Migraine and other primary headaches

Migraine

- ***a recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures***
- the second most common cause of headache
- most common headache-related, and indeed neurologic, cause of disability in the world
- episodic headache associated with sensitivity to light, sound, or movement; nausea and vomiting often accompany
- three phases: (may overlap)
  - premonitory (prodrome),
  - headache phase
  - postdrome
  - Aura (in 25%)
- activators or triggers classical
  - amplified in women during the menstrual cycle
  - glare, bright lights, sounds, or other types of afferent stimulation;
  - hunger;
  - let-down from stress;
  - physical exertion;
  - stormy weather or barometric pressure changes;
  - hormonal fluctuations during menses;
  - lack of or excess sleep;
  - alcohol or other chemicals eg. nitrates

Pathogenesis

- dysfunction of monoaminergic sensory control systems located in the brainstem and hypothalamus
- Activation at trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene–related peptide (CGRP)
- second-order trigeminal neurons cross the midline and project to ventrobasal and posterior nuclei of the thalamus
- projections to the periaqueductal gray and hypo- thalamus, from which reciprocal descending systems have established antinociceptive effects
- 5-hydroxytryptamine (5-HT; also known as serotonin) also involved
- triptans are potent agonists of 5-HT1B and 5-HT1D receptors and some at ***5-HT1F (ditans)***
- **Triptans** arrest nerve signaling in the nociceptive pathways of the trigeminovascular system, nucleus caudalis and trigeminal sensory thalamus, in addition to promoting cranial vasoconstriction,
- **ditans, act only at neural and not vascular targets**
- migraine symptoms can be induced by dopaminergic stimulation.
- dopamine receptor hypersensitivity in migraineurs,
- familial h plegic migraine (FHM)
- Ca v 2.1 (P/Q)–type voltage-gated calcium channel CACNA1A gene are now known to cause FHM 1
- Na+-K+ATPase ATP1A2 gene, designated FHM 2,
- neuronal voltage-gated sodium channel SCN1A cause FHM 3.

TABLE 430-3 Simplified Diagnostic Criteria for Migraine

REPEATED ATTACKS OF HEADACHE LASTING 4–72 H IN PATIENTS WITH A NORMAL PHYSICAL EXAMINATION, NO OTHER REASONABLE CAUSE FOR THE HEADACHE, AND:	
AT LEAST 2 OF THE FOLLOWING FEATURES:	**PLUS AT LEAST 1 OF THE FOLLOWING FEATURES:**
Unilateral pain	Nausea/vomiting
Throbbing pain	Photophobia and phonophobia
Aggravation by movement	
Moderate or severe intensity	

Source: Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, Cephalalgia 38:1, 2018).

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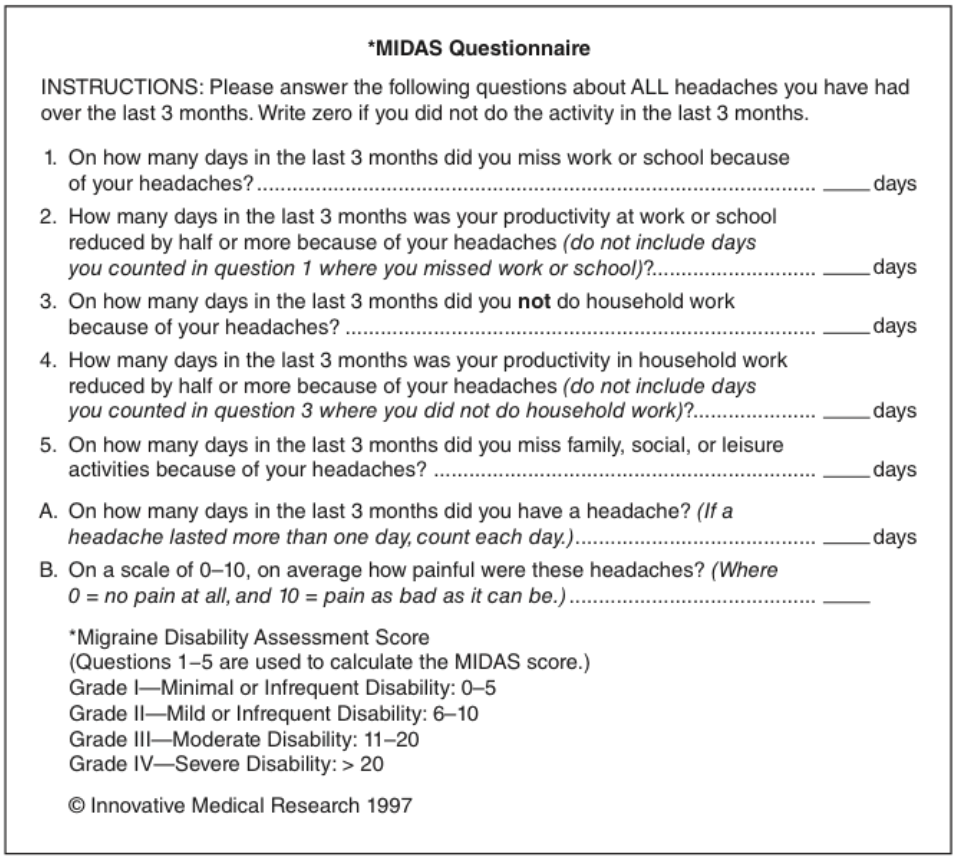
- aura, consisting of visual disturbances with flashing lights or zigzag lines moving across the visual field or of other neurologic symptoms, is reported in only 20–25% of patients (distinguished from the pan-field television static-like disturbance now recognized as the **visual snow syndrome.)**
- **prodromal**) phase consisting of some or all of the following: yawning, tiredness, cognitive dysfunction, mood change, neck discomfort, polyuria, and food cravings; this can **last from a few hours to days**
- As the headache lessens, many patients enter a postdrome, most commonly feeling tired/weary, having problems concentrating, and experiencing mild neck discomfort that can last for hours and sometimes up to a day
- episodes of migraine on 8 or more days per month and with at least 15 total days of headache per month are considered to have **chronic migraine**
- ***Migraine at its most basic level is headache with associated features, and TTH is headache that is featureless. Most patients with disabling headache probably have migraine.***
- that one-third of patients referred for vertigo or dizziness have a primary diagnosis of migraine.
- Migraine aura can have prominent brainstem symptoms, and the terms basilar artery and basilar-type migraine have now been replaced by **migraine with brainstem aura**

Treatment

- assess the extent of a patient's disease and disability with The Migraine Disability Assessment Score (MIDAS)



***MIDAS Questionnaire**

INSTRUCTIONS: Please answer the following questions about ALL headaches you have had over the last 3 months. Write zero if you did not do the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headaches? ..... ____ days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches *(do not include days you counted in question 1 where you missed work or school)*? ..... ____ days
3. On how many days in the last 3 months did you **not** do household work because of your headaches? ..... ____ days
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches *(do not include days you counted in question 3 where you did not do household work)*? ..... ____ days
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? ..... ____ days

A. On how many days in the last 3 months did you have a headache? *(If a headache lasted more than one day, count each day.)* ..... ____ days

B. On a scale of 0–10, on average how painful were these headaches? *(Where 0 = no pain at all, and 10 = pain as bad as it can be.)* ..... ____

*Migraine Disability Assessment Score
(Questions 1–5 are used to calculate the MIDAS score.)
Grade I—Minimal or Infrequent Disability: 0–5
Grade II—Mild or Infrequent Disability: 6–10
Grade III—Moderate Disability: 11–20
Grade IV—Severe Disability: > 20

FIGURE 430-4 The Migraine Disability Assessment Score (MIDAS) Questionnaire.

NONPHARMACOLOGIC MANAGEMENT

- patients can identify reliable triggers, their avoidance can be useful.
- A regulated lifestyle is helpful, including a healthy diet, regular exercise, regular sleep patterns, avoidance of excess caffeine and alcohol, and avoidance of acute changes in stress levels
- overresponsiveness to changes in stress appears to be the issue

ACUTE ATTACK THERAPIES FOR MIGRAINE

TABLE 430-4 Treatment of Acute Migraine

DRUG	TRADE NAME	DOSAGE
Simple Analgesics		
Acetaminophen, aspirin, caffeine	Excedrin Migraine	Two tablets or caplets q6h (max 8 per day)
NSAIDs		
Naproxen	Aleve, Anaprox, generic	220–550 mg po bid
Ibuprofen	Advil, Motrin, Nuprin, generic	400 mg po q3–4h
Tolfenamic acid	Clotam Rapid	200 mg po; may repeat ×1 after 1–2 h
Diclofenac K	Cambia	50 mg po with water
5-HT$_{1B/1D}$ Receptor Agonists—Triptans		
Oral		
Ergotamine 1 mg, caffeine 100 mg	Cafergot	One or two tablets at onset, then one tablet q½h (max 6 per day, 10 per week)
Naratriptan	Amerge	2.5-mg tablet at onset
Rizatriptan	Maxalt	5–10-mg tablet at onset
	Maxalt-MLT	
Sumatriptan	Imitrex	50–100-mg tablet at onset
Frovatriptan	Frova	2.5-mg tablet at onset
Almotriptan	Axert	12.5-mg tablet at onset
Eletriptan	Relpax	40 or 80 mg at onset
Zolmitriptan	Zomig	2.5-mg tablet at onset
	Zomig Rapimelt	
Nasal		
Dihydroergotamine	Migranal Nasal Spray	Prior to nasal spray, the pump must be primed 4 times; 1 spray (0.5 mg) is administered, followed in 15 min by a second spray
	Trudhesa Nasal Spray	One spray into each nostril
Sumatriptan	Imitrex Nasal Spray	5–20 mg intranasal spray as 4 sprays of 5 mg or a single 20 mg spray
Zolmitriptan	Zomig	5 mg intranasal spray as one spray
Parenteral		
Dihydroergotamine	DHE-45	1 mg IV, IM, or SC at onset and q1h (max 3 mg/d, 6 mg per week)
Sumatriptan	Imitrex Injection	6 mg SC at onset (may repeat once after 1 h for max of 2 doses in 24 h)
	Alsuma	
	Sumavel DosePro	
CGRP Receptor Antagonists—Gepants		
Oral		
Rimegepant	Nurtec	75 mg ODT po
Ubrogepant	Ubrelvy	50 or 100 mg po; a second dose may be taken 2 hours after the first, if needed.
5-HT$_{1F}$ Receptor Agonist—Ditans		
Oral		
Lasmiditan	Reyvow	50, 100, or 200 mg po
Dopamine Receptor Antagonists		
Oral		
Metoclopramide	Reglan,[a] generic[a]	5–10 mg/d
Prochlorperazine	Compazine,[a] generic[a]	1–25 mg/d
Parenteral		
Chlorpromazine	Generic[a]	0.1 mg/kg IV at 2 mg/min; max 35 mg/d
Metoclopramide	Reglan,[a] generic	10 mg IV
Prochlorperazine	Compazine,[a] generic[a]	10 mg IV
Other		
Oral		
Acetaminophen, 325 mg, *plus* dichloralphenazone, 100 mg, *plus* isometheptene, 65 mg	Midrin, generic	Two capsules at onset followed by 1 capsule q1h (max 5 capsules)
Parenteral		
Opioids	Generic[a]	Multiple preparations and dosages; see Table 13-1
Other		
Neuromodulation		
Single-pulse transcranial magnetic stimulation (sTMS)	sTMSmini	Two pulses at onset followed by two further pulses
Noninvasive vagus nerve stimulation (nVNS)	gammaCore	Two doses each of 120 s
Remote electrical neuromodulation	Nerivio	30- to 45-min stimulation to the upper arm
Transcutaneous supraorbital nerve stimulation	Cefaly	60-min stimulation

[a]Not all drugs are specifically indicated by the FDA for migraine. Local regulations and guidelines should be consulted.

Note: Antiemetics (e.g., domperidone 10 mg or ondansetron 4 or 8 mg) or prokinetics (e.g., metoclopramide 10 mg) are sometimes useful adjuncts.

Abbreviations: 5-HT, 5-hydroxytryptamine; NSAIDs, nonsteroidal anti-inflammatory drugs; ODT, orally disintegrating tablets.

TABLE 430-5 Clinical Stratification of Acute Specific Migraine Treatments	
CLINICAL SITUATION	**TREATMENT OPTIONS**
Failed NSAIDs/analgesics	**First tier** Sumatriptan 50 mg or 100 mg PO Almotriptan 12.5 mg PO Rizatriptan 10 mg PO Eletriptan 40 mg PO Zolmitriptan 2.5 mg PO Rimegepant 75 mg Ubrogepant 50 or 100 mg Lasmiditan 50, 100, or 200 mg **Slower effect/better tolerability** Naratriptan 2.5 mg PO Frovatriptan 2.5 mg PO **Infrequent headache** Ergotamine/caffeine 1–2/100 mg PO Dihydroergotamine nasal spray 2 mg
Early nausea or difficulties taking tablets	Zolmitriptan 5 mg nasal spray Sumatriptan 20 mg nasal spray Rizatriptan 10 mg MLT wafer
Headache recurrence	Ergotamine 2 mg (most effective PR/usually with caffeine) Naratriptan 2.5 mg PO Almotriptan 12.5 mg PO Eletriptan 40 mg Rimegepant 75 mg Ubrogepant 50 or 100 mg
Tolerating acute treatments poorly	Naratriptan 2.5 mg Almotriptan 12.5 mg Rimegepant 75 mg Ubrogepant 50, 100 mg Single-pulse transcranial magnetic stimulation Noninvasive vagus nerve stimulation
Early vomiting	Zolmitriptan 5 mg nasal spray Sumatriptan 25 mg PR

	Sumatriptan 6 mg SC
Menses-related headache	**Prevention** Ergotamine po at night Estrogen patches Rimegepant 75 mg po taken during the menses **Treatment** Triptans Dihydroergotamine nasal spray
Very rapidly developing symptoms	Zolmitriptan 5 mg nasal spray Sumatriptan 6 mg SC Dihydroergotamine 1 mg IM

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

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- Mild migraine attacks can u ally be managed by oral agents;
- Severe migraine attacks may require parenteral therapy
- five major pharmacologic classes: **nonsteroidal anti-inflammatory drugs; 5-HT 1B/1D receptor agonists—triptans; CGRP receptor antagonists—gepants; 5-HT 1F receptor agonists—ditans; and dopamine receptor antagonists**
- adequate dose of whichever agent is chosen should be used as soon as possible after the onset of an attack. If additional medication is required within 60 min because symptoms return or have not abated, the initial dose should be increased for subsequent attacks or a different class of drug tried as first-line treatment
- Repeat dosing of the same medicine at 2 hours while safe, has been established to be **ineffective for triptans**. An exception to this rule may be **gepants, for which there are data to show that retreatment with the same dose is helpful**
- NSAIDs
  - NSAIDs are most effective when taken early in the migraine attack.
  - less than optimal in moderate or severe migraine attacks.
  - combination of acetaminophen (paracetamol), aspirin, and caffeine has been approved for the treatment of mild to moderate migraine
  - combination of aspirin and metoclopramide has been shown to be comparable to a single dose of oral sumatriptan
- TRIPTANS
  - Ergotamine and dihydroergotamine are nonselective r tor agonists, whereas the triptans are selective 5-HT 1B/1D receptor agonists.
  - triptans—sumatriptan, almotriptan, e riptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan—are available for the treatment of migraine.
  - Rizatriptan and eletriptan are the most efficacious
  - Sumatriptan and zolmitriptan have similar rates of e cacy as well as time to onset, with an advantage of having multiple formulations
  - almotriptan has a similar rate of efficacy to sumatriptan and is better tolerated
  - frovatriptan and naratriptan are somewhat slower in onset and are also well tolerated.
  - efficacy appears to be related more to the t max(time to peak plasma level)
  - not effective in migraine with aura unless given after the aura is completed and the headache initiated
  - contraindicated in individuals with a history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes.
  - coadministration of a longer-acting NSAID, naproxen 500 mg, with sumatriptan will augment the initial effect of sumatriptan and, importantly, reduce rates of headache recurrence
  - Oral (excluding sublingual) formulations of ergotamine also contain 100 mg caffeine (theoretically to enhance ergotamine absorption and possibly to add additional analgesic activity) average 2mg ergotamine
  - Nasal formulations of dihydroergotamine, zolmitriptan, or sumatriptan can be useful in patients requiring a nonoral route of administration. rapid onset but efficacy only 50-60%
  - injection, such as d ergotamine and sumatriptan, is approved by the FDA for the rapid relief of a migraine attack
  - peak plasma levels of dihydroergotamine are achieved 3 min after IV dosing, 30 min after intramuscular (IM) dosing, and 45 min after subcutaneous (SC) dosing.

- Sumatriptan, 4–6 mg SC, is effective in ~50–80% of patients and can now be administered by a needle-free device.
- CALCITONIN GENE-RELATED PEPTIDE (CGRP) RECEPTOR ANTAGONISTS—GEPANTS
  - approved by the FDA: rimegepant and ubrogepant
  - extremely well tolerated with only a few percent of patients reporting troublesome side effects, such as mild nausea.
- 5-HT 1F RECEPTOR AGONISTS—DITANS
  - Lasmiditan, a highly selective, orally available, 5-HT receptor agonist, has been approved by the FDA for the acute1F treatment of migraine
  - o vascular effects because the 5-HT 1F receptor is located in the central and peripheral nervous system but not vasculature
  - fills a gap in therapy for patients with cardiovascular and cerebrovascular disease
  - Dizziness and somnolence major side effects
- DOPAMINE RECEPTOR ANTAGONISTS
  - Oral dopamine receptor antagonists can be considered as adjunctive therapy
  - absorption is impaired d ing migraine because of reduced gastrointestinal motility
  - Delayed absorption occurs even in the absence of nausea and is related to the severity of the attack and not its duration
  - when oral NSAIDs and/or triptan agents fail, the addition of a dopamine receptor antagonist, such as metoclopramide 10 mg or domperidone 10 mg (not available in the United States), should be considered to enhance gastric absorption
  - Dopamine receptor antagonists (e.g., chlorpromazine, prochlorperazine, metoclopramide) by injection can also provide significant acute relief of migraine; they can be used in combination with parenteral 5-HT 1B/1Dreceptor agonists.
- Others
  - acetaminophen, dichloralphenazone, and isometheptene combination FDA as “possibly” effective in the treatment of migraine
  - Opioids are modestly effective in the acute treatment of migraine. For example, IV meperidine (50–100 mg) is given frequently in the emergency department (ED).
  - opioids are clearly suboptimal for patients with recurrent headache. Opioids do not treat the underlying headache mechanism; rather, they act to alter the pain sensation
  - opioid use in migraine be limited to patients with severe, but infrequent, headaches that are unresponsive
  - Single-pulse transcranial magnetic stimulation (sTMS) is FDA approved for the acute treatment of migraine. Two pulses can be applied at the onset of an attack, and this can be repeated.
  - sTMS is safe where there is no cranial metal implant, and offers an option to patients seeking nonpharmaceutical approaches to treatment.
  - Noninvasive vagal nerve stimulation (nVNS) FDA approved for the treatment of migraine attacks in adults. One to two 120-s doses may be applied for attack treatment.
  - Remote electrical neuromodulation using a smartphone app that stimulates the upper arm for 30–45 min is also effective for treatment of acute migraine, as is transcutaneous supraorbital nerve stimulation for 60 min
- MEDICATION-OVERUSE HEADACHE
  - Acute attack medications, particularly opioid or barbituratecontaining compound analgesics aggravate headache frequency and induce a state of refractory daily or near daily headache called medication-overuse headache
  - Migraine patients who have two or more headache days a week should be cautioned about frequent analgesic use
- PREVENTIVE TREATMENTS FOR MIGRAINE
  - if increasing frequency of migraine attacks or with attacks that are either unresponsive or poorly responsive to abortive treatments
  - considered in patients with four or more attacks a month

TABLE 430-6 Preventive Treatments in Migraine[a]		
DRUG	**DOSE**	**SELECTED SIDE EFFECTS**
Beta blocker		
Propranolol	40–120 mg bid	Reduced energy
Metoprolol	25–100 mg bid	Tiredness
		Postural symptoms
		Contraindicated in asthma
Antidepressants		
Amitriptyline	10–75 mg at night	Drowsiness
Dosulepin	25–75 mg at night	
Nortriptyline	25–75 mg at night	*Note:* Some patients may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required.
Venlafaxine	75–150 mg/d	
Anticonvulsants		
Topiramate	25–200 mg/d	Paresthesias
		Cognitive symptoms
		Weight loss
		Glaucoma
		Caution with nephrolithiasis
Valproate	400–600 mg bid	Drowsiness
		Weight gain
		Tremor
		Hair loss
		Fetal abnormalities
		Hematologic or liver abnormalities
Serotonergic drugs		
Pizotifen[b]	0.5–2 mg qd	Weight gain
CGRP antagonists		
Eptinezumab	100 or 300 mg IV every 12 weeks	Nasopharyngitis
Erenumab	70 or 140 mg SC monthly	Nasopharyngitis, constipation
Fremanezumab	225 mg monthly or 675 mg q3 months, SC	Injection site reactions
Galcanezumab	240 mg loading then 120 mg monthly, SC	Nasopharyngitis
Rimegepant	75 mg every other day	Nausea abdominal pain/ dyspepsia
Other classes		

Flunarizine[b]	5–15 mg qd	Drowsiness Weight gain Depression Parkinsonism
Candesartan	4–24 mg daily	Dizziness
Memantine	5–20 mg daily	Dizziness, tiredness
Melatonin	3–12 mg nightly	Drowsiness
Neuromodulation		
Single-pulse transcranial magnetic stimulation (sTMS)	4–24 pulses per day	Lightheadedness Tingling Tinnitus
Chronic migraine		
Onabotulinum toxin type A	155 U	Loss of brow furrow
No convincing evidence from controlled trials		
Verapamil		
Controlled trials demonstrate *no effect*		
Nimodipine		
Clonidine		
Selective serotonin reuptake inhibitors: fluoxetine		

[a]Commonly used preventives are listed with typical doses and common side effects. Not all listed medicines are approved by the U.S. Food and Drug Administration; local regulations and guidelines should be consulted.

[b]Not available in the United States.

- must be taken daily, and there is usually a lag of 2–12 weeks before an effect is seen
- propranolol, timolol, rimegepant, sodium v proate, topiramate, eptinezumab, erenumab, fremanezumab, and galcanezumab are approved
- amitriptyline, c desartan, nortriptyline, flunarizine, phenelzine, and cyproheptadine. shown to be useful
- approved sTMS for the preventive treatment of migraine
- onabotulinum toxin type A in episodic migraine were negative, whereas, overall, placebo-controlled trials in chronic migraine were positive.
- Once effective s lization is achieved, the drug is continued for ~6 months and then slowly tapered, assuming the patient agrees, to assess the continued need.