ACCOUNTABLE HEALTH PARTNERS

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Best Practice Guidance for Reduction of Outpatient Migraine in Adults

Identify Migraine

- Timely diagnosis is crucial to allow initiation of pharmacotherapy as soon as possible
- ID Migraine™ is a 3 question screener that can be used in primary care to identify migraine
  - Positive response to 2 of the 3 questions indicates probable migraine with 81% sensitivity, 75% specificity, and a high positive predictive value of 93% in a primary care setting[2]
  - During the past 3 months, ≥ 2 **"yes"** answers = **probable migraines**
    - Over the last 3 months, have you limited your activity on at least 1 day because of your headaches?
    - Do lights bother you when you have a headache?
    - Do you get sick to your stomach or nauseated with your headache?
- Imaging (CT, MRI) may lead to unnecessary tests and treatment and is not needed if the patient's physical and neurological exam are normal and history is consistent with the diagnosis of migraine

Identify and Resolve Medication Overuse Headache

- It is vital to identify medication overuse headache (MOH), defined as a secondary disorder in which excessive use of acute medications causes chronic daily headache in a headache-prone patient[3]
  - Clinical diagnosis is based on 15 or more headache days per month, history of regular overuse of acute medication on more than 2-3 days per week and exclusion of other disorders causing secondary headache
  - Medication associated risk: opioids, butalbital-containing combinations or aspirin/acetaminophen/caffeine combinations > triptans > acetaminophen, aspirin, NSAIDs
  - It is important to resolve MOH prior to initiating other migraine therapies as it can render headaches refractory to treatment and reduces the efficacy of abortive therapies
  - Discontinuation of the overused medication is considered the treatment of choice (*Note:* for some agents tapering may be necessary)

Implement/Optimize Nonpharmacological Interventions

- **Caffeine:** limit intake to < 8 oz. of caffeinated beverages before noon
- **Sleep hygiene:** maintain a regular sleep schedule of at least 7 hours of sleep per night and avoidance of screen time for at least 1 hour before bed
- **Diet:** monitor and avoid foods that patient identifies as triggers, avoid fasting for more than 6 hours while awake, and eat clean by avoiding processed foods and foods high in sugar/carbohydrates, maximize intake of fresh fruits and vegetables (can reference the Healthy Eating Plate diagram published by the Harvard School of Public Health, available at: https://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/)
- **Hydration:** at least 48 oz. of non-caffeinated beverages daily, avoid soda – including sugar free
- **Exercise:** at least 20 minutes of elevated heart rate per day on 4 days per week

Acute (Abortive) Migraine Treatment[4]

- **Optimizing acute treatment effects:**
  - Treat at least 2-3 attacks before judging the effectiveness of the therapeutic choice
  - Treatment appears to be more effective when initiated early on in the course of an acute attack
  - Antiemetics (both oral and rectal options) are recommended in conjunction with abortive migraine agents, if patient has concurrent headache and nausea/vomiting given headache is not likely to improve if nausea is not treated.[5] Choices listed below show the most efficacy in clinical trials.
  - Involve patients in their treatment plan by discussing treatment options and rationale for therapy selection, and educate patients regarding expected adverse events (refer patients to American Migraine Foundation website for more information)
- **Acute treatment agent selection:**
  - There are no data to support the efficacy or safety of one triptan over another. Triptan selection should be based on cost, onset, and duration of action, along with patient-specific response and side effects.

- Risk of serotonin syndrome in patients taking both triptans and SSRIs (in the absence of other risk factors) is extremely low, giving further evidence that it is unnecessary to avoid co-prescribing[6]
- Approximately 30% of patients prescribed a triptan have an insufficient response.[7] Limited studies have demonstrated improved outcomes when switching to a second drug in the triptan class, therefore patients may benefit from different therapy options.[8] Other options include the use of a gepant (small molecule calcitonin-gene related peptide (CGRP) antagonists), or a ditan (selective serotonin 1F receptor agonist).
- Opioids are not recommended (including hydrocodone, oxycodone, hydromorphone, codeine, tramadol), as they are less effective, carry a high risk of MOH, and decrease responsiveness to other medications[9,10]
- Butalbital-containing agents should be avoided as they are less effective and carry a high risk of MOH[10]
- Caffeine-containing abortive therapies should be avoided as they carry a high risk of MOH[11]
- To avoid MOH, acute therapy should generally be limited to no more than 2-3 days per week

Acute Treatment Agents for Migraine: General Population					
Therapeutic agent, strength and dosage form *(doses listed assume normal renal/hepatic function)*	**Migraine with[C] or without aura (no comorbidities)**	**Menstrual Migraines**	**Migraine (Triptans not Tolerated)**	**Previous CV or CeV Disease[A]**	**Cost[±]**
NSAIDs – generally consider first line (shorter-acting agents have higher risk of causing rebound headache)					
Aspirin 650 mg Q4 hours Naproxen 500-550 mg BID Ibuprofen 600mg Q4h or 800 mg Q6h Diclofenac ER 50 mg BID or 100 mg daily	A	A	A	C	$5 $25 $33 $50
Ketorolac 30-60 mg IM	C	C	B	B	$54
Triptans – generally consider first line					
Sumatriptan (Imitrex®) 50-100 mg tablets *Onset: 20-30 mins Duration: Short*	A	B	D	D	$132
Zolmitriptan (Zomig®) 5 mg tablets *Onset: 45 mins Duration: Short*	A	A	D	D	$268
Rizatriptan (Maxalt®) 10 mg tablets (Maximum 5 mg if co-prescribed propranolol) *Onset: 0.5-2 hrs Duration: Short*	A	B	D	D	$176
Naratriptan (Amerge®) 2.5 mg tablets *Onset: 1-3 hrs Duration: Long*	A	A	D	D	$123
Eletriptan (Relpax®) 40 mg tablets *Onset: 30 mins Duration: Short*	B	C	D	D	$292
Almotriptan (Axert®) 12.5 mg tablets* *Onset: 0.5-2 hrs Duration: Short*	B	C	D	D	$450
Zolmitriptan (Zomig®) nasal spray *Onset: 15 mins Duration: Short*	B	C	D	D	$669
Sumatriptan (Imitrex®) nasal spray *Onset: 20-30 minutes Duration: Short*	C	B	D	D	$488
Frovatriptan (Frova®) 2.5 mg tablets *Onset: 2-3 hrs Duration: Longest*	C	B	D	D	$588
Sumatriptan/Naproxen (Tremixet®) tablets	C	C	D	D	$705
Branded Triptans	C	C	D	D	Varies
Dopamine Antagonists (Antiemetics[D]) – adjunct therapy for nausea and vomiting					
Metoclopramide[E] 5-10 mg tablets Q8h Prochlorperazine[F] 10 mg tab Q8h (or 25 mg suppository x1 prn, up to 2 times per day)	A	B	A	A	$28 $19/138
Small Molecule CGRP Antagonists – consider if insufficient response or contraindication to Triptans					
Ubrogepant (Ubrelvy™)[G] 50-100 mg tablets	C	C	B	B	$1,113
Rimegepant (Nurtec® ODT)[H] 75 mg tablets	C	C	B	B	$1,094
Selective Serotonin 1F Receptor Agonist (Ditans) – consider if insufficient response or contraindication to Triptans					
Lasmiditan (Reyvow™)[I] 50-100 mg tablets	C	C	B	B	$834
Ergot Alkaloids – reserve for refractory migraines due to adverse events and cost					
Dihydroergotamine (Trudhesa™) nasal spray	C	C	C	D	$2767

[A]CV: cardiovascular, CeV: cerebrovascular; cardiovascular disease includes unstable angina, previous MI, bypass surgery, plasty; or cerebrovascular disease includes TIA, stroke, not subarachnoid hemorrhage or ABM; [C] If aura is present, avoid estrogen-containing products; [D]Ondansetron is commonly used for nausea, but evidence is lacking; [E]Limit use to no more than 4 days per week; Efficacy supported by RCTs in combination with ASA or sumatriptan, daily use is not recommended due to the risk of extrapyramidal side effects; [F]Associated with risk of QTc prolongation and torsades de pointes; [G]Maximum 200 mg dose per day, many drug interactions; [H]Maximum dose 75 mg dose per day, many drug interactions; [I]Classified as a Schedule-V controlled substance (low potential for abuse), do not drive within 8 hours after taking medication, may potentially cause MOH, & coadministration with triptan or gepant not yet assessed; *almotriptan may be better tolerated for patients who have not tolerated other triptans previously (chest pain, flushing, dizziness, etc.)

Acute Treatment Agents for Migraine: Populations with Limited Treatment Options	
Population	**Agents Recommended**
Pregnancy	Acetaminophen (B) Metoclopramide (B)/ondansetron (B)

Preventive Treatment for Episodic[12]

- **Importance of initiating preventive therapy:** Although the literature suggests that 38% of patients with headache would benefit from preventive treatment, only 3-13% currently use it.[13] Preventive therapies can decrease the occurrence of migraines by 50-80% and reduce the severity and duration of episodes.[1]
- **Candidates for preventive treatment:** Offer preventive therapy to patients reporting ≥4 migraines per month and/or ≥6 headache days per month (and <15 days per month). MOH should be addressed first if present. Initiation of preventive medications may help with MOH.
- **Preventive treatment timing:** Initiate preventive treatment as early as clinically indicated. Episodic migraine progresses to chronic migraine at the rate of 2.5% per year while chronic migraine can remit to episodic migraine at a 2-year transition rate of 26%[4] if treated appropriately.
- **Set realistic goals:** Therapeutic success may be defined as 50% reduction in attack frequency or headache days, improved response to acute medication, etc. Educate patients that the goal of therapy is to reduce frequency and severity of migraines rather than eliminate them entirely and monitor ability to resume normal daily activities. Discuss expected time to efficacy given clinical benefit may take as long as 2-3 months to manifest.
- **Preventive treatment selection:** Agents with the highest efficacy and safety are metoprolol, propranolol, topiramate, and amitriptyline. CGRP monoclonal antibodies and gepants have good evidence establishing efficacy, but are not considered cost-effective as first-line agents. Choice of preventive therapy should be based on comorbidities, side effect profile, and cost. If a patient fails a medication, consider switching classes of medications instead of trialing another medication in the same class (e.g., if a patient fails metoprolol, switching to topiramate may offer better efficacy than switching to another beta blocker).
- **Agents lacking a clear evidence base to recommend use:** Coenzyme Q10, riboflavin, magnesium, melatonin
- **Dual-use therapies**: Several migraine treatments have been shown to provide meaningful benefits as both acute and preventive therapies.[8] Among pharmacotherapies, rimegepant (Nurtec® ODT) is the only agent FDA approved for both abortive and preventive therapy. Additionally, frovatriptan is an established acute treatment option that can have a role in short-term prevention of menstrual-related migraine.
- **When to refer to Neurology:** Patients should try (and fail) at least 1 acute abortive medication and 1 preventive treatment prior to receiving a referral for episodic migraine. Refer to neurology for chronic migraine (≥15 headache days per month) preventive treatment options.

Preventive Treatment Agents for Episodic Migraine

Definition of episodic migraine: headache burden of <15 days per month[14]

Therapeutic Agent	Migraine	Women of Child-Bearing Age	Depression/Anxiety	Bipolar Disorder	HTN	Obesity	Insomnia	Nephrolithiasis	Attention/ Cognitive Issues	Cost±
Metoprolol ER	A				✓					$20
Propranolol ER	A				✓		✓			$57
Topiramate	A	⚠ *Use effective contraception*				✓	✓	×	×	$73
Amitriptyline	A		✓				✓			$17
Divalproex sodium *No evidence supporting therapeutic drug monitoring*	B	⚠ *Use effective contraception*		✓						$89
Atenolol	B	⚠ *Other agents preferred*			✓					$12
Nadolol	B	⚠ *Other agents preferred*			✓					$79
Candesartan	B	⚠ *Avoid in women of reproductive potential*			✓					$97
Venlafaxine ER	B		✓							$116
Cefaly Device*	B									$500
Zonisamide	C	⚠ *Use effective contraception*					✓	×		$91
Memantine	C								✓	$275
CGRP[A] antagonists Eptinezumab (Vyepti®) Erenumab (Aimovig®)[B] Fremanezumab (Ajovy®) Galcanezumab (Emgality®)	C	⚠ *Avoid; limited data at this time*								$375 – 700
Small molecule CGRP[A] antagonists Rimegepant (Nurtec® ODT)[C] Atogepant (Qulipta™)	C	⚠ *Other agents preferred*								$1,094 – 1,197

[A]Not considered first-line agents given lack of long-term safety data and high cost; should demonstrate inability to tolerate or inadequate response after a minimum 3-6 month trial of at least 2 other A or B rated preventative treatment agents. May be a reasonable option for patients with significant migraine disability who failed or did not tolerate other preventative therapies. [B]Not recommended in patients with a latex allergy or constipation, as use has been associated with cases of severe constipation. [C]May be used for both acute and preventive treatment, up to 18 doses per month. **Cefaly® is an FDA-approved, non-drug, wearable device that provides stimulation of the trigeminal nerve. It is available with a prescription and comes as a preventive device as well as an acute treatment device. Insurance typically does not cover the cost of a Cefaly® device, but the cost listed above is a one-time cost.*

✓ Indicates a comorbidity where there may be additional clinical benefit, based on medication pharmacology

× Indicates a comorbidity where avoidance of this medication might be recommended, due to adverse effects (>10% incidence in clinical trials)

⚠ Indicates women should ensure adequate contraception before initiating and while taking these medications, when appropriate (data from medication package inserts and clinical trials)

Preventive Treatment Agents for Episodic Migraine: Populations with Limited Treatment Options	
Population	**Agents Recommended**
Menstrual Migraine	Naratriptan (A) Frovatriptan (B) Zolmitriptan (B)
Pregnancy	Cefaly® Device (A) Memantine (B) Cyproheptadine (B)

Rating Key:

A rating: safe and effective for use in this population	**C rating:** safety or cost concerns may outweigh benefit in this population
B rating: benefits generally outweigh potential safety or cost concerns in this population	**D rating:** avoid use; side effect/tolerability/safety concerns preclude the use of this agent in this population

‡Costs reported are average monthly cash prices from www.goodrx.com when available and average wholesale price (AWP) when GoodRx prices were unavailable. Costs are estimates as of document completion date and will vary based on individual insurance plan, pharmacy, strength, and day supply.

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