Migraine Headache

Diagnosis

Abortive treatment

Preventive treatment

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Diagnosis

- The ICHD-3 criteria define major categories of disorders: primary headaches, secondary headaches, and cranial neuralgias and facial pain.

- The major primary headache disorders are migraine, tension-type headache, and trigeminal autonomic cephalalgias.

- For tension-type headache, the prevalence is 30.8% for women and 21% for men, whereas the prevalence rates for migraine are 19% for women and 10% for men.

- Although tension-type headache is the most common primary headache disorder in the general population, migraine is overwhelmingly the most common primary headache disorder presenting to clinicians, especially neurologists.

Gender ratio

- Predominantly a dis of women 2-3:1
- Actually migraine is commoner in young boys than young girls.
- Women often develop migraine soon after puberty
- The incidence of new cases of migraine in males rises steadily at least until 30.
- Most migraine will have revealed itself by the age of about 30 in women and 40 in men.
- It is appropriate to undertake more investigations in new cases of headache in patients older than this.

Frequency

- Very variable

- The majority of patients with episodic migraine seen in neurology clinic have between one attack every 2 months and two attacks weekly

- In most cases episodic attacks gradually become more frequent and this apparent “transformation“ can be explained by , for example, the overuse of potentially addictive analgesics such as codein or triptan, female hormones such as OCP or hormone therapy or a depressive state. Other risk factors for chronic rather than episodic migraine include a high BMI, a lower level of education and Smoking. Sometimes spontaneously.

Medication-overuse headache:

- Headache occurring on ≥15 days/month in a patient with a preexisting headache disorder
- Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache,

- Overuse is defined by the use of all acute medication on >10 days per month except for simple analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs), for which overuse is defined as use on >15 days per month.

- Avoid opioid and barbiturates because of risk of addiction

Typical migraine attack may have four phases:

- 1. Prodromal phase
- 2. Aura
- 3. Headache
- 4. Postdrome

1. Prodromal phase:

- Hours or days before headache (usually lasted less than 12)
- Hyper/hypoactivity, yawning, polyuria, food cravings, mood changes, irritability, light sensitivity, neck pain, and cognitive dysfunction.
- Around 80% of people with migraine report premonitory symptoms
- Hypothalamic activation: polyuria, yawning, food cravings
- The locus coeruleus : sleep disturbances.
- Trigeminocervical complex, brainstem and upper cervical spinal cord: Neck stiffness

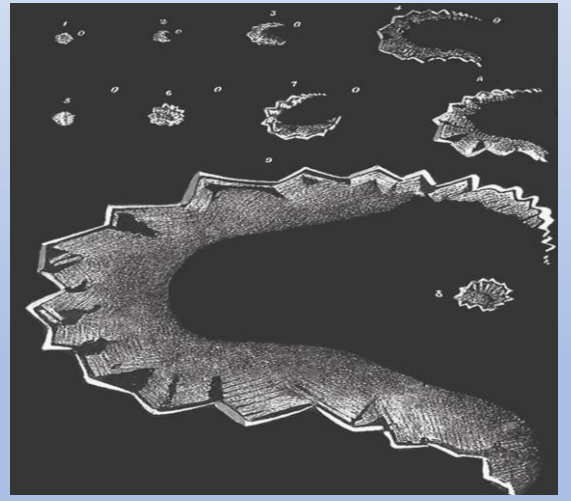
Pathophysiology

2. Aura

- Transient neurological symptoms usually lasting a few minutes to an hour before headache
- Traditionally, aura has been described as preceding the headache phase; however, this phase can overlap with headache, and it is not rare for the aura to occur in the absence of headache.
- About one-third of migraineurs experience an aura associated with at least some of their attacks.
- Aura may consist of visual, sensory, motor, language, or brainstem disturbances.
- Some patients have more than one aura, the commonest combination being visual and sensory symptoms.

Visual symptoms

- It is generally held that photophobia and blurring of vision are ***NOT*** wholly typical migrainous aura symptoms



- Disturbances of the visual field akin to a ‘broken windscreen’ or a ‘wet windscreen’

- Scotomas, or visual loss with or without a bright zigzag disturbance sometimes in a curve, usually on the temporal side of the field.

- In many cases the visual disturbance moves across the visual field from close to the fixation point towards the periphery over 20– 40 minutes

- Many patients complain of paraesthesiae or numbness, most commonly in the parts of the body most heavily represented on the cortex— the lips, the face, and the fingertips

- It is typical and almost pathognomonic of migraine that the sensory disturbance should migrate, taking perhaps 20– 30 minutes to pass from the shoulder to the fingertips or vice versa. (last only a few minutes before resolving)

- Speech disturbances, including expressive and/ or receptive dysphasias and paraphrasia are also commonly found. Dysarthria can also occur

3. Headache

- Migraine pain is mediated by the trigeminovascular pathway.

- Some experts maintain that nociceptive activation of the peripheral trigeminal nociceptors is necessary for the perception of head pain and implicate cortical spreading depolarization and peripheral sensitization of perivascular sensory nerve terminals.

- Others argue that migraine pain is the result of abnormal central processing of otherwise normal sensory input from the peripheral trigeminal sensory system.

4. Postdrome

- The most common postdromal symptom were tiredness, difficulty concentrating, and neck stiffness. The person may have diarrhea or urine frequency

- Occurs once the headache has resolved.

- More than 80% of patients report non-headache symptoms during the 24 to 48 hours following resolution of their migraine headaches

- It has been proposed that the brain regions and mechanisms responsible for the prodromal phase could also play a role in the postdromal phase.

Interictal Phase

Although patients are relatively symptom free during this phase, they often describe:

- hypersensitivity to light, sounds, and odors
- Dizziness or a sense of being off balance
- Sensory hypersensitivity
- Autonomic symptoms
- Cognitive dysfunction

Migraine types

- Episodic Migraine without aura
- Migraine with aura
- Chronic Migraine
- Migraine with brainstem aura
- Vestibular migraine
- Hemiplegic migraine
- Retinal migraine

The most frequent subtypes

Migrane without aura:

Diagnostic criteria:

A. At least five attacks[1] fulfilling criteria B-D

B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity

D. During headache at least one of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

- First, at least five attacks meeting the criteria are required for the diagnosis. This avoids misdiagnosing a sinister secondary headache
- Second, no single feature is either necessary or sufficient to make the diagnosis;
- Third, in patients who meet either the pain criteria or the associated symptom criteria, the diagnosis is probable migraine:
  - ✓ A bilateral and generalized squeezing headache of moderate intensity that causes avoidance of routine physical activity and is not associated with photophobia or nausea meets criteria for probable migraine.

- Individuals who have had fewer than five attacks should be coded probable migraine without aura.
- When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.
- In children and adolescents (aged under 18 years), attacks may last 2-72 hours

Box 1.1 Criteria for migraine with aura

A At least two attacks fulfilling criteria B and C.

B One or more of the following fully reversible aura symptoms:

- **1** Visual
- **2** Sensory
- **3** Speech and/or language
- **4** Motor
- **5** Brainstem
- **6** Retinal.

C At least three of the following six characteristics:

- **1** At least one aura symptom spreads gradually over ≥5 minutes
- **2** Two or more aura symptoms occur in succession
- **3** Each individual aura symptom lasts 5–60 minutes[1]
- **4** At least one aura symptom is unilateral[2]
- **5** At least one aura symptom is positive[3]
- **6** The aura is accompanied, or followed within 60 minutes, by headache.

D Not better accounted for by another ICHD-3 diagnosis.

Notes

1 When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 × 60 minutes. Motor symptoms may last up to 72 hours.

2 Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

3 Scintillations and pins and needles are positive symptoms of aura.

Criteria for chronic migraine

A. Headache (migraine- like or tension- type- like)[1] on ≥15 days/ month

for >3 months, and fulfilling criteria B and C.

B. Occurring in a patient who has had at least five attacks fulfilling criteria B– D for *Migraine without aura* and/ or criteria B and C for 1.2 *Migraine with aura*.

C. On ≥8 days/ month for >3 months, fulfilling any of the following:

1 Criteria C and D for 1.1 *Migraine without aura*.

2 Criteria B and C for 1.2 *Migraine with aura*.

3 Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

D. Not better accounted for by another ICHD- 3 diagnosis.

The long- term prognosis

- Many women, especially if their attacks have been linked to the menstrual cycle, find that they fade after the menopause, particularly if they are able to avoid hormone- replacement therapy

- There may be as many women who start at the menopause as there are those whose headaches settle down. The prevalence in older men, in contrast, is certainly lower than in younger men

• Migraine Trigger Factors

- Trigger factors increase the probability of a migraine at usually within 48 hours
- Many patients report a craving for certain food products prior to the migraine attack, so these factors could be considered premonitory factors instead of trigger factors

Table 7.1 Potential triggers for migraine

Weather and other atmospheric variables	Temperature Relative humidity High altitude (hypoxia) Possibly other variables (see Chapter 54)
Nutritional	Alcohol Beer Wine (red and white) Cheese Chocolate Caffeine Ice cream Meat Fish Milk (and other dairy products) Vegetables Citrus fruits Lipids Aspartame Monosodium glutamate Sugar Fasting or skipping meals Fluid deprivation
Stress	Psychological stressors
Hormonal	Female hormones
Lifestyle	Fatigue and sleep Smoking Physical activity Sexual activity
Pharmacological	Nitric oxide donors Calcitonin gene-related peptide Pituitary adenylate cyclase-activating polypeptide Prostaglandins

Abortive treatment

- Nonpharmacologic treatment of acute attack
- Pharmacologic therapies
- Status migraine and severe headache
- Pregnancy and lactation

Nonpharmacologic treatments for acute headache

- Rest in dark and quiet space
- Hydration
- Ice pack
- Creams containing menthol, oils and lidocaine
- Deep breathing and meditation
- Biofeedback

Neuromodulation Dosing and Side Effects

TABLE 3-4

Device	Dosing	Side effects
External trigeminal stimulation	1 hour during migraine attack	Paresthesia
Single-pulse transcranial magnetic stimulation	Three pulses up to 3 times per attack as needed	Lightheaded, tingling, tinnitus
Noninvasive vagus nerve stimulation	Bilateral 120 seconds to right and left of neck within 20 minutes of onset of attack; repeat once after 15 minutes	Application site discomfort, nasopharyngitis
Remote electrical neuromodulation	To upper arm for 45 minutes within 1 hour of onset; increase stimulation until perceptible but nonpainful	Transient warmth, redness, or tingling sensation into the arm

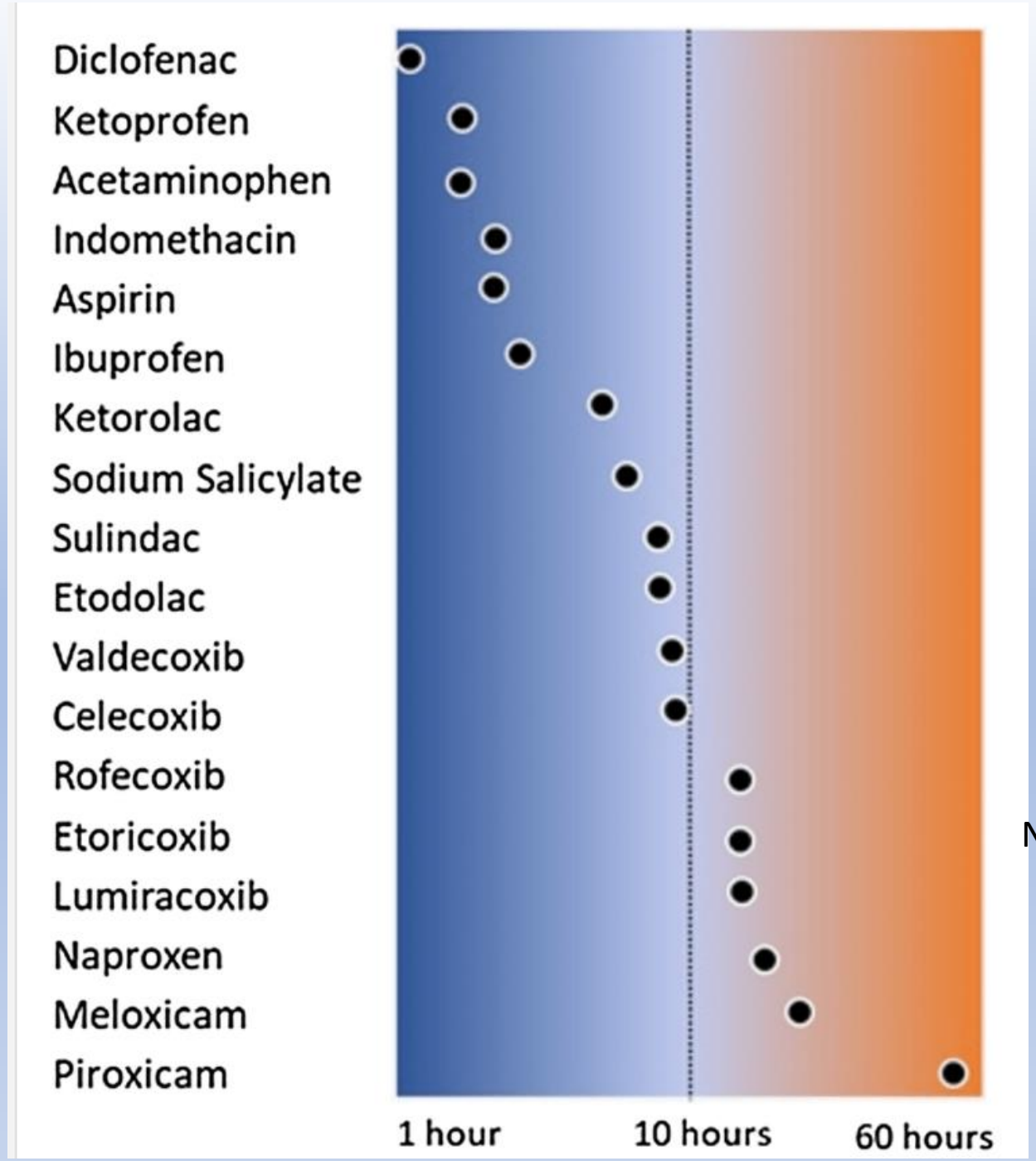
Recommendation for abortive drug selection

- Moderate headache: Acetaminophen (1000 mg), ASA (500), Ibuprofen (200/400), Naproxen (500), Diclofenac potassium(50/100)

- Moderate to severe headache: Triptans (Rizatriptan, Sumatriptan, Zolmitriptan)

- Refractory headache: Combination of triptan and NSAIDs, dopamine antagonists and opioids, Codeine, Tramadol (Acetaminophen1000+metoclopramide 10), (Novafen, ACA, sumatriptan85/naproxen500)

- New drugs: Rimegepants(75), Ubrogepant(50/100), Zavegepant(nasal), Lasmiditans(50/100/200)



NSAID plasma half-life (Log Scale)

Maximum dosage of analgesics per day:

- Acetaminophen: 4000 mg per day
- Ibuprofen: 2400 mg per day
- Diclofenac potassium: 100 mg per day
- Naproxen: 1375 mg per day
- ASA: 4000 mg per day
- Indomethacin (Tab,Supp): 200 mg per day
- Ketorolac IM: 60-120 mg per day
- Sumatriptan:200 mg daily maximum 8-10 days per month
- Rizatriptan: 30 mg daily maximum 8-10 days per month
- Amp sumatriptan: 6-12 mg per day maximum 8-10 days per month

Triptans

- Triptans are selective 5-hydroxytryptamine, serotonin (5-HT)1B/D agonists (some also have an affinity for the 5-HT1F receptor)
- Triptans are first-line treatment for moderate to severe migraine attacks
- **Side effects** of triptans include fatigue, dizziness, chest discomfort, somnolence, and nausea
- **Contraindications** include a history of MI or other IHD or CADs, cerebrovascular event including TIA, arrhythmias, coronary artery vasospasm, uncontrolled HTN, severe hepatic impairment, or ischemic bowel disease
- Although triptans carry a warning regarding potential for serotonin syndrome, the risk in co-prescription with other serotonergic medications is exceedingly low and in clinical practice such events are extraordinarily rare.

- Take optimum dose of Abortive Medication as soon as possible, before allodynia. Large single dose tends to work better than repetitive small doses. Triptans should be given as soon as a migraine or headache develops, while it is still mild to moderate.

- In the acute phase of hemiplegic migraine, retinal migraine or migraines with brainstem aura, it is better to use adequate doses of simple analgesics like aspirin or NSAIDs as triptans may not be safe.

- SC sumatriptan has the best and fastest effect although it induces more nausea and vomiting (best choice when the patient wakes up with headache or has nausea and vomitting)

- Melt forms of zolmitriptan and rizatriptan induce less vomiting.

Antiemetics

- Metocloptamide IV and prochlorperazine IM can be used as monotherapy with/without diphenhydramine to prevent akathisia and acute dystonic reaction (Not causing QT prolongation)

- Other antiemetics (haloperidol, chlorpromazine. ondansetron,) cause dose- dependent QT prolongation

- Ondansetron and domperidone do not have EPS but no proven effect on headache.

Ergot

- Ergots have been used to treat migraine since the Middle Ages but have poor tolerability because of nausea, vomiting, and cardiovascular effects.

- DHE has fewer side effects than previously used ergots. DHE is an agonist at 5-HT1B/1D/1F receptors and binds to 5-HT1A and 5-HT2A receptors and to adrenergic, cholinergic, and dopaminergic receptors.

- Its slow dissociation from 5-HT1B/1D receptors may explain why it can have a longer efficacy.

- Its wide effects may result in better efficacy for migraine, especially in patients who do not respond to triptans, but having more side effects

Non-oral treatments when:

- Nausea and vomiting
- Gastric stasis
- Faster onset

Includes:

- Intranasal forms (lidocaine, triptans..)
- Eye drops: Timolol
- Injectable: Sumatriptan, ketorolac
- Suppositories: Indomethacin, promethazin

Status Migraine (Migraine lasting more than 72h)

- IV DHE: Not available: 0.5-1 mg every 8 h
- Oral or parenteral metoclopramide or chlorpromazine (0.1 mg/kg IV up to a maximum dose of 25mg) plus diphenhyramin 12.5 mg before to prevent EPS. Ondansetron and domperidone do not have EPS but no proven effect on headache.
- Sodium valproate (15mg/kg IV bolus then 5mg/kg evey 8h for maximum of 10 doses)
- Magnesium sulfate: 1-2 gIV
- Corticosteroid: Dexamethasone 10-30 mg, Methylprednisolone 1mg/kg (rapid tapering in 3-4 days)

Treatment of severe headache in emergency

First Step:

1. IV NSAIDs such as ketorolac
2. SC sumatripotan
3. Nasal zolmitriptan
4. With or without antiemetics

Second step:

- IV corticosteroid, Sodium valproate or opioid With or without antiemetics
- Nerve block

Acute migraine treatment in pregnancy

- Acetaminophen and metoclopramide are the recommended first-line treatments for migraine in pregnancy
- NSAIDs could be used in the second trimester (but before 30 weeks of gestation) (Ibuprofen, Naproxen, Diclofenac)
- Triptans are currently not recommended during pregnancy, although studies of teratogenicity have long suggested that they are safe.
- IV metoclopramide, IV magnesium , Nerve block
- Low dose caffeine (<200mg per day) is safe
- Low dose Aspirin(<100mg per day) use in T1 and T2 is safe.

Acute migraine treatment in pregnancy

Agent or Class	US Food and Drug Administration (FDA) Class[a]	Some Potential Risks and Comments
Acetaminophen	B	Attention deficit hyperactivity disorder
Lidocaine	B	Safety data largely from peripheral injection and not IV use, central nervous system depression
Ondansetron	B	Cleft palate
Dopamine antagonists (metoclopramide)	C (B)[b]	Prolonged QTc interval on ECG, extrapyramidal symptoms
Opiates (oxycodone)	C (B)[c]	All cross placenta, neonatal respiratory suppression (dependence [maternal and fetal])
Butalbital compounds	C	Congenital heart defects
Triptans	C	Preterm labor, uterine atony, postpartum hemorrhage
Bupivacaine	C	Maternal cardiac conduction abnormalities
Prednisone, methylprednisolone (dexamethasone)	C (D)[d]	Orofacial clefts, intrauterine growth restriction, some cross placenta
Nonsteroidal anti-inflammatory drugs	C (first trimester/second trimester)	First trimester: inhibit implantation, cardiac abnormalities, gastroschisis
	D (third trimester)	Third trimester: premature ductus arteriosus closure, oligohydramnios, periventricular hemorrhage
Magnesium sulfate	D	Bone loss[a]
Valproate	X	Neural tube defects, clefts, lower IQ and developmental delay, autism, cardiovascular and genitourinary abnormalities
Dihydroergotamine	X	Uterine ischemia, increased uterine contractility, prematurity

Acute migraine treatment in lactation

- Contraindicated: ketorolac, Ergots, High dose aspirin (Axar/ACA: 162/325/32)

- Use with caution: naproxen, Indomethacin, Codeine, Metoclopramide, Prochlorprazine Dexamethasone, other Triptans

- Considered safe:

Acetaminophen, Caffeine, Ibuprofen, Diclofenac, Low dose aspirin(75-160 mg per day), Eletriptan, Sumatriptan, prednisolone, lidocaine, bupivacaine, Ondansetron

Preventive Treatment

- Pharmacological therapies
- Non-pharmacological therapies
- Pregnancy and lactation

Lifestyle Modifications

- Getting adequate and good-quality sleep
- Good hydration
- Eating well-balanced frequent meals
- Avoiding alcohol
- Keeping caffeine to a modest level and at a regular time each morning
- Participating in regular physical activity
- Intentional stress management
- Dietary changes should be considered a form of intervention and assessed with the same rigor as any other preventive treatment.

Criteria for considering preventive therapy:

- Two severe or disabling
- Four less disabling migraine attacks per month
- Acute migraine treatment is ineffective or contraindicated
- Medication overuse headache is present
- Highly disabling migraine attacks (Hemiplegic migraine or migraine with BS aura)
- Patient preference

Pharmacological preventive Treatment

- Drugs should be initiated at a low dose and increased slowly to the target dose
- Attention should be paid to the coexisting disease
- Although monotherapy is the best method, a combination of two drugs may sometimes produce better effect.(Adding SNRI or SSRI is preferred to increasing TCA dose)
- About 3 months should be allowed for the administered drug to achieve the optimum effect.
- A 50% reduction in the headache frequency indicates success.

Preventive drug can be stopped when:

- Intolerance or marked adverse effect
- No partial efficacy is seen after 2 months

- The headache may subside on its own, eg at older age. So, reevaluation is necessary during treatment. The recommended duration of prophylactic treatment is 6-9 months.

Consideration for Selecting a drug for migraine prevention

- Patient’s age and gender
- Coexisting disease like PCO or psychiatric problems
- Type of migraine (with aura, without aura, with BS aura, Vestibular migraine)
- Social or occupational conditions and need for concentration
- Effect and side effects of the drug
- Patients inclination for losing-gaining weight

Classes of treatments used for migraine prevention

- Antiepileptic drugs (Na-Valproate, Topiramate, Gabapentin)
- Antidepressant drugs (TCA, SNRI)
- Beta blockers(propranolol, Metoral)
- Other antihypertensives(Verapamil, Lisinopril)
- Onabotulinum Toxin A
- CGRP monoclonal antibodies
- Nutritional and Herbal: Magnesium, Riboflavin, Co-Q10, Melatonin

TABLE 4-2 **Medications Used for Prevention of Migraine**

Medication	Target dosing[a]	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Divalproex sodium	250-500 mg 2 times a day or 500-1000 mg delayed release once daily	A	May cause thrombocytopenia or hepatotoxicity; monitoring is required; contraindicated during pregnancy; use limited by side effect burden despite efficacy
Topiramate	100 mg once daily or 50 mg 2 times a day	A	May cause weight loss, which some patients find beneficial; contraindicated in patients with nephrolithiasis
Metoprolol	50 mg 2 times a day	A	Unlikely to worsen asthma (highly cardioselective)
Propranolol	60 mg once daily or 2 times a day	A	Contraindicated in people with asthma; evidence that beta-blockers worsen depression has been challenged in recent years
OnabotulinumtoxinA	155 units subcutaneous monthly	A	Lack of systemic side effects and drug interactions makes this a high-priority option for patients with chronic migraine
Amitriptyline	50 mg nightly	B	Generally better tolerated when started at lower doses and increased slowly

Medication	Target dosing[a]	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Venlafaxine	75-225 mg extended release once daily	B	May worsen headaches in some patients; withdrawal syndrome can be prolonged and bothersome
Candesartan	8-16 mg once daily	C	Generally well tolerated
Lisinopril	10-40 mg once daily	C	Generally well tolerated
Cyproheptadine	4-8 mg once daily or divided 2 times a day	C	Use limited by sedation and weight gain
Gabapentin	900-3600 mg total daily dose, divided 3 times a day	U	Frequently used despite lack of clinical trial data; dose amounts and frequency have high variability
Verapamil	120-240 mg once daily	U	Frequently used despite lack of clinical trial data, likely because of the benign side effect profile
Memantine	10 mg 2 times a day	None	Generally well tolerated
Duloxetine	60 mg once daily	None	Used in place of venlafaxine because of decreased risk of withdrawal syndrome; better evidence for use in pain conditions globally
Levetiracetam	500-1000 mg 2 times a day	None	Recent evidence suggests possible benefit[11]
Nortriptyline	50 mg once daily	None	Used in place of amitriptyline because of decreased anticholinergic effects
Pregabalin	25-75 mg 3 times a day	None	Used if gabapentin is effective but not tolerated or loses efficacy

TABLE 4-5 **Herbal and Nutritional Supplements for Prevention of Migraine**

Name	Common dosing	Common side effects	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Magnesium	400-600 mg once daily or 200-300 mg 2 times a day	Diarrhea, nausea	B	Best studied/bioavailable formulations are magnesium oxide, magnesium gluconate/glycinate/aspartate (sometimes sold as chelated magnesium)
Riboflavin (vitamin B_2)	400 mg once daily	Diarrhea, frequent urination, yellow urine discoloration	B	Recent systematic review showed benefit in adults but not children[43]
Coenzyme Q10	300 mg once daily	None reported	C	Level C evidence in 2012 guidelines
Melatonin	3 mg nightly	Sedation, fatigue	None	Recent pediatric trial was positive; randomized controlled trial results in adults have been conflicting[44,45]
Feverfew	50-300 mg once daily	Nausea, bloating; avoid in people with allergies to ragweed or chamomile	B	Recent systematic review found conflicting evidence[46]
***Petasites* (butterbur)**	Use not recommended		A	Not recommended because of risk of hepatotoxicity

TABLE 4-3 **Preventive Medication Choices Based on Side Effects, Contraindications, and Comorbidities**

Area of concern	Consider	Avoid
Side effects[a]		
General	Verapamil and memantine well tolerated; lisinopril and candesartan if normal blood pressure	Valproate, topiramate, amitriptyline
Weight gain	Topiramate, venlafaxine	Valproate, amitriptyline, cyproheptadine
Fatigue/exercise intolerance	Topiramate, venlafaxine	Beta-blockers, amitriptyline, verapamil
Cognitive symptoms	Verapamil, lisinopril, candesartan, venlafaxine, memantine	Antiepileptic drugs
Contraindications		
Hypotension		Antihypertensive drugs
Nephrolithiasis		Topiramate, zonisamide
Possibility of pregnancy	Propranolol first line; amitriptyline, verapamil, coenzyme Q10 second line	Valproate, topiramate, lisinopril, candesartan, feverfew
Glaucoma		Topiramate (narrow-angle glaucoma), amitriptyline
Comorbidities		
Insomnia	Amitriptyline, melatonin	Memantine
Anxiety	Beta-blockers	Topiramate
Depression	Venlafaxine	Beta-blockers
Hypertension	Antihypertensive drugs	Erenumab, venlafaxine, duloxetine
Obesity	Topiramate	Valproate, amitriptyline
Frequent migraine aura	Verapamil, valproate, magnesium, topiramate	None identified

TCA not recommended in:

- Urinary retention
- Constipation
- Palpitation
- Epilepsy
- Obese patients
- Old age
- Hemiplegic migraine and migraine with brain stem aura

Beta blocker not recommended in:

- Asthma
- COPD
- AV block
- Raynaud’s disease
- Peripheral vascular disease
- Severe diabetes
- Impotence
- Depression
- Old age
- Hemiplegic migraine and migraine with brain stem aura

- The dose of rizatriptan must be adjusted downward in those taking propranolol, since propranolol increases rizatriptan dose by 70 percent.

SNRIs not recommended in

- Epilepsy
- Insomnia

Drug choice in Migraine associated with:

- Depression: TCA, SNRI
- Obesity: Topiramate (Avoid TCA and Sodium valproate)
- Insomnia (TCA, Avoid SNRI)
- Epilepsy (Topiramate and sodium valproate)

Short term preventive treatment:

- In certain situations like menstural migraine or migraine due to ascending to a high altitude:

- When menstruation is normal, administration of naproxen or a triptan with longer half-life starting 2 days prior to the expected start of migraine for 3-5 days

- A single dose of indomethacine is prescribed for exercise-induced headache.

Migraine in Pregnancy

- Headaches tend to be worst leading up to conception (presumably because of the discontinuation of treatment) and during the first several weeks postconception, a period of time when hormonal fluctuations and other symptoms of pregnancy can exacerbate migraine.

- With rising estrogen and endogenous opioid levels, migraine stabilizes as the pregnancy progresses, with up to 83% of women having improvement or complete resolution of migraine symptomatology by the third trimester.

- This improvement appears to be more common in women who have migraine without aura compared to those with aura

- Those who have aura may not have such a remission.
- Many studies have shown that women with a history of menstrually related migraine experience the most benefit during pregnancy
- Headache attacks aggravates in 5-10% of migraine patients during pregnany
- Headache attacks may have No change in 5-30% of migraine patients during pregnany

- The peripartum period is characterized by sudden drop in estrogen immediately following delivery, leading to a number of symptoms, including headache.

- More than one-third of women will experience the reappearance of migraine within 1 week postdelivery, and almost two-thirds will have an attack within a month.

- The attacks have been described as worse than those experienced during pregnancy, with reports of attacks both similar to or worse than prepregnancy attacks.

- The exacerbating effects of rapid estrogen drop can be ameliorated by breastfeeding. Lactating mothers experience ovulatory suppression because of elevated levels of prolactin, thereby limiting fluctuations in estradiol and resulting migraine. Furthermore, lactation is associated with secretion of vasopressin and oxytocin, which have antinociceptive properties likely to play a role in migraine inhibition.

- Sleep deprivation and other stressors of early motherhood and infant care should be addressed

Preventive Headache Therapies and Their Potential Safety Concerns in Pregnant Women

TABLE 7-3

Agent	Class	US Food and Drug Administration (FDA) Class[a]	Potential Risks and Comments
Magnesium oxide	Nutraceutical	Not ranked	Neonatal hypotonia, bone demineralization associated with IV use
Riboflavin	Nutraceutical	Not ranked	Largely unknown in typical migraine doses of 400 mg/d
Memantine	*N*-methyl-D-aspartate (NMDA) receptor antagonist	B	Unknown
Cyproheptadine	Antihistamine/serotonergic	B	Unknown
Propranolol (pindolol)	Beta-blocker	C (B)[b]	Intrauterine growth restriction
Amitriptyline	Tricyclic antidepressant	C	Limb reduction, cardiac defects, neonatal withdrawal
Verapamil	Calcium channel blocker	C	Intrauterine growth restriction, fetal bradycardia, tocolysis
Gabapentin	Antiepileptic	C	Unknown, but crosses placenta
OnabotulinumtoxinA	Neurotoxin	C	Largely unknown
Aspirin	Cyclooxygenase inhibitor	C/D	Safe <150 mg/d
Candesartan	Angiotensin receptor blocker	D	Renal agenesis, oligohydramnios, craniofacial and limb deformities
Topiramate	Antiepileptic	D	Oral cleft, hypospadias, low birth weight
Valproic acid	Antiepileptic	X	Neural tube defects, clefts, lower IQ and developmental delay, autism, cardiovascular and genitourinary abnormalities

Migraine prevention in pregnancy

- First line therapy in pregnancy: lowest dose of propranolol (gradually taper over 4 weeks before delivery and stop 3 days before child birth)

- Second line therapy: TCA (Amitriptylin > Nortriptylin 10-25mg per day) gradually taper over 4 weeks before delivery . No teratogenic effect at doses up to 50 has been reported)

- Safe: Verapamil and lamotrigine, cyproheptadine, melatonin, lidocaine, ropivacaine

- Cautions: SSRI (esp after 20 week), venlafaxine, Valproate, topiramate, gabapentin, bupivacaine

Migraine prevention in lactation

- The minimum effective dose should be administerd with carefuly monitoring the baby
- B-blockers are safe
- Small amounts of TCS (drowsiness and anticholinergic symptoms may occur in the infant)
- Seems safe: Valproate seems safe (should be avoided in childbearing age). Nerve lock. Low dose melatonin
- Caution: verapamil. SNRI. Topiramate. triamcinolone

TABLE 9-6 **Preventive Treatments Studied for Pediatric Migraine Prevention**

Treatment	Dose	Side effects	Comments	2019 AAN-AHS Guideline Comment[9]
Antiepileptics[9]				
Topiramate	2-3 mg/kg/d; typical dose 100 mg/d; maximum dose 200 mg/d	Paresthesia, anorexia, weight loss, fatigue, cognitive impairment, decreased perspiration Serious side effects: renal stones, depression, teratogenicity, angle closure glaucoma	Lowers potency of oral contraceptive pill, especially when more than 200 mg/d; recommend folic acid supplementation	Probably more likely than placebo to decrease frequency of headache days
Divalproex sodium	15-30 mg/kg/d up to 1000 mg/d	Nausea, weight gain, dizziness, somnolence, tremor, alopecia; monitor for thrombocytopenia, lymphopenia, elevated liver enzymes Serious side effects: pancreatitis, hyperammonemia, hepatotoxicity, teratogenicity	Recommend folic acid supplementation Not recommended for females of child-bearing age due to teratogenicity	Insufficient evidence
Zonisamide[109]	4-10 mg/kg/d, usual maximum 200 mg/d	Somnolence, anorexia, weight loss, paresthesia, dizziness, fatigue	Sometimes used if topiramate side effects intolerable	Not reviewed (no pediatric trials)
Levetiracetam[110]	20-40 mg/kg/d divided into twice daily dosing (usual maximum 3000 mg/d)	Somnolence, fatigue, irritability, behavior/mood change		Not reviewed (no pediatric trials)
Antidepressants[9]				
Amitriptyline	0.25-1 mg/kg/d (at bedtime)	Sedation, dizziness, dry mouth, weight gain; may cause prolonged QTc		Insufficient evidence when used alone; refer to entry for cognitive-behavioral therapy
Antihypertensives[9]				
Propranolol	20-40 mg 3 times a day	Sedation, hypotension, bradycardia, weight gain; may worsen depression and exercise-induced asthma		Possibly more likely than placebo to cause 50% reduction in headache frequency
Flunarizine[111]	5-10 mg at bedtime	Sedation, weight gain	Not available in the United States	Insufficient evidence
Cinnarizine	1.5 mg/kg/d for <30 kg; 50 mg/d for >30 kg	Sedation, weight gain	Not available in the United States	Probably more likely than placebo to decrease headache frequency
Nimodipine	10-20 mg 3 times a day	Abdominal discomfort		Insufficient evidence
Antihistamine[9]				
Cyproheptadine[112]	0.25-0.5 mg/kg/d, maximum 16 mg given either at bedtime or divided 2 times a day	Sedation, increased appetite, weight gain	Liquid dosing option, can also treat cyclic vomiting and gastrointestinal pain	Not reviewed (no pediatric migraine trials)
Toxin[9]				
OnabotulinumtoxinA	74 units or 155 units injected per PREEMPT protocol[113] every 12 weeks	Injection site pain, weakness, worsened headache		Insufficient evidence
Nutraceuticals[114]				
Riboflavin	50-400 mg/d either once daily or divided into two doses	Urine discoloration	Limited studies	Not included
Magnesium	Elemental magnesium 9 mg/kg/d with food (magnesium oxide divided 3 times a day; others used)	Diarrhea	Limited studies, some positive	Not included
Coenzyme Q10	1-3 mg/kg/d in the morning with food	Insomnia, gastrointestinal upset	Limited studies, some positive	Not included
Vitamin D	Studies have used 400 IU/d for children with normal blood level of Vitamin D; 800 IU/d for mild and 5000 IU/d for moderate Vitamin D deficiency	Well tolerated	Limited studies	Not included
Melatonin[115]	2-3 mg every day at bedtime	Sedation	Limited studies, some positive	Not included