Acute Treatment for Migraine

Executive Summary: Acute treatment for migraines should be individualized to each patient and consider the individual characteristics of the patient's migraines. Use of OTC agents and prescription NSAIDs should be recommended for less severe migraines. Adverse effects often limit the use of select agents, mainly cardiovascular effects that preclude use of triptans and ergotamines. Caution should be used to avoid risk of medication overuse headache.

All patients with a migraine should be offered a trial of acute treatment. The individual characteristics of migraine headaches should be taken into consideration, such as intensity, presence of nausea/vomiting, onset of pain, and duration of pain, when developing treatment plans for your individual patient.

Mild-moderate migraine	Moderate-severe migraine, or mild-moderate that responded poorly to initial treatment
· Non-opioid analgesics · NSAIDs · Caffeinated analgesic combinations	· Triptans · Ergotamine derivatives · Antiemetics · Serotonin 5-HT1f agonist (lasmiditan) · CGRP receptor blockers (discussed in detail in an upcoming article)

Pearls for selecting abortive therapy

1. Choose a non-oral route of administration for severe nausea or vomiting
2. Account for tolerability and safety issues
    a. NSAID risk for gastrointestinal and cardiovascular side effects
    b. Triptans and DHE should be avoided or used with caution in patients with CAD, PVD, uncontrolled hypertension, and stroke
    c. Lasmiditan may cause fatigue, lethargy, and somnolence, patients should not drive or operate machinery for 8 hours after a dose
3. Take into consideration the tempo of headache pain escalation
    a. For migraine headaches that escalate in intensity very rapidly, or that are fully developed upon awakening:
        i. Subcutaneous sumatriptan is the most effective
        ii. Other medications to consider include rizatriptan, eletriptan, nasal sumatriptan, or nasal zolmitriptan
    b. For less severe attacks that build up more slowly but have a relatively long duration:
        i. Choose longer acting options such as naproxen and/or frovatriptan
4. Consider self-administered rescue
    a. Patients may require rescue medication when first-line acute treatment does not bring relief
    b. Choice of rescue agent depends on initial treatment, options include:
        i. SubQ sumatriptan
        ii. DHE injection or intranasal spray
        iii. Dexamethasone

iv. IM ketorolac

c. Consider prescribing in patients with severe attacks and those with a history of nonresponse/variable response to acute treatment

5. Combination therapy
   a. Using agents together is often more efficacious than using them as monotherapy
   b. Triptans, NSAIDs, and antiemetics are commonly used as part of combination therapy
   c. Antiemetics can improve absorption, and therefore improve effectiveness of triptans and NSAIDs
   d. Triptans and lasmiditan have similar mechanisms of action and should avoid combination use together until more information is available
   e. Triptans and ergotamines should not be used within 24 hours of each other due to additive vasoconstrictive effects
6. Avoid medication overuse
   a. Limit acute treatment to an average of 2 headache days per week
      i. Offer preventive treatment to those exceeding this limit
      ii. Patients who exceed this limit despite use of preventive treatment may require:
         1. Escalation in dose
         2. Change in preventive therapy, or
         3. Addition of another preventive treatment
7. Opioids and barbiturates
   a. Although can be effective for acute treatment of migraines, use of opioids and barbiturates (e.g., butalbital) are not recommended as first line or for long-term use as they are habit forming and contribute to medication overuse headache and chronic migraine
   b. Opioids can be considered as a last resort in patients who have contraindications to or fail migraine-specific treatments
      i. Limit to 9 days per month or less to avoid medication overuse headache
      ii. Continue to focus on preventive and behavioral aspects of migraine care

Drug class	Drug names	Pearls
Non-opioid analgesics	· Aspirin · Acetaminophen · Aspirin/acetaminophen/caffeine	· Effervescent aspirin has a faster onset than oral tablets
NSAIDs	· Diclofenac · Ibuprofen · Naproxen · Ketorolac nasal spray	· Diclofenac powder for oral solution and ketorolac nasal spray have a faster onset of action than oral tablets (both significantly more expensive than tablet/capsule)
Triptans	· Almotriptan · Naratriptan · Frovatriptan · Sumatriptan – tablets, nasal spray, nasal powder, and SubQ injection · Sumatriptan/naproxen · Rizatriptan · Eletriptan	· Differ by onset of action, duration of action, route of administration, and cost · Failure with one triptan does not predict failure with another · Strong vasoconstricting effects caused by activation of serotonin receptor 1B

	·Zolmitriptan – tablets, nasal spray	
Ergotamine derivatives	· Ergotamine sublingual · Caffeine/ergotamine · Dihydroergotamine IM, SC, nasal spray	·Significant nausea and vomiting limit use – use antiemetics ·Strong vasoconstricting effects result in cardiovascular adverse effects
Antiemetics	· Metoclopramide · Prochlorperazine · Promethazine	·Take at onset of migraine ·Efficacy in treating acute migraine even in the absence of nausea and vomiting ·Serotonin antagonist antiemetics (e.g., ondansetron) are not effective for migraine headache pain
Serotonin 5-HT1F receptor agonist	·Lasmiditan (Reyvow)	·No vasoconstricting serotonin effects as seen with triptans ·Schedule V controlled substance ·Can be used in patients at high cardiovascular risk ·Avoid in severe hepatic impairment

References:

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Migraine Prevention

Executive Summary: Migraine prophylactic treatment should be considered in patients who are experiencing or at risk for medication overuse headaches, experiencing multiple migraines or migraine days per month, have difficulty tolerating acute therapy or have certain migraine subtypes. A combination of lifestyle management and pharmacotherapy should be employed to reduce migraine frequency. Remember to titrate prophylactic agents every 2-4 weeks and consider a combination of agents or a second line agent if initial therapy is not efficacious.

Migraines can be triggered by a variety of things and are specific to individual patients. Identification of an individual's triggers can be aided by things like suggesting the use of a headache diary. Once triggers are identified, symptoms may be managed by avoidance of triggers or treatment of underlying conditions.

Common migraine triggers					
Additives	Alcohol	Artificial sweeteners	Caffeine (overconsumption or withdrawals)	Missed or delayed meals	Exercise
Foods	Light	Menses	Odors	Oral contraceptives	Red wine
Sleep disturbances	Smoke	Stress	Weather changes		

Considerations for starting prophylactic treatment:

- four or more headaches a month or at least eight headache days a month
- debilitating attacks despite appropriate acute management
- difficulty tolerating or having a contraindication to acute therapy
- medication-overuse headache
- patient preference
- presence of certain migraine subtypes (i.e., hemiplegic migraine; migraine with brainstem aura; migrainous infarction; or frequent, persistent, or uncomfortable aura symptoms)

There are a variety of medications that have varying levels of evidence for efficacy. Included on the table below are medications with the best evidence of efficacy. Not included are Calcitonin Gene-Related Peptide (CGRP) agents that can be used for migraine prevention, which will be discussed in an upcoming article.

Recommended Medications for Episodic Migraine Prevention		
First-Line Agents	**Initial dose**	**Maximum dose**
Divalproex/Valproic acid	500mg PO daily	1000mg/day
Metoprolol tartrate	25mg PO BID	200mg/day
Propranolol	40-80mg/day PO	160mg/day
Timolol	10mg PO BID	30mg/day
Topiramate	25mg PO daily	100mg/day
Frovatriptan*	2.5mg PO daily	2.5mg PO BID
Second-Line Agents	**Initial dose**	**Maximum dose**
Amitriptyline	10-25mg/day PO	150mg/day
Atenolol	25mg PO daily	100mg daily
Nadolol	20mg PO daily	240mg/day
Venlafaxine ER	37.5mg PO daily	75-150mg/day
Naratriptan*	1mg PO BID	
Zolmitriptan*	2.5mg PO BID	2.5mg TID

*Efficacious for short-term prevention of menstrual associated migraine. Dosed starting 2 days prior to onset of menses and continued through to 5 days after the onset of menses (7 days total).

In 2012 the American Academy of Neurology and the American Headache Society provided an update to the 2000 guidelines for migraine prevention. The original guideline concluded that calcium channel blockers were probably effective, but were later found to have conflicting evidence on the basis of the current classification criteria and thus the recommendation was downgraded to a Level U (evidence is conflicting or inadequate to support or refute the use for migraine prevention).

Additionally, onabotulinumtoxinA (Botox) has FDA approval for prophylaxis of chronic migraine (15 or more headache days per month). Clinical trials showed clinically significant reduction in frequency of headache days compared to placebo relative to baseline. Study results have been mixed in prevention of episodic migraine (14 or less headache days per month) and does not have FDA approval for this indication.

Medications should be initiated at the lowest dose and be titrated every 2 to 4 weeks until effective. Maximal efficacy may take up to 6 months. A different medication can be considered after 2 months if it is not efficacious, or side effects are not well tolerated. A different first line agent should be trialed or a combination of first line agents. If continued treatment failure, a second line agent should be considered.

Although there is data to support use of pharmacological treatment for migraine prevention, there is not enough data to establish how to choose optimal therapy or to support the use of one first line option over another. **Regimens should be prescribed on a case to case basis taking into account efficacy, adverse effects, comorbidities and personal considerations. Trial and error is often required.**

Special populations:

Children: There are currently no approved medications with proven efficacy for migraine prevention in children. Topiramate and propranolol have shown conflicting results in studies and other commonly

prescribed medications such as cyproheptadine, amitriptyline, and valproic acid lack sufficient data in children.

Pregnancy: Nonpharmacological treatment options should be explored prior to initiating drug therapy. Preventive medications may have teratogenic effects. If treatment is absolutely necessary, select a treatment with the lowest risk of adverse effects to the fetus.

Resources:

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Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonist Overview

Executive Summary: CGRP is a naturally occurring neuropeptide associated with migraines. CGRP antagonists are a newer class of medications that may be used for preventative or abortive therapy in migraine patients. CGRP-related therapies have proven efficacy, safety, and tolerability for episodic and chronic migraine prevention and treatment in phase II and phase III randomized, placebo-controlled clinical trials. Benefits of CGRP-related therapies include minimal adverse effects, no vasoconstriction, easy dosing, and rapid efficacy, however this should be weighed against the cost (addressed separately) and lack of head-to-head efficacy data on other treatment modalities.

Calcitonin Gene-Related Peptide (CGRP) occurs naturally in the central and peripheral nervous system and acts as a potent vasodilator. Levels increase during a migraine and is believed to be directly involved in pathophysiologic processes underlying migraines. CGRP causes a cascade of events contributing to neurogenic inflammation, including mast-cell degranulation, vasodilation and protein extravasation when bound to its receptor. CGRP antagonists block the release of CGRP at all migraine pathway locations and prevent vasodilation and neurogenic inflammation.[1] In this way, they act as a migraine preventative.

Large molecule monoclonal antibodies acting as CGRP ligand antagonists, such as fremanezumab (Ajovy), galcanezumab (Emgality), and eptinezumab (Vyepti), bind to CGRP ligands and block its ability to bind to its receptor. Erenumab (Aimovig), a CGRP receptor antagonist monoclonal antibody, binds to the receptor site and antagonizes the receptor's function. These large molecule agents effectively prevent migraine headaches.[2] There is no evidence that supports one mechanism of action is superior to another (ligand antagonists vs receptor antagonist). Rimegepant (Nurtec) and ubrogepant (Ubrelvy) are small molecule CGRP receptor antagonists which provide acute relief of migraine.

Efficacy Summary:

- Migraine prophylaxis: Prophylactic agents significantly reduced the number of migraine days per month compared to placebo (1-3.5 migraine days per month reduction vs placebo), and significantly increased the number of patients experiencing a 50% reduction in monthly migraine days compared to placebo (10-25% more patients vs placebo).
- Acute migraine treatment: Agents with the indication for acute treatment have demonstrated significant improvement in the proportion of patients pain-free at 2 hours, with 7.5-10% more patients' pain free compared to placebo. There was also significant improvement in more bothersome symptom freedom at 2 hours, with around 10% more patients experiencing symptom freedom when compared to placebo.

Clinical Pearls:

- Target the trigeminal pain system; therefore, this class of medication is more specific and causes far fewer adverse effects than traditional migraine preventative agents.[3]
- Do not constrict blood vessels, unlike other first-line therapies for migraine, so these agents may be useful in patients with cardiovascular contraindications[3]
- The agents approved for prophylactic use (excluding rimegepant) lack hepatic and renal metabolism and clearance, so there are no drug interactions with concomitant medications[3]

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- Prophylactic agents do not require dose titrations, demonstrate rapid effects in treatment, and are effective in patients who have failed prior preventive treatment.[3]
- There is theoretical concern for cardiac side effects because they antagonize CGRP, which is a vasodilator. Studies to date have not shown cardiovascular effects; however, most have excluded patients with significant cardiovascular risk factors.[4,5]
- CGRP antagonists can be combined with non-CGRP oral agents.[4,5]
- Data is lacking regarding combined use of CGRP antagonists for both prophylaxis and acute treatment.[4,5]
- Data is lacking on the comparative efficacy between CGRP antagonists and other prophylactic therapies; however, as concluded from a systematic review and meta-analysis, triptan drugs were shown to be significantly more efficacious compared with CGRP antagonists, such as rimegepant, in the treatment of migraine headaches with or without aura in adult patients for pain freedom 2 hours after dosing and pain relief.[6]
- Subcutaneous injections: Hypersensitivity reactions may occur. Counsel patients regarding signs of anaphylaxis and angioedema and what to do if they experience these reactions.
- Fetal harm was observed in animal studies with Nurtec, Ubrelvy, and Reyvow. Little data is available for Aimovig, Ajovy, Emgality or Vyepti. It is not known if any CGRP antagonist agents are present in breastmilk.

Drug	Place in Therapy	Pearls for Use
Erenumab (Aimovig)	Migraine prophylaxis	• Do not use if latex allergy • Monitor for new or worsening HTN • Severe constipation may occur • Patient may self-administer subQ injection
Fremanezumab (Ajovy)	Migraine prophylaxis	• Patient may self-administer subQ injection
Galcanezumab (Emgality)	Migraine prophylaxis Episodic cluster headache	• Patient may self-administer subQ injection
Eptinezumab (Vyepti)	Migraine prophylaxis	• Common side effects include nasopharyngitis • Administer via IV infusion only
Rimegepant (Nurtec (ODT))	Migraine prophylaxis Acute migraine treatment with or without aura	• Common side effects include abdominal pain, indigestion, and nausea • Open blister pack with dry hands. Do not push the tablet through the foil. • Let dissolve completely on/under tongue (should dissolve within a few seconds) • Avoid use in ESRD • Avoid use in severe hepatic impairment • Drug interactions with CYP3A4 inhibitors, avoid strong inhibitors
Ubrogepant (Ubrelvy)	Acute migraine treatment with or without aura	• Common side effects include nausea, sedation and dry mouth • A second dose may be taken at least 2 hours after initial dose if needed • Oral administration • Avoid grapefruit juice • Contraindicated with strong CYP3A4 inhibitors

Cluster Headache: often misdiagnosed as migraine; most common of the primary headache disorders ("trigeminal autonomic cephalalgias"); attacks occur in cyclical patterns, or clusters[2]

Resources:

AMG Guideline – CGRP Antagonist Medications for Episodic & Chronic Migraines

References:

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CGRP Use: Cost and Avera Health Plans Utilization Management

Executive Summary: Oral and injectable Calcitonin Gene-Related Peptide Receptor (CGRP) antagonists and inhibitors are safe and effective agents for treating and preventing migraines. However, these agents come at a substantial cost relative to alternative drug classes without providing clear additive benefits. In addition, no phase 3/4 clinical trials exist that demonstrate the efficacy of combined preventive and abortive CGRPs. As a result, several utilization management strategies have been put in place by third-party payers including step-therapy, prior authorization, quantity limits, and network restriction.

Abortive Migraine Agents

Drug [generic] (Drug Class)	Quantity Limit (30 days)	Approximate Cost (30 days)
Ubrelvy [ubrogepant] (CGRP antagonist)	12 tablets	$1,200
Nurtec ODT [rimegepant] (CGRP antagonist)	8 tablets	$1,000
Reyvow [lasmiditan] (serotonin 5-HT1F antagonist)	8 tablets	$800
Sumatriptan 25mg, 50mg (triptan)	18 tablets	$4
Sumatriptan 100mg (triptan)	9 tablets	$7
Naratriptan(triptan)	18 tablets	$29
Zolmitriptan 2.5mg (triptan)	12 tablets	$90
Zolmitriptan 5mg (triptan)	6 tablets	$45
Rizatriptan 5mg (triptan)	24 tablets	$14
Rizatriptan 10mg (triptan)	12 tablets	$29
Frovatriptan (triptan)	18 tablets	$1,000
Eletriptan 20mg (triptan)	12 tablets	$250
Eletriptan 40mg (triptan)	6 tablets	$100
Fioricet [butalbital, acetaminophen, and caffeine] (barbiturate, non-opioid analgesic)	180 tablets	$26

Preventive Migraine Agents

Drug [generic] (Drug Class)	Approximate Cost (30 days)	Comments
Ajovy [fremanezumab] (CGRP antagonist)	$750	
Aimovig [erenumab] (CGRP antagonist)	$750	
Emgality [galcanezumab] (CGRP antagonist)	$750	
Vyepti [eptinezumab] (CGRP antagonist)	$600	Medical benefit drug. Given via IV infusion (cost does not reflect costs associated with infusion).
Nurtec ODT [rimegepant] (CGRP antagonist)	$2,400 (quantity limit 18 tablets/30 days)	Approved for episodic migraine only (≤ 14 migraines/month)

Propranolol ER (beta-blocker)	$60	
Amitriptyline (tricyclic antidepressant)	$7	
Valproate ER (anticonvulsant)	$25	
Topiramate (anticonvulsant)	$2	

Combination of Abortive and Preventive CGRP Inhibitors

A phase 1b clinical trial, a two patient case study, and a currently unpublished abstract presented at the 2021 American Headache Society Annual Scientific Meeting have evaluated the use of combination injectable/oral CGRPs.[1-3] These studies have shown that combination use is safe with no increase in adverse effects and no significant pharmacokinetic drug interactions. However, no randomized prospective data is available to evaluate the efficacy of combined oral/injectable CGRP use at this time.

Avera Health Plans Prior Authorization Criteria

CGRPs for Migraine Prevention (Aimovig, Ajovy, Emgality, Vyepti, Nurtec, and Ubrelvy)

1. Patient must be 18 years of age or older
2. First cluster episode occurred 6 months or greater ago
3. Patient has greater than or equal to 4 but less than or equal to 14 headache days per month for episodic prophylaxis
4. Patient has 15 or more headaches lasting 4 hours or more in a 28-day period (50% or more of these headaches must be migraine/probably migraine in nature) for chronic prophylaxis
5. Patient has documented treatment failure, intolerance, or contraindication to a minimum of two triptan therapies
6. Patient must have a treatment failure, intolerance, or contraindication to two migraine prophylactic medication classes:
    a. Antidepressants
    b. Anti-epileptic agents
    c. Beta-blockers/calcium channel blockers
7. No medication in this class can be used concurrently with another medication in this class
8. Patient is not on concurrent Botox therapy for migraine prevention
9. Patient will need to try and fail self-injectable CGRP prior to IV CGRP

Additional Utilization Management Criteria

All CGRPs with the exception of Vyepti (medical benefit drug given by IV infusion) are considered specialty drugs restricted to dispensation by the Avera Health Plan Specialty Pharmacy Network. No more than a 30 day supply of medication may be dispensed at any time (with the exception of every 3 month dosing regimens).

Botox

Approved only for prevention of chronic migraine. Can be used in combination with an abortive CGRP. Avera Health Plan prior authorization criteria is similar to that of the CGRP criteria.

References

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