

Therapy of Migraine

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Migraine Headache

- Mechanisms of migraine are not completely understood.
- **Vasodilation** of **intracranial extracerebral** blood vessels results in the **activation** of the perivascular **trigeminal nerves** that **release vasoactive neuropeptides** (calcitonin gene-related peptide (CGRP), neurokinin A, and substance P) from perivascular axons.
- The released neuropeptides interact with dural blood vessels to promote vasodilation and dural plasma extravasation, **resulting in neurogenic inflammation.**

Migraine Headache

- 5-HT receptors are also implicated in the pathophysiology of migraine headache.
- Activation of vascular 5-HT_{2B} and/or 5-HT₇ receptors may lead to dilation of cerebral blood vessels and concomitant activation of sensory trigeminovascular afferents and initiation of head pain.

Migraine Headache

- 5-HT₂ antagonists, pizotifen, prevent migraine attack from starting. (It is also an antihistamine).
- 5-HT₇ receptor antagonist may also reduce dural vasodilation.
- **Specific antimigraine drugs (ergot alkaloids and triptans)** are **agonists** at vascular and neuronal 5-HT₁ receptor subtypes, → **vasoconstriction of meningeal blood vessels and inhibition of vasoactive neuropeptide release and pain signal transmission.**

Nonpharmacologic Migraine Therapy

- Rest or sleep in a dark, quiet environment.
- Regular sleep, exercise, and eating habits, smoking cessation, and limited caffeine intake.
- **Identification and avoidance of migraine triggers.**
- Behavioral interventions such as relaxation therapy, biofeedback, and cognitive therapy, are preventive treatment options.

Nonpharmacologic Migraine Therapy

Commonly Reported Triggers of Migraine:

A. Food triggers:

- Alcohol
- Caffeine/caffeine withdrawal
- Chocolate
- Fermented and pickled foods
- Monosodium glutamate (in Chinese food, seasoned salt, and instant foods)
- Nitrate-containing foods (processed meats)
- Saccharin/aspartame (diet foods or diet sodas)
- Tyramine-containing foods

Nonpharmacologic Migraine Therapy

B. Environmental triggers:

- Glare or flickering lights
- High altitude
- Loud noises
- Strong smells and fumes
- Tobacco smoke
- Weather changes

C. Hormones:

- Changes in **estrogen** levels (menarche, menstruation, pregnancy, menopause, and oral contraceptive use) can trigger, intensify, or alleviate migraine. **A drop in estrogen precipitates attacks.**

Nonpharmacologic Migraine Therapy

D. Behavioral/Physiologic triggers:

- Excess or insufficient sleep
- Fatigue
- Menstruation, menopause
- Sexual activity
- Skipped meals
- Strenuous physical activity (prolonged overexertion)
- Stress or post-stress

Migraine Therapy

Goals of acute migraine treatment:

1. Terminate migraine attacks rapidly.
2. Reduce recurrence rate significantly.
3. Restore the patient's ability to function normally.
4. Cause **minimal** or **no** therapy-related adverse effects.

Migraine Therapy

Goals of long-term migraine treatment:

1. Reduce migraine frequency, severity, and disability.
2. **Reduce reliance** on poorly tolerated, ineffective, or unwanted acute pharmacotherapies.
3. Improve quality of life.
4. Prevent headache.
5. **Avoid escalation of headache-medication use.**
6. Educate and enable patients to manage their disease.
7. Reduce headache-related distress and psychological symptoms.

Migraine Therapy

General Approach to Treatment:

- Drug therapy is the mainstay of treatment for most patients.
- Pharmacotherapeutic management of migraine can be acute (**abortive**) or **preventive**.
- Coexisting illnesses can limit and/or dictate treatment choices.
- Abortive or acute therapies can be **migraine-specific** (ergots and triptans) or **nonspecific** (analgesics, antiemetics, nonsteroidal antiinflammatory drugs [NSAIDs], and corticosteroids).
- **These drugs are most effective when administered at the onset of migraine.**

Migraine Therapy

- Initial treatment is based on headache-related disability and symptom severity.
- It is advised to use **nonspecific agents** for **mild - moderate headache** NOT causing disability while reserving **migraine-specific medications** for more **severe attacks**.
- **The absorption and efficacy of orally administered drugs can be compromised by gastric stasis or nausea and vomiting that accompany migraine.**
- Therefore, pretreatment with antiemetic agents or the use of non-oral treatment (suppositories, nasal sprays, or injections) is advisable when nausea and vomiting are severe.

Migraine Therapy

Analgesics:

- Acetaminophen

Nonsteroidal antiinflammatory drugs:

- Aspirin, Ibuprofen, Naproxen, Diclofenac.

Ergot alkaloids:

- Ergotamine/caffeine, Dihydroergotamine

Serotonin agonists (triptans):

- Sumatriptan, Zolmitriptan, Rizatriptan, Almotriptan, Frovatriptan, Eletriptan.

Miscellaneous:

- Metoclopramide, Prochlorperazine.

Migraine Therapy

- The frequent or excessive use of acute migraine medications can result in medication-overuse headache (or rebound headache).
- In this case **the headache returns as the medication is eliminated**, leading to use of more drug for relief.
- The patient experiences a daily or near-daily headache with superimposed episodic migraine attacks.

Migraine Therapy

- Discontinuation of the offending agent leads to a gradual decrease in headache frequency and severity and a return of the original headache characteristics.
- Detoxification can be accomplished on an outpatient basis.
- Hospitalization may be necessary for the control of refractory rebound headache and other withdrawal symptoms (nausea, vomiting, asthenia, restlessness, and agitation).

Migraine Therapy

- Regulation of nociceptive systems and renewed responsiveness to therapy usually occur within 2 months following medication withdrawal.
- It is recommend to limit the use of acute migraine therapies to **< 10 days per month** to avoid the development of medication-overuse headache.
- Preventive migraine therapies are administered on a daily basis to reduce the frequency, severity, and duration of attacks and improve responsiveness to symptomatic migraine therapies.

Pharmacologic Management of Acute Migraine

Analgesics and NSAIDs:

- Simple analgesics and NSAIDs are effective and are first-line choice for treatment of **mild-to-moderate** migraine attacks.
- Of the NSAIDs, aspirin, diclofenac, ibuprofen, naproxen sodium, and the combination of acetaminophen plus aspirin / caffeine have demonstrated the most consistent evidence of efficacy.
- Acetaminophen alone is **NOT** generally recommended.
- They may have comparable efficacy to triptans in acute migraine.

Pharmacologic Management of Acute Migraine

- NSAIDs prevent inflammation in the trigeminovascular system through the inhibition of prostaglandin synthesis.
- Metoclopramide increases the absorption of analgesics and alleviate migraine-related nausea and vomiting.
- Suppository analgesic preparations are an option when nausea and vomiting are severe.
- Monitor for NSAIDs adverse reactions:
- Gastrointestinal (previous ulcer disease), CNS (somnolence, dizziness), renal disease, or hypersensitivity reactions, cardiovascular (hypertension, heart failure),

Pharmacologic Management of Acute Migraine

Antiemetics:

- **Adjunctive antiemetic therapy is useful for combating the nausea and vomiting of migraine headaches and that of medications used to treat attacks (ergotamine tartrate).**
- **A single dose of an antiemetic, such as metoclopramide, chlorpromazine, or prochlorperazine, administered 15 - 30 minutes before ingestion of oral abortive migraine medications is often sufficient.**
- **Metoclopramide is also useful to reverse gastroparesis and improve absorption from the GI tract during severe attacks.**

Pharmacologic Management of Acute Migraine

Ergot Alkaloids and Derivatives:

- **Ergotamine tartrate** and **dihydroergotamine** can be used in moderate-to-severe migraine attacks.
- They are nonselective 5-HT₁ receptor agonists that constrict intracranial blood vessels and inhibit the development of neurogenic inflammation in the trigeminovascular system.
- Ergotamine tartrate is available for oral, sublingual, and rectal administration.
- Oral and rectal preparations contain caffeine to enhance absorption and potentiate analgesia.

Pharmacologic Management of Acute Migraine

- Dihydroergotamine is available for intranasal, intramuscular, subcutaneous, and IV routes.
- Mixing with 1-2% lidocaine can reduce burning at the injection site.

Adverse effects:

1. Nausea and vomiting (resulting from stimulation of the chemoreceptor trigger zone) are among the most common adverse effects of the ergotamine derivatives. Therefore, their use requires pretreatment with antiemetic agents.

Pharmacologic Management of Acute Migraine

- 2. Abdominal pain, weakness, fatigue, paresthesias, muscle pain, diarrhea, and chest tightness (are common).**
- 3. Severe ischemia include: cold, numb, painful extremities, continuous paresthesias, diminished peripheral pulses, claudication and gangrenous extremities. Myocardial infarction, hepatic necrosis, and bowel and brain ischemia have also been reported.**

Pharmacologic Management of Acute Migraine

- 4. Ergotamine derivatives are contraindicated in patients with renal or hepatic failure; coronary, cerebral, or peripheral vascular disease; uncontrolled hypertension; and sepsis; and in women who are pregnant or nursing.**
- 5. Rebound headache: more with ergotamine tartrate than dihydroergotamine.**

Pharmacologic Management of Acute Migraine

Serotonin Receptor Agonists (Triptans):

- They represent a significant advance in migraine therapy.
- The first member of this class, sumatriptan, and the second-generation agents zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan are selective agonists at the 5-HT_{1B} and 5-HT_{1D} receptors.
- The triptans are appropriate first-line therapy for patients with mild to severe migraine and are used for rescue therapy when nonspecific medications are ineffective.

Pharmacologic Management of Acute Migraine

Relief of migraine headache is the result of three key actions:

- 1) Normalization of dilated intracranial arteries through enhanced vasoconstriction.**
- 2) Inhibition of vasoactive peptide release from perivascular trigeminal neurons.**
- 3) Inhibition of transmission through second-order neurons ascending to the thalamus.**

Pharmacologic Management of Acute Migraine

- Sumatriptan is available for subcutaneous, oral, and intranasal administration.
- Subcutaneous sumatriptan has a more rapid onset of action than the oral formulation.
- It is available as an autoinjector device for self-administration.
- Intranasal sumatriptan also has a faster onset of effect than the oral formulation.
- In general, triptans can be divided into those with a **faster onset and higher efficacy** and those with a **slower onset and lower efficacy**.

Pharmacologic Management of Acute Migraine

- Compared with other triptans, **frovatriptan and naratriptan** have the longest half-lives, the slowest onset of action, and less headache recurrence.
- Faster-acting triptans are more efficacious when a rapid onset is necessary.
- **Individual responses cannot be predicted, and if one triptan fails, a patient can be switched successfully to another triptan.**

Pharmacologic Management of Acute Migraine

Major Adverse effects:

1. Local adverse effects are subcutaneous injection site reactions and **taste perversion**, nasal discomfort after intranasal use.
2. “Triptan sensations,” including **tightness, pressure, heaviness, or pain in the chest, neck, or throat.**
3. Frequent use of the triptans has been associated with the development of medication-overuse headache.

Pharmacologic Management of Acute Migraine

Contraindications:

- 1. History of ischemic heart disease (angina pectoris, Prinzmetal's angina, or previous myocardial infarction), uncontrolled hypertension, cerebrovascular disease, and hepatic diseases.**
 - Postmenopausal women, men older than 40 years of age, and patients with uncontrolled risk factors should receive a cardiovascular assessment prior to triptan use and have initial doses administered under medical supervision.**
- 2. Hemiplegic and basilar migraine.**
- 3. Pregnancy.**

Pharmacologic Management of Acute Migraine

Drug Interactions:

- 1. The triptans should NOT be given within 24 hours of the ergotamine derivatives.**
- 2. Administration of sumatriptan, rizatriptan, and zolmitriptan within 2 weeks of therapy with monoamine oxidase inhibitors (MAOIs) is NOT recommended. (MAOIs slow triptan's metabolism).**
- 3. Eletriptan should NOT be administered with cytochrome P450 3A4 inhibitors such as macrolide antibiotics, antifungals, and some antiviral therapies.**

Pharmacologic Management of Acute Migraine

4. Concomitant therapy with the selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine, and mirtazapine) can potentially cause “**Serotonin syndrome**”.

Migraine Prevention

β-Adrenergic antagonists:

- Propranolol, Atenolol, Metoprolol XL, Nadolol.

Anticonvulsants:

- Topiramate, Valproic acid.

Antidepressants:

- Amitriptyline, Venlafaxine.

Nonsteroidal antiinflammatory drugs:

- Ibuprofen, Ketoprofen, Naproxen

Serotonin agonists (triptans):

- Frovatriptan, Naratriptan, Zolmitriptan.
- others

Migraine Prevention

Preventive therapy should be considered in the following cases:

- 1) Recurring migraines that produce significant disability despite acute therapy.**
- 2) Frequent attacks occurring more than twice per week with the risk of developing medication-overuse headache.**
- 3) Symptomatic therapies that are ineffective or contraindicated, or produce serious adverse effects.**

Migraine Prevention

- 4) Uncommon migraine variants that cause profound disruption and/or risk of permanent neurologic injury (hemiplegic migraine, basilar migraine, and migraine with prolonged aura).**
- 5) Preventive therapy also may be administered intermittently when headaches recur in a predictable pattern (exercise-induced migraine or menstrual migraine).**
- 6) Patient's preference.**

Migraine Prevention

- Only **propranolol, timolol, divalproex sodium, and topiramate** **have established efficacy**, although other agents may be effective.
- The selection of an agent typically is based on its adverse effect profile and the patient's coexisting comorbid conditions.
- **2 - 3 months are needed to achieve clinical benefit, but some reduction in attack frequency can be evident by the first month of therapy.**
- **Maximal benefits are typically observed by 6 months of treatment.**

Migraine Prevention

- Drug therapy **should be initiated with low doses** and gradually increased until a therapeutic effect is achieved or side effects become intolerable.
- Drug doses for migraine prophylaxis are often lower than those necessary for other indications.
- **Overuse of acute headache medications will interfere with the effects of preventive treatment.**
- Prophylactic treatment usually is continued for at least 6 - 12 months after the frequency and severity of headaches have diminished, then gradual tapering or discontinuation may be reasonable.

Prophylactic Pharmacologic Therapy of Migraine

β-Adrenergic Antagonists:

- Are among the most widely used drugs for migraine prophylaxis.
- Metoprolol, propranolol, and timolol reduce the frequency of attacks by 50% in greater than 50% of patients.
- Their precise mechanism of antimigraine action is unknown.

Prophylactic Pharmacologic Therapy of Migraine

Anticonvulsants:

- The anticonvulsants valproate, divalproex, and topiramate all having established prophylactic efficacy.
- They are particularly useful in patients with comorbid seizures, anxiety disorder, or bipolar illness.
- The benefits of topiramate are observed as early as 2 weeks after initiation of therapy, with significant reductions in migraine frequency within the first month.
- ~ 50% of patients treated have 50% or greater reduction in mean headache frequency.

Prophylactic Pharmacologic Therapy of Migraine

Nonsteroidal antiinflammatory drugs:

- Nonsteroidal antiinflammatory drugs are modestly effective for reducing the frequency, severity, and duration of migraine attacks.
- They can be used intermittently to prevent menstrual migraine.
- For migraine prevention, the evidence for efficacy is strongest for naproxen and weakest for aspirin.

Prophylactic Pharmacologic Therapy of Migraine

Triptans:

- Triptans are also useful for the **prevention of menstrual migraine.**
- Frovatriptan has established efficacy, while naratriptan and zolmitriptan are probably effective.
- The triptan is usually started 1 or 2 days before the expected onset of headache and continued during the period of vulnerability.