Migraine Pharmacotherapy

Primarily based on the 2021 American Headache Society (AHS) Consensus Statement: Update on integrating new migraine treatments into clinical practice and 2024 AHS position statement update on CGRP-targeting therapies for the prevention of migraine. *See the full review on Pyrls for the recommendations from the American College of Physicians (ACP).*

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Acute Treatment

Acute Treatment Goals

- Achieve fast relief and freedom from symptoms
- Achieve functional recovery
- Minimize need for additional doses or medications
- Optimize self-care and reduce need for resources
- Minimize adverse events
- Maintain cost-effective management

Important Considerations

- Start treatment ASAP after onset of headache
- Individualized **lifestyle modifications** are important
- Acute treatment should be offered to **all patients** with confirmed migraine diagnosis
- Use acute treatment medications at the onset of attack, **at the first sign of pain**

Acute Treatment Options

Migraine-specific Agents

Established efficacy	Probably effective
• Triptans (e.g., sumatriptan, rizatriptan, zolmitriptan) • Combination triptan/NSAID or triptan/acetaminophen • Ergotamine derivatives (e.g., dihydroergotamine) • Small molecule CGRP receptor antagonists ("gepants"; e.g., rimegepant, ubrogepant, zavegepant) • Selective serotonin receptor agonist (e.g., lasmiditan)	• Ergotamine • Other forms of dihydroergotamine

Non-specific Agents

Established efficacy	Probably effective
• NSAIDs (aspirin, diclofenac, ibuprofen, naproxen, celecoxib oral solution) • Acetaminophen • Combination acetaminophen/aspirin/caffeine • Butorphanol nasal spray	• NSAIDs (flurbiprofen, ketoprofen, IV or IM ketorolac) • IV magnesium (in migraine with aura) • Isometheptene-containing compounds • Antiemetics (chlorpromazine, droperidol, metoclopramide, prochlorperazine, promethazine)

Acute Treatment Recommendations

Mild to moderate attacks
Non-specific agents recommended

Moderate to severe attacks
Migraine-specific agents recommended

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Inadequate response to non-specific agents → **Triptan***

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Inadequate response to initial treatment → **Second triptan**

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Criteria for initiating small molecule CGRP receptor antagonists, lasmiditan, or neuromodulatory devices

- Prescribed/recommended by a licensed clinician for an adult patient (certain neuromodulatory devices can be used in younger patients)
- ICHD-3 diagnosis of migraine (with aura, without aura, or chronic)
- Either of the following regarding triptans:
  (1) Triptans are either contraindicated or not tolerated
  (2) Inadequate response to at least **two** oral triptans (per clinician's attestation or patient-reported outcome questionnaire)

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Small molecule CGRP receptor antagonists, lasmiditan, or neuromodulatory devices

**Triptans are generally considered the first-line migraine-specific options; nonoral options, such as dihydroergotamine, may be considered when traditional oral options are inappropriate (e.g., for patients with severe nausea/vomiting)*

Preventive Treatment

Preventive Treatment Goals

- Reduce attack frequency, severity, and duration
- Reduce disability associated with migraine attacks
- Improve treatment response, prevent escalation
- Improve function
- Reduce need for intolerable, ineffective, unwanted acute treatment
- Reduce overall cost of migraine treatment
- Provide sense of control; allow self-management
- Improve health-related quality of life
- Reduce psychological burdens of migraine

When to Consider Preventive Treatment

Consider preventive treatment in **any** of these situations

- Significant interference in daily life from migraine attacks despite acute treatment
- Frequent attacks (see *Definitions* below)
- Contraindication to acute treatments or failure of acute treatments
- Adverse effects associated with acute treatment
- Overuse of acute treatments (see *Definitions* below)
- Patient preference
- Certain uncommon migraine types (e.g., hemiplegic or prolonged aura)
- History of migrainous infarction (regardless of attack frequency)

Prevention Recommendations

Current AHS recommendations for migraine prevention are addressed for the following conditions:

- **Episodic migraine** with or without aura (**4 to 14 monthly migraine days**) based on ICHD-3 with at least moderate disability (MIDAS ≥11 or HIT-6 >50)
- **Chronic migraine** with or without aura (**≥15 monthly headache days**) based on ICHD-3

Per AHS, preventive options for either episodic or chronic migraine are summarized below:

- Topiramate
- Divalproex/valproate sodium
- Beta-blocker (metoprolol, propranolol, timolol, atenolol, nadolol)
- Candesartan
- TCA (amitriptyline, nortriptyline)
- SNRI (venlafaxine, duloxetine)
- CGRP mAbs (e.g., eptinezumab, erenumab, fremanezumab, galcanezumab)
- CGRP receptor antagonist (e.g., atogepant, rimegepant*)
- Other preventive treatments^ that have established efficacy or are probably effective (see the *Preventive Treatment Options* table)

Rimegepant is an option specifically for* **episodic *migraine*
^OnabotulinumtoxinA is an option specifically for ***chronic*** *migraine*

Preventive Treatment Options

Oral Agents

Established efficacy	Probably effective
• Candesartan • Antiseizure medications (divalproex sodium, valproate sodium, topiramate) • Beta-blockers (metoprolol, propranolol, timolol) • CGRP receptor antagonists (rimegepant [for episodic migraine], atogepant) • Frovatriptan (for short-term prevention of menstrual-related migraine)	• Lisinopril • Antidepressants (amitriptyline, venlafaxine) • Beta-blockers (atenolol, nadolol) • Memantine

Parenteral Agents

Established efficacy	Probably effective
• CGRP mAbs (eptinezumab, erenumab, fremanezumab, galcanezumab) • OnabotulinumtoxinA (for chronic migraine)	• OnabotulinumtoxinA + CGRP mAb (for chronic migraine)

Definitions

Frequent attacks (for prevention criteria)

Offer preventive treatment if:
- ≥6 MHD, even if they cause no disability
- ≥4 MHD, if they cause some disability
- ≥3 MHD, if they cause severe disability

Consider preventive treatment if:
- 4 or 5 MHD with no disability
- 3 MHD with some disability
- 2 MHD with severe disability

Overuse (for prevention criteria)

- ≥10 days/month for ergot derivatives, triptans, opioids, combination analgesics, and a combination of drugs from different classes that are not individually overused
- ≥15 days/month for nonopioid analgesics, acetaminophen, and NSAIDs

Adequate trials

- Oral agents: at least **8 weeks** at target dose
  - Patients with partial response may experience additional benefit over 6-12 months
- Parenteral CGRP mAbs:
  - At least **3 months** (if administered monthly)
  - At least **6 months** (if administered quarterly)

CGRP: calcitonin gene-related peptide **HIT-6:** Headache Impact Test-6 **ICHD-3** International Classification of Headache Disorders, 3rd edition **mAb:** monoclonal antibody **MHD:** monthly headache days **MIDAS:** Migraine Disability Assessment **MMD:** monthly migraine days **NSAID:** nonsteroidal anti-inflammatory drug **SNRI:** serotonin and norepinephrine reuptake inhibitor **TCA:** tricyclic antidepressant

References available at pyrls.com

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