Headache

- Headache may be a primary, or a secondary disorder due to an underlying medical condition.
- The International Headache Society (IHS) classifies primary headaches as **migraine**, **tension-type, or cluster and other trigeminal autonomic cephalalgias**.
- Tension-type headachesappear to be more common than migraine, and both are morecommon in women than in men. Cluster is a less commonchronic headache syndrome that affects predominantly men.
- The pain experienced with headache is likely due to overactivityin the trigeminovascular system of the brain.

❖ Cluster Headache and Other Trigeminal Autonomic Cephalalgias

Cluster headache disorders are the most uncommon and severe primary headache syndromes. Unlike migraine andtension-typeheadache(TTH), cluster headaches occur more frequently in men. Onset commonly occurs prior to age 30.
Pain associated with cluster headache differs from migraine andTTH in that it is severe, intermittent, and short in duration.Headaches typically occur at night, but attacks may occur multipletimes per day. The pain is usually unilateral, but unlikemigraine it is not described as pulsatile. Aura is not a feature.

Clinical Presentation and Diagnosis of Cluster Headache

Patients experiencing cluster headache may display the following headache symptoms and characteristics:
1. Unilateral pain
2. **Orbital**, **supraorbital**, or temporal pain
3. Sharp and stabbing pain

One or more of the following present:
1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or **rhinorrhea**
3. Eyelid edema

Duration of pain: 2 seconds to 10 minutes

Frequency of attacks: One or more per day more than half of the time
Criteria for diagnosis: Twenty or more attacks fulfilling the above criteria are necessary for diagnosis

TENSION-TYPE HEADACHE

Tension-type headache, the most common type of primary headache, is more common in women than men. Pain is usually mild to moderate and nonpulsatile. Episodic headaches may become chronic in some patients.

Tension-type headache pain differs from migraine pain in that it is usually reported to be mild to moderate, non-pulsating, and bilateral

PATHOPHYSIOLOGY

• Pain is thought to originate from myofascial factors and peripheral sensitization of nociceptors. Central mechanisms are also involved. Mental stress, nonphysiologic motor stress, a local myofascial release of irritants, or a combination of these may be the initiating stimulus.

CLINICAL PRESENTATIONand Diagnosis

Patients experiencing tension-type headache may display the following headache symptoms and characteristics:
Two or more of the following present:
1. Bilateral pain
2. Non-pulsating pain
3. Mild or moderate pain intensity

Both of the following present:
1. No nausea or vomiting (anorexia possible)
2. Either photophobia or phonophobia (not both)

Duration: 30 minutes to 7 days

Criteria for diagnosis:

Ten or more attacks fulfilling the above criteria occurring on average less than 1 day permonth are necessary for diagnosis

TREATMENT

- **Nonpharmacological therapies**

Stress management, relaxation training. Physical therapeutic options (eg, heat orcold packs, ultrasound, electrical nerve stimulation, massage) have performed inconsistently.

- **pharmacological therapies**

• **Simple analgesics** (alone or in combination with caffeine) and **NSAIDs** are the mainstay of acute therapy. **Acetaminophen**, **aspirin**, **diclofenac**, **ibuprofen**, **naproxen**, **ketoprofen**, and **ketorolac** are effective.

• High-dose NSAIDs and the combination of aspirin or acetaminophen with **butalbital**, or rarely, **codeine** are effective options. Avoid the use of butalbital and codeine combinations when possible.

• Consider preventive treatment if headache frequency is more than two per week, duration is longer than 3 to 4 hours, or severity results in medication overuse or substantial disability.
• The **TCAs** are used most often for prophylaxis of tension headache, but **venlafaxine**, **mirtazapine**, **gabapentin**, and **topiramate** may also be effective.
A novel therapy specific to cluster headaches is the administration of high-flow-rate oxygen: 100%at 5 to 10 L/minute by facemask for approximately15 minutes**No side effects** are seen with short-term oxygen use.
If oxygen therapy is not wholly effective, then pharmaceuticalsare useful as adjunctive therapy:

- ✓ The triptan classagents are safe and effective. Intranasal or subcutaneous sumitriptanhas demonstrated efficacy in decreasing clusterheadache pain.Oral triptans are also effective, but theirdelayed onset of action may limit their applicability in acutecluster headache treatment.
- ✓ Intranasal, intramuscular, or intravenous ergotamineagents are an alternative to triptan use
- ✓ Octreotide is a somatostatin analogue that has a shorterhalf-life, and it is available for subcutaneous administration

MIGRAINE HEADACHE

- Migraine, a common, recurrent, primary headache of moderate to severe intensity, interferes with normal functioning and is associated with gastrointestinal (GI), neurologic, and autonomic symptoms. In migraine with aura, focal neurologic symptoms precede or accompany the attack.
- **An aura** is a perceptual disturbance experienced by some with migraines or seizures before either the headache or seizure begins. It often manifests as the perception of a strange light, an unpleasant smell, or confusing thoughts or experiences.

PATHOPHYSIOLOGY

• Activation of trigeminal sensory nerves triggers the release of vasoactive neuropeptides, including calcitonin gene-related peptide, neurokinin A, and substance P from perivascular axons. Vasodilation of dural blood vessels may occur with extravasation of dural plasma resulting in inflammation.

• Specific populations of serotonin (5-HT) receptors appear to be involved in thepathophysiology and treatment of migraine headache. Ergot alkaloids and triptanderivatives are agonists of vascular and neuronal 5-HT1 receptors, resulting in vasoconstriction and inhibition of vasoactive neuropeptide release.

CLINICAL PRESENTATION AND DIAGNOSIS

• Migraine headache is characterized by recurring episodes of throbbing head pain, frequently unilateral.

• Neurologic symptoms (phonophobia, photophobia, hyperosmia, and difficulty concentrating) are most common, but psychological (anxiety, depression, euphoria, irritability, drowsiness, hyperactivity, and restlessness), autonomic (eg, polyuria, diarrhea, and constipation), and constitutional (eg, stiff neck, yawning, thirst, food cravings, and anorexia) symptoms may also occur.

• A migraine aura is experienced by approximately 25% of migraineurs. Aura evolves over 5 to 20 minutes and lasts less than 60 minutes. Headache usually occurs within 60 minutes of the end of the aura.

• Migraine headache may occur at any time but usually occurs in the early morning.

Pain is usually gradual in onset, peaking in intensity over minutes to hours and lasting 4 to 72 hours. Pain is typically is moderate to severe.

Headache is usually unilateral and throbbing with GI symptoms (eg, nausea and vomiting) almost invariably accompanying the headache. Other systemic symptoms include anorexia, constipation, diarrhea, abdominal cramps, nasal stuffiness, blurred vision, diaphoresis, facial pallor, and localized facial, scalp, or periorbital edema.

TREATMENT

• Goals of Treatment:

The goal is to achieve consistent, rapid headache relief with minimal adverse effects and symptom recurrence, and minimal disability and emotional distress, thereby enabling the patient to resume normal daily activities.

• Limit use of acute migraine therapies to fewer than 10 days per month to avoid development of medication-misuse headache.

Nonpharmacological Treatment

• Apply ice to the head and recommend periods of rest or sleep, usually in a dark, quiet environment.

• Identify and avoid triggers of migraine attacks.

• Behavioral interventions (relaxation therapy, biofeedback, and cognitive therapy) may help patients who prefer nondrug therapy or when drug therapy is ineffective or not tolerated.

Pharmacologic Treatment of Acute Migraine

•Administer acute migraine therapies at the onset of migraine.

TABLE 54–2 Dosing of Acute Migraine Therapies[a]

Drug	Dose
Analgesics	
Acetaminophen (Tylenol)	1,000 mg at onset; repeat every 4–6 hours as needed
Acetaminophen 250 mg/aspirin 250 mg/ caffeine 65 mg (Excedrin Migraine)	2 tablets at onset and every 6 hours
Nonsteroidal Antiinflammatory Drugs	
Aspirin	500–1,000 mg every 4–6 hours
Ibuprofen (Motrin)	200–800 mg every 6 hours
Naproxen sodium (Aleve, Anaprox)	550–825 mg at onset; can repeat 220 mg in 3–4 hours
Diclofenac (Cataflam, Voltaren)	50–100 mg at onset; can repeat 50 mg in 8 hours
Ergotamine Tartrate	
Oral tablet (1 mg) with caffeine 100 mg (Cafergot)	2 mg at onset; then 1–2 mg every 30 minutes as needed
Sublingual tablet (2 mg) (Ergomar)	
Rectal suppository (2 mg) with caffeine 100 mg (Cafergot, Migergot)	Insert 0.5 to 1 suppository at onset; repeat after 1 hour as needed

•Pretreatment with an antiemetic (eg, metoclopramide, chlorpromazine, or prochlorperazine)15to 30 minutes before oral or non-oral migraine treatments (rectalsuppositories, nasal spray, or injections) may be advisable when nausea and vomitingare severe. In addition to its antiemetic effects, metoclopramide helps reverse gastroparesisand enhances absorption of oral medications.

•Frequent or excessive use of acute migraine medications can result in increasing headache frequency and drug consumption known as *medication-overuse headache*.

This occurs commonly with overuse of simple or combination analgesics, opiates, ergotamine tartrate, and triptans. Limit use of acute migraine therapies to 2 or 3days per week.

❖ ANALGESICS AND NONSTEROIDAL ANTIINFLAMMATORY DRUGS

•Simple analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are firstlinetreatments for mild to moderate migraine attacks; some severe attacks are alsoresponsive. Aspirin, diclofenac, ibuprofen, ketorolac, naproxen sodium, and the combination of acetaminophen plus aspirin and caffeine areeffective.

•NSAIDs appear to prevent neurogenically mediated inflammation in the trigeminovascularsystem by inhibiting prostaglandin synthesis.

•In general, NSAIDs with a long half-life are preferred, as less frequent dosing isneeded. Rectal suppositories and intramuscular (IM) ketorolac are options forpatients with severe nausea and vomiting.

❖ ERGOT ALKALOIDS AND DERIVATIVES

•Ergot alkaloids are useful for moderate to severe migraine attacks. They are nonselective 5HT1 receptor agonists that constrict intracranial blood vessels and inhibitthe development of neurogenic inflammation in the trigeminovascular system. Venousand arterial constriction occurs. They also have activity at dopaminergic receptors.

•Ergotamine tartrate is available for oral, sublingual, and rectal administration. Oraland rectal preparations contain caffeine to enhance absorption and potentiate analgesia.Titrate to an effective dose that is not nauseating.

•Dihydroergotamine (DHE) is available for intranasal and parenteral (IM, IV, orsubcutaneous [SC]) administration. Patients can self-administer IM or SC DHE.

•Nausea and vomiting are common with ergotamine derivatives, so consider antiemeticpretreatment. Other common side effects include abdominal pain, weakness,fatigue, paresthesias, muscle pain, diarrhea, and chest tightness. Symptoms of severeperipheral ischemia (ergotism) include cold, numb, painful extremities; continuousparesthesias; diminished peripheral pulses; and claudication. Gangrenous extremities,myocardial infarction (MI), hepatic necrosis, and bowel and brain ischemia haveoccurred rarely with ergotamine. Do not use ergotamine derivatives and triptanswithin 24 hours of each other.

•**Contraindications** to use of ergot derivatives include renal and hepatic failure; coronary,cerebral, or peripheral vascular disease; uncontrolled hypertension; sepsis; andwomen who are pregnant or nursing.

•DHE does not appear to cause rebound headache, but dosage restrictions for ergotaminetartrate should be strictly observed to prevent this complication.

❖ SEROTONIN RECEPTOR AGONISTS (TRIPTANS)

• The **triptans** are appropriate first-line therapies for patients with mild to severe migraine or as rescue therapy when nonspecific medications are ineffective.
• They are selective agonists of the 5HT1B and 5HT1D receptors. Relief of migraine headache results from (1) normalization of dilated intracranial arteries, (2) inhibition of vasoactive peptide release
• **Sumatriptan**SC injection is packaged as an auto injectordevice for self-administration. Compared with the oral formulation, SC administration offers enhanced efficacy and more rapid onset of action. Intranasal sumatriptan also has a faster onset of effect than the oral formulation and produces similar rates of response.
• Second-generation triptans (all except sumatriptan) have higher oral bioavailability and longer half-lives than oral sumatriptan, which could theoretically reduce headache recurrence. However, comparative clinical trials are necessary to determine their relative efficacy.
• Lack of response to one triptan does not preclude effective therapy with another triptan.
• **Side effects** of triptans include paresthesias, fatigue, dizziness,flushing, warm sensations. Minor injection site reactions are reported with SC use, and taste perversion and nasal discomfort may occur with

intranasal administration.Up to 25% of patients report chest tightness; pressure; heaviness; or pain in the chest, neck, or throat. The mechanism of these symptoms is unknown, but a cardiac source is unlikely in most patients. Isolated cases of MI and coronary vasospasm with ischemia have been reported.

• **Contraindications** include ischemic heart disease, uncontrolled hypertension, and cerebrovasculardisease.

Do not give triptans within 24 hours of ergotamine derivative administration or within 2 weeks of therapy with monoamine oxidase inhibitors. Concomitant use of triptans with selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors can cause serotonin syndrome, a potentially life-threatening condition.

• **Use triptans cautiously in** patients at risk for unrecognized coronary artery disease. Do a cardiovascular assessment before giving triptans to postmenopausal women,men over 40 years of age, and patients with uncontrolled risk factors, and administerthe first dose under medical supervision

❖ **OPIOIDS**

• Reserve opioids and derivatives (eg, **meperidine**, **butorphanol**, **oxycodone**, and **hydromorphone**) for patients with moderate to severe infrequent headaches in whom conventional therapies are contraindicated or as rescue medication after failure to respond to conventional therapies. Closely supervise opioid therapy.

Pharmacologic Prophylaxis of Migraine

• Prophylactic therapies are administered daily to reduce the frequency, severity, and duration of attacks, and to increase responsiveness to acute therapies.Consider prophylaxis in the setting of recurring migraines that produce significantdisability; frequent attacks requiring symptomatic medication more than twice perweek; symptomatic therapies that are ineffective, contraindicated, or produce seriousside effects.

•Preventive therapy may also be given intermittently when headaches recur in a predictablepattern (eg, exercise-induced or menstrual migraine).

•Because efficacy of various prophylactic agents appears to be similar, drug selectionis based on side effect profiles and comorbid conditions. Response to an agent is unpredictable, and a 2- to 3-month trial is necessary to judge efficacy.

•**Only** propranolol, timolol, divalproex sodium, and topiramate are Food and DrugAdministration (FDA) approved for migraine prevention.

•Initiate prophylaxis with low doses, and advance slowly until a therapeutic effect isachieved or side effects become intolerable.
Continue prophylaxis for at least 6 to 12 months after headache • frequency and severity have diminished, and then gradual tapering or discontinuation may be reasonable

- **B-ADRENERGIC ANTAGONISTS**

•Propranolol, timolol, and metoprolol reduce the frequency of migraine attacks by50 %in more than 50% of patients. Atenolol and nadolol are probably also effective.β-Blockers with intrinsic sympathomimetic activity are ineffective.
•Broncho-constrictive and hyperglycemic effects can be minimized with β1-selectiveβ-blockers.
•Side effects include drowsiness, fatigue, sleep disturbances, vivid dreams, memorydisturbance, depression, sexual dysfunction, bradycardia, and hypotension.
•Use with caution in patients with heart failure, peripheral vascular disease, atrioventricularconduction disturbances, asthma, depression, and diabetes.

- **ANTIDEPRESSANTS**

•The tricyclic antidepressants (TCA) amitriptyline and venlafaxine are probablyeffective for migraine prophylaxis. There are insufficient data to support or refute theefficacy of other antidepressants.
•Their beneficial effects in migraine prophylaxis are independent of antidepressantactivity and may be related to downregulation of central 5HT2 and adrenergicreceptors.
•TCAs are usually well tolerated at the doses used for migraine prophylaxis, but anticholinergiceffects may limit use, especially in elderly patients or those with benignprostatic hyperplasia or glaucoma. Evening doses are preferred because of sedation.

- **ANTICONVULSANTS**

•Valproic acid, divalproex sodium (a 1:1 molar combination of valproate sodiumand valproic acid), and topiramate can reduce the frequency, severity, and durationof headaches.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs)**

Effective for reducing the frequency, severity, and duration of migraine attacks, but potential GI and renal toxicity limit daily or prolonged use.
• They may be used intermittently to prevent headaches that recur in a predictable pattern (eg, menstrual migraine). Treatment should be initiated 1 or 2 days before the time of headache vulnerability and continued until vulnerability is passed.

• For migraine prevention, evidence for efficacy is strongest for naproxen and weakestfor aspirin.

References

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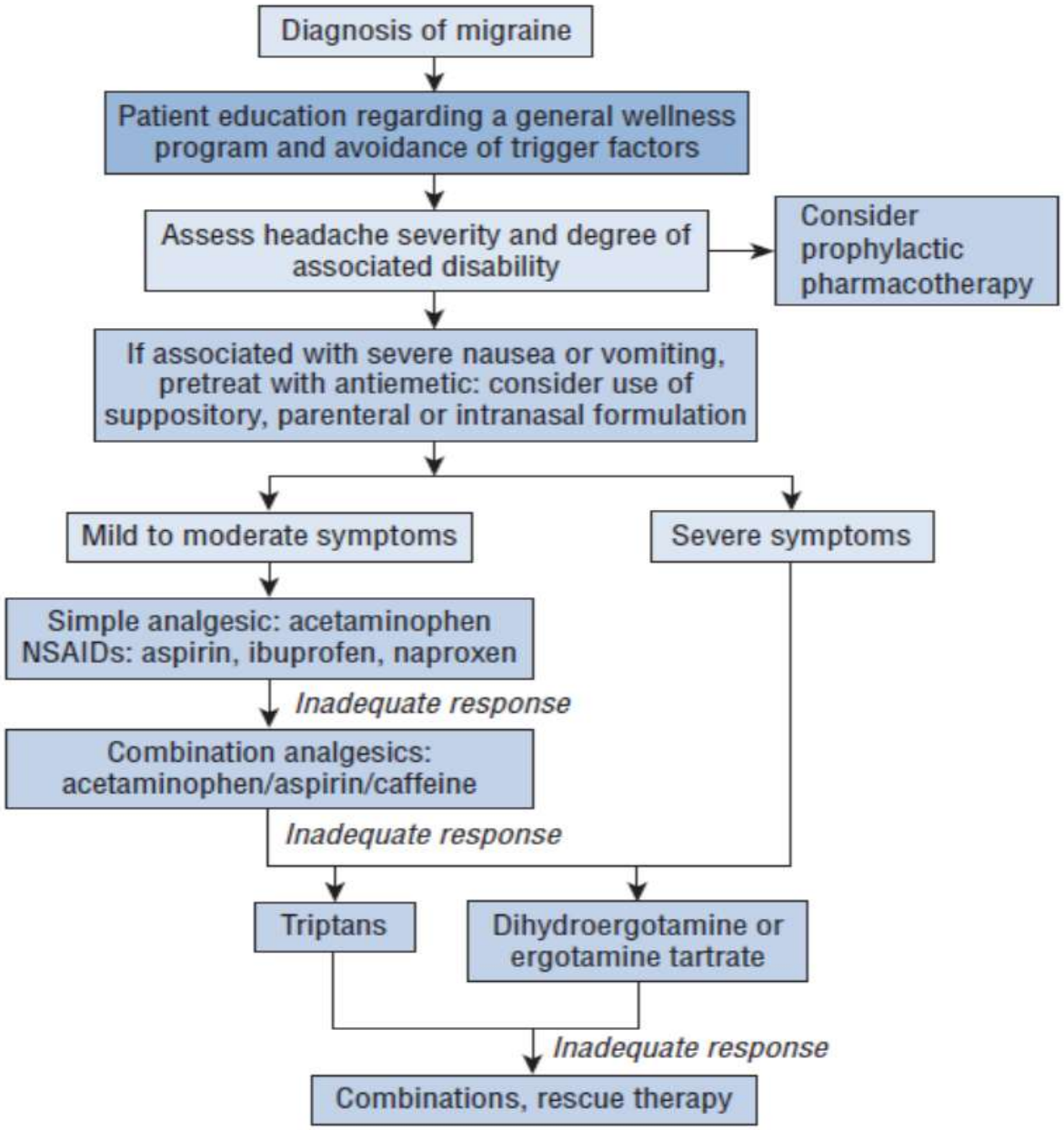

FIGURE 54–1. Treatment algorithm for migraine headaches.