome of pain freedom at 2 hours was not studied in any of the included trials.<sup>11</sup>

All included studies had some aspect of bias, most often because of lack of data reported on study methodology. Aspirin 1000 mg was found to be associated with a lower use of rescue medication use compared to placebo based on 2 studies, 14% versus 31% (low-quality evidence).<sup>11</sup> Very low-quality evidence found patients treated with aspirin 1000 mg to be more satisfied with treatment compared to placebo-treated patients (NNT 6). Very low-quality evidence found no statistical difference in the incidence of adverse events between ASA 1000 mg and placebo, approximately 15 out of 100 people treated.<sup>11</sup> There was insufficient evidence to compare ASA to active treatments.

#### AHRQ – Management of Primary Headaches in Pregnancy

The Agency for Healthcare Research and Quality (AHRQ) reviewed the efficacy and safety of headache treatment in those that are pregnant (or attempting to become pregnant), postpartum, or breastfeeding with a history of primary headache.<sup>12</sup> Primary headache disorders are comprised of migraine, tension headache, cluster headache and other trigeminal autonomic cephalgias (TACs). Sixteen primary studies and 26 systematic reviews were identified from a search lasting until June 5, 2020.<sup>12</sup> Most studies were done in patients with migraine. Studies had a high to moderate risk of bias.

There is no available evidence on the efficacy of preventative pharmacotherapy in this population.<sup>12</sup> For the treatment of acute attacks of primary headaches in pregnant women, the use of triptans may not be more harmful than their use before pregnancy to the infant. There may be worse child emotionality and activity outcomes at 3 years of age in women treated with triptans (low quality of evidence).

The use of the combination of metoclopramide and diphenhydramine may reduce migraine or tension headache severity during pregnancy more than codeine (low-quality evidence; based on 1 study).<sup>12</sup> No increase in harms were reported. Low dose aspirin was not associated with an increased risk of adverse events (moderate quality of evidence); however, the use of acetaminophen, prednisolone, indomethacin, ondansetron, antipsychotics and IV magnesium may be with increased fetal adverse events (low-quality evidence).<sup>12</sup>

There is insufficient direct evidence on harms of topiramate but indirect evidence suggests increased risk of fetal/child adverse events (moderate-quality evidence).<sup>12</sup> Gabapentin, carbamazepine, and valproate may have a similar risk (low- to moderate-quality evidence). Lamotrigine may have a lower risk of

adverse events (moderate quality evidence). Venlafaxine, tricyclic antidepressants (TCAs), benzodiazepines, beta blockers, prednisolone, and oral magnesium may also have increased risk of adverse fetal/child adverse events.<sup>12</sup> Antihistamines and nifedipine may have a lower risk of adverse events.

### AHRQ – Acute Treatments for Episodic Migraine

In 2020 a comparative effectiveness review was done by AHRQ to evaluate pharmacological and nonpharmacological treatments for adults with acute episodic migraine.<sup>2</sup> This review will focus on pharmacological treatments. There were 186 RCTs of triptans that met inclusion into the review which included the following triptans: sumatriptan, zolmitriptan, eletriptan, naratriptan, almotriptan, rizatriptan, and frovatriptan. There were 5 systematic reviews that provided evidence for the use of NSAIDs in migraine. Ibuprofen was most commonly used, followed by diclofenac and ketorolac. Evidence for the use of antiemetics, dihydroergotamine, ergotamine plus caffeine, and acetaminophen was available from 135 RCTs. Fifteen studies evaluated the use of butorphanol, meperidine, morphine, hydromorphone, and tramadol in combination with acetaminophen. There were 5 RCTs included for the evaluation of lasmiditan and 14 studies for the use of CGRP inhibitors.<sup>2</sup>

The main outcome of interest was pain relief at 2 hours. There was evidence for efficacy for the use of triptans, NSAIDs, dihydroergotamine, antiemetics, and acetaminophen.<sup>2</sup> Studies evaluating newer therapies; CGRP inhibitors and 5-HT<sub>1F</sub> receptor agonists (i.e., lasmiditan) demonstrated pain relief at 2 hours, 1 day and at 1 week.<sup>2</sup> There was insufficient evidence to recommend the use of opioids over other treatments.

#### NSAIDs/Triptans<sup>2</sup>:

- There were 186 RCTs which provided evidence for triptans and 5 RCTs for NSAIDs. Two systematic reviews provided evidence for combination therapy of triptans and NSAIDs.
- There is high-quality evidence that triptans resolve pain at 2 hours and 1 day.
- Mild and transient adverse events are present with triptans compared to placebo based on high quality evidence.
- In placebo-controlled comparisons, NSAIDs probably are more effective for outcomes of pain at 2 hours and at 1 day based on moderate strength of evidence.
- There is moderate-quality evidence that there is an increased risk of adverse events with NSAIDs compared to placebo.

#### OPIOIDS<sup>2</sup>:

- Only a small number of studies (13 RCTs) were available for review. No data is available on predicting risk for opioid misuse when used to manage headaches.
- Based on low quality of evidence tramadol/acetaminophen may reduce pain at 2 hours and 1 day, compared to placebo.
- Butorphanol may reduce pain at 2 hours, 1 day and 1 week compared to placebo based on low quality of evidence.
- The use of meperidine plus hydroxyzine may be worse than dihydroergotamine plus metoclopramide and morphine may be worse than IV dexamethasone based on pain relief at 2 hours (both low quality of evidence). The use of hydromorphone may be worse than metoclopramide and worse than diphenhydramine plus prochlorperazine for pain relief at 2 hours, based on low quality of evidence.

#### CGRP inhibitors<sup>2</sup>:

- CGRP inhibitors used for acute migraine treatment (i.e., rimegepant and ubrogepant) probably improve pain relief at 2 hours and increase chance of being pain-free at 2 hours, 1 day and at 1 week (moderate- to high-quality evidence). There is moderate- to high-quality evidence that CGRP inhibitors increased the likelihood of being pain free at 2 hours and sustained pain free for 1 day and 1 week.

Lasmiditan<sup>2</sup>:

- There is moderate to high strength of evidence that lasmiditan restores function at 2 hours, resolves pain at 2 hours, 1 day and at 1 week.
- Lasmiditan was associated with significantly more gastrointestinal and neurological adverse events compared to placebo.
- Serious adverse events were more common in patients receiving lasmiditan compared to placebo.

Miscellaneous Agents<sup>2</sup>:

- There is high-quality evidence that dihydroergotamine reduces pain when compared to placebo at 2 hours and 1 day and 1 week. There is evidence that dihydroergotamines may improve function and offer sustained pain relief at 2 hours and 1 day, based on moderate and high-quality evidence, respectively.
- Ergotamine combined with caffeine probably improves pain relief at 2 hours based on moderate strength of evidence.
- Low-quality evidence suggests that antiemetics (i.e., prochlorperazine, chlorpromazine, metoclopramide, droperidol and haloperidol) may resolve pain at 2 hours and 1 day when compared to placebo.

Low-quality evidence found that dexamethasone, magnesium sulfate, and octreotide suggest possible effectiveness in reducing migraine pain.<sup>2</sup>

After review, 10 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).<sup>12,21-30</sup>

**New Guidelines:**

High Quality Guidelines:

VA/DoD – Management of Headache

In 2023 the VA/DoD updated guidance for the treatment of headache.<sup>3</sup> Evidence used for recommendations are graded and designated by the Work Group as Strong or Weak. Strength of recommendation text is described in **Table 2** and based on the quality of evidence.

**Table 2. Strength and Direction of Recommendations and General Corresponding Text<sup>3</sup>**

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend
Weak for	We suggest
Neither for nor against	There is insufficient evidence to recommend for or against
Weak against	We suggest against
Strong against	We recommend against

Abortive and preventative treatment recommendations are presented for migraines, headaches, tension-type headaches, cluster headache, and MOH.<sup>3</sup> For general headache prevention the guidelines found that there wasn't evidence neither for nor against for the following products: coenzyme Q10, feverfew, melatonin, omega-3, vitamin B6, fluoxetine and venlafaxine.<sup>3</sup> For the prevention of chronic tension-type headaches amitriptyline is weakly recommended as

preventative therapy.<sup>3</sup> There is weak evidence against the use of botulinum/neurotoxin injection for the prevention of chronic tension-type headaches. There is weak evidence that ibuprofen (400 mg) or acetaminophen (1000 mg ) is recommended for the acute treatment of TTH.<sup>3</sup>

There was insufficient evidence to recommend for or against any therapy for prevention or withdrawal strategy for the treatment of MOH. Recommendations for migraine treatment are presented below in **Tables 3 and 4.**<sup>3</sup> For the acute treatment of migraine there is insufficient evidence to recommend one treatment over another. For the prevention of migraine, tension headache or cluster headache there is insufficient evidence for or against the use of any specific medication over another. Treatment recommendations for the other types of headaches are presented in **Tables 5 and 6.**<sup>3</sup> There is insufficient evidence to recommend any specific combination of therapies for the prevention of headache. There is insufficient evidence for the use of specific treatments for posttraumatic headaches.

**Table 3. Pharmacotherapy for Migraine Preventative Treatments<sup>3</sup>**

Pharmacotherapy	Indication	Strength
Candesartan or telmisartan	Prevention of episodic migraine	Strong*
Erenumab, fremanezumab or galcanezumab	Prevention of episodic or chronic migraine	Strong*
Intravenous eptinezumab	Prevention of episodic or chronic migraine	Weak*
Lisinopril	Prevention of episodic migraine	Weak
Magnesium	Prevention of migraine	Weak
Topiramate	Prevention of episodic and chronic migraine	Weak*
Propranolol	Prevention of migraine	Weak
Valproate	Prevention of episodic migraine	Weak*
Memantine	Prevention of episodic migraine	Weak*
Atogepant	Prevention of episodic migraine	Weak*
OnabotulinumtoxinA injection	Prevention of chronic migraine	Weak
AbobotulinumtoxinA or onabotulinumtoxinA injection	Prevention of episodic migraine	Weak
Rimegepant	Prevention of episodic migraine	Neither for nor against*
Gabapentin	Prevention of episodic migraine	Weak against*
Levetiracetam	Prevention of episodic migraine	Neither for nor against*
Key: * New recommendation		

**Table 4. Pharmacotherapy for Migraine Abortive Treatments<sup>3</sup>**

Pharmacotherapy	Indication	Strength
Eletriptan, frovatriptan, rizatriptan, sumatriptan (oral or subcutaneous), the combination of sumatriptan and naproxen, or zolmitriptan (oral or intranasal)	Acute treatment of migraine	Strong*

Aspirin/acetaminophen/caffeine	Acute treatment of migraine	Strong*
Acetaminophen, aspirin, ibuprofen or naproxen	Acute treatment of migraine	Weak
Rimegepant or ubrogepant	Acute treatment of migraine	Weak *
Intravenous ketamine	Acute treatment of migraine	Weak
Lasmiditan	Acute treatment of migraine	Neither for nor against*
Key: * New recommendation		

**Table 5. Pharmacotherapy for Cluster Headache Treatments<sup>3</sup>**

Pharmacotherapy	Indication	Strength
Galcanzumab	Prevention of episodic cluster headache	Weak
Galcanzumab	Against the use for prevention of chronic cluster headache	Weak*
Verapamil	Prevention of episodic or chronic cluster headache	Neither for nor against*
Subcutaneous sumatriptan (6 mg) or intranasal zolmitriptan (10 mg)	Acute treatment of cluster headache	Weak*
Normobaric oxygen therapy	Acute treatment of cluster headache	Weak
Key: * New recommendation		

**Table 6. Pharmacotherapy for Tension-Type Headache<sup>3</sup>**

Pharmacotherapy	Indication	Strength
Ibuprofen (400 mg) or acetaminophen (1000 mg)	Acute treatment for chronic tension-type headache	Weak
Amitriptyline	Prevention of chronic tension-type headache	Weak

#### SIGN – Pharmacological Management of Migraine

The Scottish Intercollegiate Guidelines Network (SIGN) published updated guidance on the diagnosing and management of migraine in March of 2023.<sup>1</sup> Literature was searched from 2016 to 2022. The evidence was graded using GRADE methodology and assigned a number of 1 (high quality) to 4 (expert opinion) (**Table 7**).<sup>1</sup> Recommendations are formulated from the evidence and an explanation of forms of recommendations are provided in **Appendix 3**.

**Table 7. Levels of Evidence<sup>1</sup>**

1 <sup>++</sup>	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2 <sup>++</sup>	High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2 <sup>+</sup>	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2 <sup>-</sup>	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, case reports, case series
4	Expert opinion

Recommendations for the acute treatment of migraine and preventative therapies are presented in **Table 8**.<sup>1</sup> When patients are treated with migraine therapies for acute migraine symptoms the potential for MOH should be discussed. Acetaminophen is recommended as a first-choice option for people that are pregnant requiring short-term relief mild to moderate headaches during any trimester of pregnancy and ibuprofen is also appropriate in the first and second trimesters.<sup>1</sup> Triptans also appear to be safe in pregnancy and can be considered when the use of acetaminophen or ibuprofen fail to relieve migraine pain. Antiemetics can be used in combination with acute migraine treatments and should be used in patients with nausea and vomiting associated with migraine.

**Table 8. Recommendation from SIGN for the Treatment of Migraine<sup>1</sup>**

Medication	Recommendation	Efficacy Evidence Rating
<b>Acute Treatment of Migraine</b>		
Aspirin 900 mg	First-line treatment for patients with acute migraine	1 <sup>++</sup>
Ibuprofen 400 mg (dose should be increased to 600 mg if 400 mg is ineffective)	First-line treatment for patients with acute migraine	1 <sup>++</sup>
Acetaminophen (1000 mg)	Can be considered for treatment of patients with acute migraine who are unable to take other acute therapies	1 <sup>++</sup>
Triptans – sumatriptan (50-100 mg) is the first choice. Consider other options if sumatriptan fails	First-line treatment for patients with acute migraine	1 <sup>++</sup>
Metoclopramide (10 mg ) or prochlorperazine (10 mg)	Can be considered for migraine and should be considered if presenting with nausea and vomiting	1 <sup>+</sup>
Combination therapy – sumatriptan (50 to 85 mg) and naproxen (500 mg)	Combination should be considered for the treatment of patients with acute migraine`	1 <sup>++</sup>
<b>Preventative Treatment of Migraine</b>		
Propranolol (80 – 160 mg daily)	First-line prophylactic treatment for patients with episodic or chronic migraine	1 <sup>++</sup>
Topiramate (50-100 mg daily)	Prophylactic treatment option for patients with episodic or chronic migraine	1 <sup>++</sup>
Amitriptyline (25 – 150 mg at night)	Option should be considered as a prophylactic treatment for patients with episodic or chronic migraine	1 <sup>++</sup>
Candesartan (16 mg daily)	Can be considered as a prophylactic treatment for patients with episodic or chronic migraine	1 <sup>+</sup>

Sodium valproate (400 to 1,500 mg daily)	Can be considered as a prophylactic treatment for patients over the age of 55 with episodic or chronic migraine	1++
Botulinum toxin A	Recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have been appropriately treated with three or more oral migraine prophylactic treatments	1++
Erenumab, fremanezumab, galcanezumab, and eptinezumab	Recommended for the prophylactic treatment of patients with chronic migraine where medication overuse has been addressed and patients have not benefited from appropriate trials of three or more oral migraine prophylactic treatments	1++
Fremanezumab, galcanezumab, and eptinezumab	Can be considered for the prophylactic treatment of patients with episodic migraine where medication overuse has been addressed and patients have not benefited from appropriate trials of three or more oral migraine prophylactic treatments	1++

Adverse events of migraine treatments should be considered. Aspirin and NSAIDs are gastrointestinal irritants and may cause nausea, vomiting and photophobia.<sup>1</sup> Triptans are associated with only mild to moderate adverse events but should be avoided in patients with uncontrolled hypertension and symptomatic cerebrovascular and cardiovascular disease. The use of aspirin is not recommended for people that are pregnant and should not be used in the third trimester of pregnancy.<sup>1</sup> In general, the use of CGRP inhibitors are well tolerated, with injection site reactions being the most common adverse event.

#### NICE – Headaches in Over 12s: Diagnosis and Management

In 2024 NICE updated previous versions of their recommendations for headache management in individuals over 12 years of age.<sup>4</sup> Headache type should be diagnosed as TTH, migraine or cluster. Providers should be aware of the potential for MOH. This usually occurs when people have headaches that have developed or worsened while taking any of the following drugs for 3 months or more: triptans, opioids, ergots or combination analgesics on 10 days per month or more. Medication overuse headache should be considered in those taking acetaminophen, ASA or NSAIDs, either alone or in combination, on 15 days per month or more.<sup>4</sup>

NICE Recommendations based on headache type:

#### Acute Treatment of Tension-type Headache<sup>4</sup>:

- Consider aspirin, acetaminophen, or NSAID (do not offer aspirin to those under 16 due to the potential of Reye’s syndrome).
- Do not offer opioids for acute treatment.

#### Prophylactic Treatment of Tension-type Headache<sup>4</sup>:

- Consider acupuncture, 10 sessions over 5 to 8 weeks.

#### Acute Migraine Treatment with or without Aura<sup>4</sup>:

- Combination treatment with an NSAID and oral triptan or acetaminophen and an oral triptan.
- For patients who are 12-17 years of age consider a nasal triptan in preference to an oral triptan.
- If the patient preference is for just one drug, consider an oral triptan, NSAID, aspirin (900 mg) or acetaminophen.
- Consider and anti-emetic in addition to acute treatment even in the absence of nausea and vomiting.

- 
- Do not offer ergots or opioids.
  - If oral preparations are not ineffective or not tolerated offer a non-oral metoclopramide or prochlorperazine with or without a non-oral NSAID or triptan if they have not been tried.

#### Prophylactic Migraine Treatment<sup>4</sup>:

- Topiramate should not be used in women who are pregnant or of childbearing potential.
- Offer topiramate or propranolol for prophylaxis to appropriate patients (see above). The risks of fetal malformations and the importance of contraception should be discussed.
- Amitriptyline can also be considered for prophylaxis.
- Do not offer gabapentin.
- Acupuncture can be tried if topiramate or propranolol are ineffective or unsuitable.
- Review needs for ongoing prophylaxis at 6 months after start of prophylactic therapy.
- Riboflavin 400 mg once daily may be effective in reducing migraine frequency.
- Do not offer hormonal contraceptive to women and girls who have migraine with aura.

#### Menstrual-related Migraines<sup>4</sup>:

- If migraines are predictable and unresponsive to standard treatment, consider frovatriptan (2.5 mg twice daily) or zolmitriptan (2.5 mg 2-3 times daily) on the days migraines are expected.

#### Migraine during Pregnancy<sup>4</sup>:

- Acetaminophen for the acute treatment. Consider triptan or an NSAID after discussing the risks and benefits.

#### Cluster Headache Acute Treatment<sup>4</sup>:

- Offer oxygen and/or subcutaneous or nasal triptan for the acute treatment.
- Do not offer acetaminophen, NSAIDs, opioids, ergot or oral triptans for treatment.

#### Cluster Headache Prophylactic Treatment<sup>4</sup>:

- Consider verapamil treatment.

#### Medication Overuse Headache<sup>4</sup>:

- Advise stopping all overused headache medications for at least 1 month by abruptly stopping them.
- Consider prophylactic therapy for underlying primary headache disorder.

#### NICE – Atogepant for Preventing Migraine

In May of 2024 NICE reviewed the safety and efficacy of atogepant.<sup>8</sup> Atogepant is approved for the preventative treatment of migraine taken orally daily. Evidence demonstrates that atogepant decreases monthly migraine days more than placebo. There is insufficient direct comparative evidence to other preventative therapies for migraine. After a review of evidence NICE recommends the following<sup>8</sup>:

- 
- Atogepant is an option for adult patients who have at least 4 migraine days a month and have tried and failed at least 3 preventative medications.
  - The benefits, harms and cost should be discussed with the patient.
  - Reassessment of migraine frequency should be done after 12 weeks.
  - The treatment should be continued only if the frequency of episodic migraines (e.g., defined as fewer than 15 headache days per month) has been reduced by at least 50%.
  - For patients with chronic migraine (e.g., defined as 15 or more headache days per month, with at least 8 of those having features of migraine) there should be 30% or fewer migraines.

#### NICE – Rimegepant for Preventing Migraine

The National Institute for Health and Care Excellence evaluated the use of rimegepant for the prevention of migraine in June of 2023.<sup>31</sup> Rimegepant is an orally disintegrating tablet indicated as preventative therapy for episodic migraine and acute treatment of migraine with or without aura. Rimegepant reduces monthly migraine days more than placebo.

NICE recommends the following for rimegepant therapy<sup>31</sup>:

- An option for preventing episodic migraine in those who have at least 4, and fewer than 15 migraine attacks per month, and if at least 3 prior preventative therapies have not worked.
- Efficacy should be reevaluated at 12 weeks and rimegepant should be discontinued if frequency of migraine attacks does not reduce by at least 50%.

#### American Academy of Neurology – Acute Treatment of Migraine in Children and Adolescents

In 2019 the AAN updated guidance for migraine therapy use in children (individuals younger than 12 years) and adolescents (individuals aged 12-17 years).<sup>5</sup> This guideline updates 2004 guideline recommendations. Methods were clearly outlined. Authors had conflicts of interest which were reviewed by an oversight committee to minimize direct potential conflicts. A literature search lasting through August 2017 was performed.<sup>5</sup> Six new studies on acute migraine treatments were identified since the last guideline. Migraine studies were included for participants 0-18 years of age. Recommendations were graded A, B, C, U or R using the modified Delphi process. Levels A (must), B (should) and C (may) are associated with strength of recommendations. A U is used when there is insufficient evidence. An R is assigned if balance of harms and benefits are unknown or if exorbitantly expensive or if important risks. Outcomes were pain response at 30 minutes, 1 hour, 2 hours, and relief of photophobia.

Recommendations for migraine treatment in children and adolescents are outlined in **Table 9**.<sup>5</sup> For children and adolescents there is evidence for the treatment of migraine for the use of ibuprofen, acetaminophen and triptans (mostly for adolescents). If one triptan fails, then an alternate triptan should be tried to find the most effective therapy to reduce migraine symptoms (Level B).<sup>5</sup> Non-oral therapies should be considered if the headache peaks quickly or is accompanied by nausea or vomiting (Level C). A second dose of acute migraine treatment can be considered if the initial treatment is successful, but the headache returns within 24 hours (Level B).

**Table 9. AAN Recommendations for the Acute Treatment of Migraine in Children and Adolescents<sup>5</sup>**

Recommendation	Level of Recommendation
Ibuprofen oral solution (10 mg/kg) as an initial treatment for children and adolescents with acute migraine to reduce pain	B
For adolescents with migraine sumatriptan/naproxen oral therapy (10/60, 30/180, 85/500 mg), zolmitriptan nasal spray (5 mg), sumatriptan nasal spray 20 mg, rizatriptan oral disintegrating tablets (5 or 10 mg) or almotriptan oral therapy (6.25 to 12.5 mg) should be prescribed to reduce headache pain	B
For adolescents with incomplete migraine symptom relief with a triptan, then an ibuprofen or naproxen should be offered in addition to the triptan	B
No more than 14 days of ibuprofen or acetaminophen per month, no more than 9 days of any combination of triptans, and no more than 9 days of combination therapy of triptans, analgesics or opioids* for more than 3 months should be used to avoid medication overuse headache	B
Triptans should not be used in patients with a history of ischemic vascular disease or accessory conduction pathway disorders to avoid the morbidity and mortality associated with aggravating these conditions	A
Adolescents with migraine with aura can take triptans safely but the most effective approach if it is taken at the onset of headache pain	B

Key: \* Opioids are not recommended for the treatment of migraine in children.

#### Excluded Publication:

American Headache Society – Calcitonin Gene-related Peptide-targeting Therapies are a First-line Option for the Prevention of Migraine

This publication was excluded due to poor quality rigor of development and systematic approach. It is a position statement.<sup>32</sup>

#### New Formulation:

SYMBRAVO (rizatriptan benzoate/meloxicam): A new combination product of rizatriptan and meloxicam was approved January of 2025.<sup>33</sup> The product combines a triptan with an NSAID for the acute treatment of migraine with or without aura in adults. The dose is one tablet (20 mg meloxicam and 10 mg rizatriptan) orally as needed, not to exceed one tablet. The safety of treating more than 7 headaches, on average, in a 30-day period is unknown. Approval was based on one, double-blind, controlled study comparing the combination product to monotherapy with rizatriptan 10 mg, meloxicam 20 mg or placebo.<sup>33</sup> Results for the co-primary endpoints of pain freedom at hour 2 and most bothersome symptom free at hour 2 were statistically significantly higher in the rizatriptan/meloxicam group compared to placebo, 19.9% vs. 6.7% and 36.9% and 24.4%, respectively.<sup>33</sup> Combination therapy compared to rizatriptan, meloxicam, or placebo monotherapy were not statistically different. There is a box warning for the risk of CV thrombotic events due to meloxicam and the product is contraindicated in coronary bypass graft (CABG) surgery. The risk of gastrointestinal bleeding is also increased due to meloxicam.

#### New FDA Safety Alerts:

**Table 10. Description of new FDA Safety Alerts**

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Atogepant <sup>33</sup>	QULIPTA	April 2023	Warnings	Serious hypersensitivity reactions such as anaphylaxis and angioedema

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## Appendix 1: Current Preferred Drug List

### CGRP Inhibitors

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>	<u>PDL</u>
erenumab-aooe	AIMOVIG AUTOINJECTOR	AUTO INJCT	SUBCUT	Y
fremanezumab-vfrm	AJOVY AUTOINJECTOR	AUTO INJCT	SUBCUT	Y
fremanezumab-vfrm	AJOVY SYRINGE	SYRINGE	SUBCUT	Y
ubrogepant	UBRELVY	TABLET	ORAL	Y
atogepant	QULIPTA	TABLET	ORAL	N
eptinezumab-jjmr	VYEPTI	VIAL	INTRAVEN	N
galcanezumab-gnlm	EMGALITY PEN	PEN INJCTR	SUBCUT	N
galcanezumab-gnlm	EMGALITY SYRINGE	SYRINGE	SUBCUT	N
rimegepant sulfate	NURTEC ODT	TAB RAPDIS	ORAL	N
zavegepant HCl	ZAVZPRET	SPRAY	NASAL	N

**Serotonin Agonists, Nasal**

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>	<u>PDL</u>
sumatriptan	IMITREX	SPRAY	NASAL	Y
sumatriptan	SUMATRIPTAN	SPRAY	NASAL	Y
zolmitriptan	ZOLMITRIPTAN	SPRAY	NASAL	Y
zolmitriptan	ZOMIG	SPRAY	NASAL	Y
sumatriptan	TOSYMRA	SPRAY	NASAL	N
sumatriptan succinate	ONZETRA XSAIL	AER POW BA	NASAL	N

**Serotonin Agonists, Oral**

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>	<u>PDL</u>
naratriptan HCl	NARATRIPTAN HCL	TABLET	ORAL	Y
sumatriptan succinate	IMITREX	TABLET	ORAL	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	TABLET	ORAL	Y
zolmitriptan	ZOLMITRIPTAN ODT	TAB RAPDIS	ORAL	Y
zolmitriptan	ZOLMITRIPTAN	TABLET	ORAL	Y
zolmitriptan	ZOMIG	TABLET	ORAL	Y
almotriptan malate	ALMOTRIPTAN MALATE	TABLET	ORAL	N
celecoxib	ELYXYB	SOLUTION	ORAL	N
eletriptan hydrobromide	ELETRIPTAN HBR	TABLET	ORAL	N
eletriptan hydrobromide	RELPAK	TABLET	ORAL	N
frovatriptan succinate	FROVA	TABLET	ORAL	N
frovatriptan succinate	FROVATRIPTAN SUCCINATE	TABLET	ORAL	N
lasmiditan succinate	REYVOW	TABLET	ORAL	N
rizatriptan benzoate	MAXALT MLT	TAB RAPDIS	ORAL	N
rizatriptan benzoate	RIZATRIPTAN	TAB RAPDIS	ORAL	N
rizatriptan benzoate	MAXALT	TABLET	ORAL	N
rizatriptan benzoate	RIZATRIPTAN	TABLET	ORAL	N
sumatriptan succ/naproxen sod	SUMATRIPTAN SUCC-NAPROXEN SOD	TABLET	ORAL	N
sumatriptan succ/naproxen sod	TREXIMET	TABLET	ORAL	N

**Serotonin Agonists, Subcutaneous**

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>	<u>PDL</u>
sumatriptan succinate	IMITREX	CARTRIDGE	SUBCUT	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	CARTRIDGE	SUBCUT	Y
sumatriptan succinate	IMITREX	PEN INJCTR	SUBCUT	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	PEN INJCTR	SUBCUT	Y
sumatriptan succinate	SUMATRIPTAN SUCCINATE	VIAL	SUBCUT	Y
sumatriptan succinate	ZEMBRACE SYMTOUCH	PEN INJCTR	SUBCUT	N

## Non-opioid Combination Analgesics, Oral

<u>Generic</u>	<u>Brand</u>	<u>Form</u>	<u>Route</u>	<u>PDL</u>
acetaminophen/d-brompheniramin	ACTIDOGESIC	TABLET	PO	N
acetaminophen/d-brompheniramin	ACTIDOGESIC-DF	TABLET	PO	N
acetaminophen/d-brompheniramin	DOLOGEN 325	TABLET	PO	N
acetaminophen/d-brompheniramin	DOLOGESIC	TABLET	PO	N
acetaminophen/d-brompheniramin	DOLOGESIC-DF	TABLET	PO	N
acetaminophen/diphenhydramine	THERAFLU SEVERE COLD RELIEF NT	POWD PACK	PO	N
acetaminophen/diphenhydramine	ACETADRYL	TABLET	PO	N
acetaminophen/diphenhydramine	ACETAMINOPHEN PM	TABLET	PO	N
acetaminophen/diphenhydramine	ACETAMINOPHEN PM XTRA STRENGTH	TABLET	PO	N
acetaminophen/diphenhydramine	EAZZZE THE PAIN	TABLET	PO	N
acetaminophen/diphenhydramine	EXT STR PAIN RELIEF/SLEEP	TABLET	PO	N
acetaminophen/diphenhydramine	HEADACHE PM	TABLET	PO	N
acetaminophen/diphenhydramine	MIDOL PM	TABLET	PO	N
acetaminophen/diphenhydramine	NIGHT TIME PAIN MEDICINE	TABLET	PO	N
acetaminophen/diphenhydramine	NON-ASPIRIN PM	TABLET	PO	N
acetaminophen/diphenhydramine	NON-ASPIRIN PM & SLEEP AID	TABLET	PO	N
acetaminophen/diphenhydramine	NON-ASPIRIN SLEEP AID	TABLET	PO	N
acetaminophen/diphenhydramine	PAIN & SLEEP	TABLET	PO	N
acetaminophen/diphenhydramine	PAIN RELIEF PM	TABLET	PO	N
acetaminophen/diphenhydramine	PAIN RELIEVER PM	TABLET	PO	N
acetaminophen/diphenhydramine	PM PAIN RELIEF	TABLET	PO	N
acetaminophen/diphenhydramine	TYLENOL PM EXTRA STRENGTH	TABLET	PO	N
acetaminophen/diphenhydramine	UNISOM PM PAIN	TABLET	PO	N
acetaminophen/diphenhydramine	WAL-NADOL PM	TABLET	PO	N
acetaminophen/phenyltoloxamine	RELAGESIC	TABLET	PO	N
aspirin/acetaminophen/diphenhyd	PAIN RELIEF PM	TABLET	PO	N
butalb/acetaminophen/caffeine	BUTALBITAL-ACETAMINOPHEN-CAFFE	CAPSULE	PO	N
butalb/acetaminophen/caffeine	FIORICET	CAPSULE	PO	N
butalb/acetaminophen/caffeine	AMERICET	TABLET	PO	N
butalb/acetaminophen/caffeine	BUTALBITAL/APAP/CAFFEINE	TABLET	PO	N
butalb/acetaminophen/caffeine	BUTALBITAL-ACETAMINOPHEN-CAFFE	TABLET	PO	N
butalb/acetaminophen/caffeine	BUTALBITAL-APAP-CAFFEINE	TABLET	PO	N
butalb/acetaminophen/caffeine	ESGIC	TABLET	PO	N
butalb/acetaminophen/caffeine	ESGIC-PLUS	TABLET	PO	N
butalb/acetaminophen/caffeine	FIORICET	TABLET	PO	N
butalb/acetaminophen/caffeine	QUALA-CET	TABLET	PO	N
butalbital/acetaminophen	BUTALBITAL-ACETAMINOPHEN	CAPSULE	PO	N
butalbital/acetaminophen	ALLZITAL	TABLET	PO	N

butalbital/acetaminophen	BUTALBITAL-ACETAMINOPHEN	TABLET	PO	N
butalbital/acetaminophen	REPAN-CF	TABLET	PO	N
butalbital/acetaminophen	TENCON	TABLET	PO	N
butalbital/aspirin/caffeine	BUTALBITAL-ASPIRIN-CAFFEINE	CAPSULE	PO	N
butalbital/aspirin/caffeine	BUTALBITAL COMPOUND	TABLET	PO	N
butalbital/aspirin/caffeine	FARBITAL	TABLET	PO	N
naproxen sod/diphenhydramine	ALEVE PM	TABLET	PO	N
Acetamin/Calcium Carb/Mag/Caff	XS HANGOVER RELIEF	LIQUID	PO	
acetaminophen/caffeine	EXCEDRIN TENSION HEADACHE	TABLET	PO	
acetaminophen/caffeine	TENSION HEADACHE	TABLET	PO	
acetaminophen/caffeine	TENSION HEADACHE PAIN RELIEVER	TABLET	PO	
acetaminophen/caffeine	TENSION HEADACHE RELIEF	TABLET	PO	
Acetaminophen/Calcium/Caf/Glyc	XS HANGOVER RELIEF	TABLET	PO	
acetaminophen/chlorpheniramine	COLD AND FLU HBP	TABLET	PO	
acetaminophen/chlorpheniramine	CONGESTANT	TABLET	PO	
acetaminophen/chlorpheniramine	CORICIDIN HBP COLD AND FLU	TABLET	PO	
acetaminophen/d-brompheniramin	DOLOGEN	TABLET	PO	
acetaminophen/d-brompheniramin	G-DOLOGEN	TABLET	PO	
acetaminophen/diphenhydramine	ALLERGY SEVERE	TABLET	PO	
acetaminophen/diphenhydramine	PERCOGESIC	TABLET	PO	
acetaminophen/diphenhydramine	PERCOGESIC EXTRA STRENGTH	TABLET	PO	
acetaminophen/diphenhydramine	SEVERE ALLERGY	TABLET	PO	
acetaminophen/diphenhydramine	TYLENOL SEVERE ALLERGY	TABLET	PO	
acetaminophen/diphenhydramine	UNISOM SLEEP AID/PAIN RELIEF	TABLET	PO	
acetaminophen/diphenhydramine	PAIN RELIEVER	TABLET SEQ	PO	
acetaminophen/dp-hydramine	GOODY'S PM	PACKET	PO	
acetaminophen/dp-hydramine	HEADACHE PM	TABLET	PO	
acetaminophen/dp-hydramine	HEADACHE RELIEF PM	TABLET	PO	
acetaminophen/dp-hydramine	MIDOL PM	TABLET	PO	
acetaminophen/pamabrom	MIDOL	TABLET	PO	
acetaminophen/pamabrom	MIDOL TEEN	TABLET	PO	
acetaminophen/pamabrom	WOMEN'S MENSTRUAL RELIEF	TABLET	PO	
acetaminophen/phenyltoloxamine	CONTRAGESIC	TABLET	PO	
acetaminophen/phenyltoloxamine	DOLOCAR	TABLET	PO	
acetaminophen/phenyltoloxamine	MEDI-GESIC	TABLET	PO	
acetaminophen/phenyltoloxamine	PAIN-GESIC	TABLET	PO	
acetaminophen/phenyltoloxamine	PHENYLTOLOXAMINE W/APAP	TABLET	PO	
acetaminophen/pyrilam/pamabrom	MENSTRUAL PAIN RELIEF	TABLET	PO	
acetaminophen/pyrilam/pamabrom	MENSTRUAL RELIEF	TABLET	PO	
acetaminophen/pyrilam/pamabrom	MIDOL PMS	TABLET	PO	

acetaminophen/pyrilam/pamabrom	MULTI-SYMPTOM PMS	TABLET	PO
acetaminophen/pyrilam/pamabrom	PMS MULTI SYMPTOM	TABLET	PO
acetaminophen/pyrilam/pamabrom	PREMSYN PMS	TABLET	PO
acetaminophen/pyrilamine mal	MIDOL	TABLET	PO
acetaminophen/pyrilamine/caff	MENSTRUAL RELIEF	TABLET	PO
acetaminophen/pyrilamine/caff	MIDOL	TABLET	PO
acetaminophen/pyrilamine/caff	MIDOL COMPLETE	TABLET	PO
acetaminophen/pyrilamine/caff	MIDOL MENSTRUAL	TABLET	PO
ASA/acetaminophen/caffeine/cal	SUPAC	TABLET	PO
ASA/dp-hydramine/sod bicarb/ca	ALKA-SELTZER PM	TABLET EFF	PO
ASA/salicylam/acetaminoph/caff	PAIN RELIEF	TABLET	PO
ASA/salicylam/acetaminoph/caff	RUMALON	TABLET	PO
aspirin/acetaminophen	GOODY'S BACK AND BODY PAIN	PACKET	PO
aspirin/acetaminophen/caffeine	BC MAX STRENGTH	POWD PACK	PO
aspirin/acetaminophen/caffeine	GOODY'S EXTRA STRENGTH	POWD PACK	PO
aspirin/acetaminophen/caffeine	ADDED STRENGTH HEADACHE	TABLET	PO
aspirin/acetaminophen/caffeine	ADDED STRENGTH PAIN RELIEF	TABLET	PO
aspirin/acetaminophen/caffeine	ADDED STRENGTH PAIN RELIEVER	TABLET	PO
aspirin/acetaminophen/caffeine	EXCEDRIN EXTRA STRENGTH	TABLET	PO
aspirin/acetaminophen/caffeine	EXCEDRIN MIGRAINE	TABLET	PO
aspirin/acetaminophen/caffeine	EXTRA PAIN RELIEF	TABLET	PO
aspirin/acetaminophen/caffeine	EXTRAPRIN	TABLET	PO
aspirin/acetaminophen/caffeine	GOODY'S MIGRAINE RELIEF	TABLET	PO
aspirin/acetaminophen/caffeine	HEADACHE PAIN	TABLET	PO
aspirin/acetaminophen/caffeine	HEADACHE RELIEF	TABLET	PO
aspirin/acetaminophen/caffeine	MIGRAINE FORMULA	TABLET	PO
aspirin/acetaminophen/caffeine	MIGRAINE RELIEF	TABLET	PO
aspirin/acetaminophen/caffeine	PAIN RELIEVER	TABLET	PO
aspirin/acetaminophen/caffeine	PAIN RELIEVER PLUS	TABLET	PO
aspirin/acetaminophen/caffeine	PAIN-OFF	TABLET	PO
aspirin/acetaminophen/caffeine	VANQUISH	TABLET	PO
aspirin/caffeine	ASPIRIN	POWD PACK	PO
aspirin/caffeine	BC ARTHRITIS	POWD PACK	PO
aspirin/caffeine	BC PAIN RELIEF	POWD PACK	PO
aspirin/caffeine	GOODY'S HANGOVER	POWD PACK	PO
aspirin/caffeine	PAIN RELIEF	POWD PACK	PO
aspirin/caffeine	STANBACK	POWD PACK	PO
aspirin/caffeine	AA & C	TABLET	PO
aspirin/caffeine	ADULT STRENGTH ANALGESIC	TABLET	PO
aspirin/caffeine	ANACIN	TABLET	PO

aspirin/caffeine	ANALGESIC	TABLET	PO
aspirin/caffeine	BACK-BODY PAIN RELIEF	TABLET	PO
aspirin/caffeine	BACK-BODY PAIN RELIEVER	TABLET	PO
aspirin/caffeine	BAYER BACK-BODY	TABLET	PO
aspirin/calcium carb/magnesium	ASPIRIN BUFFERED	TABLET	PO
aspirin/calcium carb/magnesium	ASPIRIN TRI-BUFFERED	TABLET	PO
aspirin/calcium carb/magnesium	BUFFERED ASPIRIN	TABLET	PO
aspirin/calcium carb/magnesium	BUFFERIN	TABLET	PO
aspirin/calcium carb/magnesium	TRI BUFFERED ASPIRIN	TABLET	PO
aspirin/calcium carb/magnesium	TRI-BUFFERED ASPIRIN	TABLET	PO
aspirin/calcium/mag/aluminum	ASCRIPTIN	TABLET	PO
aspirin/calcium/mag/aluminum	ASCRIPTIN MAXIMUM STRENGTH	TABLET	PO
aspirin/calcium/mag/aluminum	ASPERCIN	TABLET	PO
aspirin/calcium/mag/aluminum	ASPRIDROX	TABLET	PO
aspirin/calcium/mag/aluminum	BAYER PLUS	TABLET	PO
aspirin/diphenhydramine citrat	BAYER PM	TABLET	PO
aspirin/diphenhydramine HCl	BAYER PM	TABLET	PO
aspirin/meprobamate	EQUAGESIC	TABLET	PO
aspirin/sod bicarb/citric acid	ALKA-SELTZER	TABLET EFF	PO
aspirin/sod bicarb/citric acid	ALKA-SELTZER ORIGINAL	TABLET EFF	PO
aspirin/sod bicarb/citric acid	ANTACID & PAIN RELIEF	TABLET EFF	PO
aspirin/sod bicarb/citric acid	ANTACID PAIN RELIEVER	TABLET EFF	PO
aspirin/sod bicarb/citric acid	EFFERVESCENT ANTACID-PAIN RLF	TABLET EFF	PO
aspirin/sod bicarb/citric acid	EFFERVESCENT PAIN RELIEF	TABLET EFF	PO
aspirin/sod bicarb/citric acid	MEDI-SELTZER	TABLET EFF	PO
choline salicyl/mag salicylate	CHOLINE MAG TRISALICYLATE	TABLET	PO
choline salicyl/mag salicylate	TRICOSAL	TABLET	PO
choline salicyl/mag salicylate	TRILISATE	TABLET	PO
ergotamine tartrate/caffeine	CAFERGOT	TABLET	PO
ergotamine tartrate/caffeine	ERGOTAMINE-CAFFEINE	TABLET	PO
ibuprofen/diphenhydramine cit	ADVIL PM	TABLET	PO
ibuprofen/diphenhydramine cit	IBUPROFEN PM	TABLET	PO
ibuprofen/diphenhydramine cit	MOTRIN PM	TABLET	PO
ibuprofen/diphenhydramine HCl	ADVIL PM	CAPSULE	PO
ibuprofen/diphenhydramine HCl	IBUPROFEN PM	CAPSULE	PO
isomethept/dichlphn/acetaminop	ISOMETHEPT-DICHLORALP-ACETAMIN	CAPSULE	PO
isomethept/dichlphn/acetaminop	MIGRATINE	CAPSULE	PO
mag salicylat/acetaminoph/caff	BACK PAIN-OFF	TABLET	PO
mag salicylate/phenyltolx	MYOGESIC	TABLET	PO
magnesium salicylate/caffeine	DIUREX	TABLET	PO

sal-amide/acetaminophen/p-tlox	ASP	CAPSULE	PO
sal-amide/acetaminophen/p-tlox	DOLOREX	CAPSULE	PO
sal-amide/acetaminophen/p-tlox	CETAZONE-T	TABLET	PO
sal-amide/acetaminophen/p-tlox	DOLOREX	TABLET	PO
sal-amide/acetaminophn/caffein	RID-A-PAIN COMPOUND	TABLET	PO

## Appendix 2: Medline Search Strategy

### CGRP Inhibitors

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 27, 2024

Search Strategy:

#	Searches	Results
1	erenumab.mp.	629
2	fremanezumab.mp.	412
3	ubrogepant.mp.	167
4	atogepant.mp.	122
5	eptinezumab.mp.	227
6	galcanezumab.mp.	469
7	rimegepant.mp.	212
8	zavegepant.mp.	52
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	1404
10	limit 9 to (english language and humans and yr="2023 -Current")	322
11	limit 10 to (clinical trial, phase iii or clinical trial, phase iv or meta analysis or practice guideline or "systematic review")	56

## Serotonin Agonists

Database(s): **Ovid MEDLINE(R) ALL** 1946 to November 27, 2024

Search Strategy:

#	Searches	Results
1	sumatriptan.mp. or Sumatriptan/	3407
2	zolmitriptan.mp.	708
3	naratriptan.mp.	356
4	almotriptan.mp.	302
5	celecoxib.mp. or Celecoxib/	8482
6	eletriptan.mp.	317
7	frovatriptan.mp.	236
8	lasmiditan.mp.	211
9	rizatriptan.mp.	549
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	13174
11	limit 10 to (english language and humans and yr="2020 -Current")	1094
12	limit 11 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review")	111

## Non-opioid Combination Analgesics, Oral

Database(s): **Ovid MEDLINE(R) ALL** 1946 to February 03, 2025

Search Strategy:

#	Searches	Results
1	acetaminophen.mp. or Acetaminophen/	30042
2	aspirin.mp. or Aspirin/	76851
3	Caffeine/	26192
4	choline salicylate.mp.	75

5	ergotamine.mp. or Ergotamine/	3113
6	ibuprofen.mp. or Ibuprofen/	18793
7	isometheptene.mp.	56
8	magnesium salicylate.mp.	31
9	butalbital.mp.	179
10	naproxen.mp. or Naproxen/	8017
11	migraine.mp. or Migraine Disorders/	49216
12	headache.mp. or Headache/	107927
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	152738
14	11 or 12	134762
15	13 and 14	3831
16	limit 15 to (english language and humans and yr="2014 -Current" and (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or "systematic review"))	75

### Appendix 3: SIGN Guideline Development Group - Forms of Recommendation

Judgment	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain.	Recommendation for research and possibly conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of migraine. Edinburgh: SIGN; 2023. (SIGN publication no. 155). [March 2023]. Available from URL: <http://www.sign.ac.uk>.

### Appendix 4: Key Inclusion Criteria

<b>Population</b>	Children, adolescents and adults with migraine or headache
<b>Intervention</b>	5-HT agonists
<b>Comparator</b>	Active treatment or placebo
<b>Outcomes</b>	Headache freedom at 2 hours, sustained headache freedom, and headache frequency
<b>Timing</b>	Study of any duration
<b>Setting</b>	Outpatient

## Calcitonin Gene-Related Peptide (CGRP) antagonists

### **Goal(s):**

- Promote safe use of CGRP inhibitors in adult patients.
- Promote use that is consistent with medical evidence and product labeling for migraine prevention, acute migraine treatment and cluster headache prevention (Table 1).

### **Length of Authorization:**

- Initial: Up to 3 months
- Renewal: Up to 6 months

### **Requires PA:**

- All calcitonin gene-related peptide (CGRP) antagonist pharmacy and practitioner administered claims

### **Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

**Table 1. FDA Approved Indications for CGRP antagonists**

<b>Drug</b>	<b>FDA Approved Indication</b>
Atogepant	Preventative migraine treatment
Eptinezumab	Preventative migraine treatment
Erenumab	Preventative migraine treatment
Fremanezumab	Preventative migraine treatment
Galcanezumab	Preventative migraine treatment and cluster headache prevention
Rimegepant sulfate	Acute migraine treatment and preventative treatment of episodic migraine
Ubrogapant	Acute migraine treatment
Zavegepant	Acute migraine treatment

## Approval Criteria

1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication (Table 1)?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness
5. Do chart notes indicate headaches are due to medication overuse?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to # 6
6. Is the request for acute (abortive) migraine treatment AND the patient is an adult (18 years or older)?	<b>Yes:</b> Go to #11	<b>No:</b> Go to #7
7. Is the request for the prevention of cluster headache AND the patient is an adult (18 years or older)?	<b>Yes:</b> Go to #14	<b>No:</b> Go to #8
8. Is the request for prophylactic therapy and there is documentation that the patient has experienced 4 or more migraine days in the previous month AND the patient is an adult (18 years or older)?	<b>Yes:</b> Document migraine days per month _____ Go to # 9	<b>No:</b> Pass to RPh. Deny; medical appropriateness

## Approval Criteria

<p>9. Has the patient had an adequate trial (2-6 months) without response, or has contraindications, to at least 3 of the following OHP preferred drugs (in the same or different classes)?</p> <ul style="list-style-type: none"> <li>• Propranolol immediate-release, metoprolol, or atenolol</li> <li>• Topiramate, valproic acid, or divalproex sodium</li> <li>• Amitriptyline, nortriptyline, or venlafaxine</li> <li>• Candesartan or telmisartan</li> </ul> <p>OR</p> <p>Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the above migraine prophylaxis agents?</p>	<p><b>Yes:</b> Document agents used and dates</p> <p>_____</p> <p>_____</p> <p>Go to # 10</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at <a href="http://www.orpdl.org/drugs/">www.orpdl.org/drugs/</a></p>
<p>10. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness</p>	<p><b>No:</b> Approve for up to 3 months</p>
<p>11. In a patient with acute migraines, has the patient failed to receive benefit from adequate trials of abortive therapy (2 or more different triptans) or have contraindications to triptans?</p>	<p><b>Yes:</b> Go to #12</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness. Recommend triptan trial.</p>
<p>12. Does the patient have chronic migraines?</p>	<p><b>Yes:</b> Go to #13</p>	<p><b>No:</b> Approve for 3 months</p>
<p>13. Does the patient have a history of at least 4 migraines a month AND is on preventative migraine therapy (excluding other CGRP inhibitors)?</p>	<p><b>Yes:</b> Approve for up to 3 months</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>

## Approval Criteria

<p>14. Has the patient had an adequate trial (2-6 months) without response, or has contraindications, to at least 2 of the following OHP preferred drugs:</p> <ul style="list-style-type: none"> <li>• Lithium</li> <li>• Verapamil</li> <li>• Suboccipital steroid injection</li> <li>• Sumatriptan subcutaneous</li> <li>• Zolmitriptan nasal spray</li> </ul>	<p><b>Yes:</b> Approve for up to 3 months</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
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## Renewal Criteria

<p>1. Do chart notes indicate headaches are due to medication overuse?</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness.</p>	<p><b>No:</b> Go to #2</p>
<p>2. Is the renewal request for acute migraine treatment?</p>	<p><b>Yes:</b> Go to #5</p>	<p><b>No:</b> Go to #3</p>
<p>3. Is the renewal request for migraine prevention?</p>	<p><b>Yes:</b> Go to #4</p>	<p><b>No:</b> Go to # 6</p>
<p>4. Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?</p>	<p><b>Yes:</b> Document response. Approve for up to 6 months</p>	<p><b>No:</b> Pass to RPh. Deny; medical Appropriateness</p>

5. Has the patient demonstrated a response to therapy as indicated by a reduction in headache frequency and/or intensity?	<b>Yes:</b> Document response Approve for up to 6 months	<b>No:</b> Pass to RPh. Deny; medical Appropriateness
6. Is the renewal request for cluster headache prevention?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical Appropriateness
7. Has the provider documented a positive patient response as indicated by a reduction in the number of cluster headaches per month?	<b>Yes:</b> Document response Approve for up to 6 months	<b>No:</b> Pass to RPh. Deny; medical Appropriateness

P&T/DUR Review: 4/25 (KS), 6/23 (DE); 10/21 (KS), 8/20 (KS); 5/19; 9/18 (DE)  
Implementation: 7/1/23; 1/1/2022; 11/1/2018

## Antimigraine – Serotonin Agonists

### **Goal(s):**

- Decrease potential for medication overuse headache through quantity limits and therapeutic duplication denials.
- Promote PDL options.

### **Length of Authorization:**

- Up to 6 months

### **Requires PA:**

- Non-preferred drugs

### **Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

### **Check the Reason for PA:**

- Non-Preferred drugs will deny on initiation
- Preferred drugs will deny only when maximum dose exceeded

- Both will deny for concurrent therapy (concurrent triptans by different routes is allowed)

**Quantity Limits per Labeling.**

Generic	Brand	Max Daily Dose	Dosage Form	Quantity Limit Per 30 days
Almotriptan	Axert	25 mg	6.25 mg tab 12.5 mg tab	12 tabs
Eletriptan	Relpax	80 mg	20 mg tab 40 mg tab (blister pack 6, 12)	6 tabs
Frovatriptan	Frova	7.5 mg	2.5 mg tab (blister pack 9)	9 tabs
Lasmiditan	Reyvow	200 mg	50 mg tab 100 mg tab	8 tabs
Naratriptan	Amerge	5 mg	1 mg tab 2.5 mg tab (blister pack 9)	9 tabs
Rizatriptan	Maxalt Maxalt MLT Rizafilm	30 mg	5 mg tab 10 mg tab (blister pack 6, 12) 10 mg film	12 tabs
Rizatriptan/ meloxicam	Symbravo	10 mg/ 20 mg	10 mg/ 20 mg tab	9 tabs
Sumatriptan tablets	Imitrex & generics	200 mg	25 mg tab, 50 mg tab, 100 mg tab (blister pack 9)	9 tablets
Sumatriptan nasal spray	Imitrex & generics	40 mg	5 mg, 10 mg (box of 6)	18 spray units
Sumatriptan nasal powder	Onzetra Xsail	44 mg	22 mg (11 mg in each nostril)	6 nosepieces
Sumatriptan injectable	Imitrex & generics	12 mg	6 mg/0.5 mL	6 vials
Sumatriptan injectable	Sumavel	12 mg	6 mg/0.5 mL units (package of 6)	6 jet injectors
Sumatriptan injectable	Zembrace Symtouch	12 mg	3 mg/0.5 mL (package of 4)	12 auto- injectors

Generic	Brand	Max Daily Dose	Dosage Form	Quantity Limit Per 30 days
Sumatriptan /naproxen	Treximet	170/1000 mg (2 tablets)	85/500 mg tab (box of 9)	9 tablets
Zolmitriptan	Zomig, Zomig ZMT & generics	10 mg	2.5 mg tab and ODT 5 mg tab and ODT (blister pack, 3, 6)	6 tabs
Zolmitriptan nasal spray	Zomig NS	10 mg	5 mg (box of 6)	3 packages (18 spray units)

Abbreviations: d = days; MR = may repeat; NS = nasal spray; PO = orally

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of migraine headaches?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
3. Is requested drug a preferred product?	<b>Yes:</b> Go to #5	<b>No:</b> Go to #4
4. Will the prescriber consider a change to a preferred product?  Message: <ul style="list-style-type: none"> <li>Preferred products do not require PA within recommended dose limits.</li> <li>Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy &amp; Therapeutics Committee.</li> </ul>	<b>Yes:</b> Inform prescriber of covered alternatives in class and dose limits.	<b>No:</b> Go to #5

## Approval Criteria

<p>5. Is request for a higher dose than listed in quantity limit chart?</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness.</p> <ul style="list-style-type: none"> <li>• May recommend use of migraine prophylactic therapy and reinforce that doses above those recommended by the manufacturer increase the incidence of medication overuse headache.</li> <li>• One lifetime 90-day taper may be approved at pharmacist's discretion.</li> <li>• Document.</li> </ul>	<p><b>No:</b> Trouble-shoot claim payment (e.g., days' supply?).</p> <p>Go to #6.</p>
<p>6. Is the request for lasmiditan?</p>	<p><b>Yes:</b> Go to #9</p>	<p><b>No:</b> Go to #7</p>
<p>7. Is the request for two different oral triptans concurrently?</p>	<p><b>Yes:</b> Go to #8</p>	<p><b>No:</b> Approve for 6 months</p>
<p>8. Is this a switch in triptan therapy due to intolerance, allergy or ineffectiveness?</p>	<p><b>Yes:</b> Document reason for switch and override for concurrent use for 30 days.</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p>
<p>9. Has the patient tried two triptan products or have a contraindication to triptans?</p>	<p><b>Yes:</b> Approve for 6 months</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness. Recommend triptan trial.</p>

P&T Review: 8/20 (KS), 5/19; 3/16; 3/10; 9/09; 11/03; 5/03  
 Implementation: 9/1/20; 5/1/16, 3/23/10; 1/1/10; 7/1/06; 5/31/05; 6/30/04

## Butalbital Containing Products

### Goal(s):

- Decrease potential for dependence and medication overuse headache through quantity limits.

### Length of Authorization:

- Up to 6 months

### Requires PA:

- All butalbital products

### Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

### Check the Reason for PA:

- All butalbital products are non-preferred

**Table 1. Quantity Limits per Labeling.**

Generic	Max Daily Dose	Quantity Limit Per 30 days
Butalbital containing formulations	6 capsules or tablets	30 capsules or tablets

<b>Approval Criteria</b>		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of migraine headaches?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #3
3. Does the patient have medication overuse headache?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #4
4. Does the patients have a diagnosis of tension headache?	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

## Approval Criteria

<p>5. Has the patient had an adequate trial, without response, or has contraindications, to at least 2 of the following OHP preferred drugs for tension headache:</p> <ul style="list-style-type: none"><li>• Ibuprofen</li><li>• Acetaminophen</li><li>• Amitriptyline</li></ul>	<p><b>Yes:</b> Approve for up to 6 months. Quantities to not exceed limits provided in Table 1 above.</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness.</p>
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*P&T Review:* 04/25 (KS)  
*Implementation:* TBD