More Than Just A Headache:
Current and Upcoming Treatment Strategies For Managing Migraines

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Learning Objectives
• Recognize the signs and symptoms leading to a diagnosis of migraines, including the impact on quality of life
• Outline the non-pharmacologic and behavioral approaches for the treatment and/or prevention of migraines
• Review the current FDA approved pharmaceutical therapies used to treat migraines, including their mechanisms of action, efficacy, dosing, safety, and tolerability profiles
• Identify the novel classes of drugs currently in clinical trials for the treatment of migraines

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What is a migraine?
A chronic neurovascular disorder characterized by recurrent attacks of severe headache and autonomic nervous system dysfunction. One third of patients experience aura with neurologic symptoms.

What is aura?
Transient visual, sensory, language, or motor disturbances signaling the migraine will soon occur.

Criteria for Diagnosis of Migraine Without Aura
• The patient has at least five headaches lasting 4-72 hours each.
• The headaches have at least two of the following four characteristics:
   Unilateral location
   Pulsating quality
   Moderate or severe intensity
   Aggravation with walking, climbing stairs, or other physical activity
• During the headache, at least one of the following symptoms occurs:
   Nausea or vomiting
   Photophobia
   Phonophobia
Criteria for Diagnosis of Migraine With Aura

- The patient has at least two attacks with three of the following four criteria:
  - One or more completely reversible aura symptoms occur, indicating focal cerebral cortical or brain stem dysfunction (or both)
  - At least one aura symptom develops gradually (>4 minutes) or two or more symptoms occur in succession.
  - No aura symptom lasts > 60 minutes.
  - Headache follows aura in < 1 hour.
- There is no evidence of organic disease

Potential Migraine Triggers

- Allergies and allergic reactions
- Bright lights, loud noises, and certain odors or perfumes
- Physical or emotional stress
- Changes in sleep patterns or irregular sleep
- Smoking or exposure to smoke
- Skipping meals or fasting
- Alcohol
- Menstrual cycle fluctuations, birth control pills, hormone changes
- Tension headaches
- Foods containing tyramine (red wine, aged cheese, smoked fish, chicken livers, figs, and some beans), MSG, or nitrates
- Chocolate, nuts, peanut butter, avocado, banana, citrus, onions, dairy products, fermented or pickled foods.

What causes a migraine?

- Genetics and environmental factors both seem to play a role.
- May be caused by brainstem changes and its interactions with the trigeminal nerve, a major pain pathway. Imbalances in brain chemicals, including serotonin also may be involved.
- Serotonin levels drop during migraine attacks. This may trigger the trigeminal system to release neuropeptides, which travel to the brain's meninges, resulting in pain.

Non-Pharmacologic Treatments for Migraine

- Behavioral Treatments
  - Biofeedback therapy
  - Relaxation techniques
  - Cognitive-behavioral therapy
- Acupuncture
- Lifestyle Changes
  - Improving sleep habits
  - Avoid food triggers and eat regularly
  - Stay physically active
  - Limit estrogen-containing medications
- Herbs and Supplements
  - Riboflavin (Vitamin B2)
  - Magnesium supplements
  - Feverfew, fish oil, ginger
**Aims of Acute Migraine Treatment**

- Migraine contributes to sick days, productivity loss, and ER visits.
- In clinical trials, optimal acute migraine treatments determined by efficacy, tolerability, and safety profiles determined by end points from triptan trials.
- For acute treatment, patients ultimately want rapid long-lasting pain relief.
- Patient-centered measure: composite end point - sustained freedom from pain with no adverse events (SNAE), defined as:
  - Freedom from pain within 2 h
  - No use of rescue medication
  - No headache recurrence within 24 h
  - No adverse events.

**Preventive Treatments for Migraine**

- Following appropriate management of acute migraine, patients should be evaluated for initiation of preventive therapy.
- Preventative treatments should be considered if:
  - Patients are experiencing two or more migraines per month with disability lasting three or more days per month
  - Acute treatments fail, are contraindicated, or adverse events occur
  - Abortive medications are used more than twice per week
  - Patient have uncommon migraine conditions (e.g., hemiplegic migraine, migraine with prolonged aura, migrainous infarction).

**Preventive Medications**

- **Beta Blockers:**
  - Evidence consistently supports the use of propranolol in migraine prophylaxis
  - Timolol - comparable to propranolol
  - Limited evidence supports the use of atenolol, long-acting metoprolol, or nadolol for migraine prevention.
- **Antidepressants:**
  - Amitriptyline is a first-line agent - only antidepressant with consistent evidence supporting its effectiveness for this use.
- **Anticonvulsants:**
  - Divalproex & sodium valproate - well supported by evidence for use in migraine prevention.

Epidemiologic studies suggest approximately 38% of migraineurs need preventive therapy, but only 3%-13% actually use it.
Published studies from 1999-2009 were analyzed to classify the evidence relative to the efficacy of various medications available in the United States for migraine prevention.

- Challenging - substantial rates of nonresponse & difficulty in predicting individual response
- Use abortive therapy ASAP after symptom onset
- 1st line therapies for mild to moderate: NSAIDs & combo analgesics (APAP, aspirin, and caffeine)
- 1st line for moderate to severe: triptans
- IV antiemetics, with/without IV dihydroergotamine: effective in ER.
- Dexamethasone - useful adjunct in preventing recurrence.
- IN lidocaine, isometheptene and IN dihydroergotamine - acute relief
- Avoid opiates & barbiturates for acute migraine.
- During pregnancy, use APAP; NSAIDS (before 3rd trimester)
- APAP, ibuprofen, intranasal sumatriptan, and intranasal zolmitriptan seem to be effective in children and adolescents, (limited data).

Abortive Treatment: Nonprescription Medications

- Aspirin, acetaminophen, ibuprofen, and other aspirin-like analgesics can provide relief for mild-to-moderate migraines
- Combination products containing aspirin, acetaminophen, or both in combination with caffeine also have utility in abortive therapy.
- Caffeine
  - Has analgesic and possibly anti-inflammatory properties
  - May increase gastric acidity and perfusion, enhancing the absorption of aspirin
Abortive Therapy (cont.): Non-specific Prescription Medications

- Combination products containing an analgesic, caffeine, and butalbital or codeine are available (Fioricet, Fiorinal)
  - Butalbital useful for sedative properties
  - Excessive use can cause dependence and rebound headaches
- Combination of isometheptene (vasoconstrictor), dichloralphenazone (sedative), and acetaminophen useful for mild-to-moderate headaches (Midrin)
- Isometheptene also available in combo with acetaminophen and caffeine (Migraten)
- Opioids: Of the opioids, only butorphanol nasal spray shows evidence for efficacy
- IV metoclopramide (antiemetic), chlorpromazine, and prochlorperazine may be appropriate monotherapy in acute attacks, especially when nausea is significant

Ergot Alkaloids

- First specific antimigraine therapy available - use in the treatment of migraine has declined due to advent of triptans
- Generally regarded as a safe and useful drug for infrequent use; triptans = safer and more effective
- Useful in patients with status migrainous & patients with frequent headache recurrence
- Complex MOA, structural similarity with 5HT, DA, & epinephrine. Anti-migraine effect due to constriction of intracranial extracerebral blood vessels through 5-HT1B receptor, & inhibiting trigeminal neurotransmission by 5-HT1D receptors. Side effects arise from unwanted agonism at receptors.

Ergot Alkaloids (cont.)

- In RCTs oral ergotamine was found superior to placebo but inferior to oral sumatriptan 100mg.
- Rectal ergotamine - higher efficacy (73% headache relief) than rectal sumatriptan (63% headache relief).
- Intranasal dihydroergotamine (DHE) was found superior to placebo but less effective than SC and IN sumatriptan.
- The use of the triptans is preferable to the use of the ergotamine in the acute treatment of migraine.
  - If ergotamine is to be used the rectal route is preferable, dose should be tailored to the individual patient.
  - The IN dose of DHE (1 – 2 mg) should also be tailored to the individual patient.
  - In order to avoid drug induced headache ergotamine and DHE should not be used daily.

Daily use can lead to ergotism – a serious condition in which constriction of peripheral arteries causes severe tissue ischemia

Triptans serotonin 5-HT_{1B/1D} receptor agonists

- Significant progression from the ergots - target only the anti-migraine 5-HT_{1B} and 5-HT_{1D} receptors; have reduced or eliminated activity at most other monoamine receptor subtypes.
- One view of the triptans -really second generation ergot alkaloids
- Revolutionized the treatment of migraine
- Stimulated ground breaking research that gave insights into the anatomy, physiology, & molecular pharmacology of migraine.

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**Triptan Mechanism of Action**

- Action attributed to their agonist effects on serotonin 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors in cranial blood vessels.
- This leads to their constriction and subsequent inhibition of pro-inflammatory neuropeptide release.
- Act on serotonin receptors in nerve endings as well as the blood vessels - leads to a decrease in the release of several peptides, including CGRP and substance P.

**Contraindications for Triptan Therapy**

- Uncontrolled Hypertension
- Ischemic Heart Disease
- Prinz-Metal Angina
- Cardiac Arrhythmias
- Multiple Risk Factors for Atherosclerotic Vascular Disease
- Primary Vasculopathies
- Basilar and Hemiplegic Migraine

Intracranial blood vessels have a rich supply of 5-HT\textsubscript{1B} receptors. 5-HT\textsubscript{1B} receptors are also found to a smaller degree in the coronary arteries; hence, 5-HT\textsubscript{1B} agonists would cause some degree of vasoconstriction in the coronary arteries.

**The Triptans Are They Safe??**

- The Triptan CV Safety Expert Panel of the American Headache Society after reviewing dozens of studies and AE reports on triptans from the FDA, concluded that, while serious CV events have been reported, their occurrence appears to be on the order of less than one in 1 million.
- Such figures put triptans in a better safety position than OTC NSAIDs.
- Two recent studies found no evidence of increased risk of heart attacks, stroke or death in those who used triptans.

The risk of heart attack or sudden cardiac death for patients taking triptans is the same as the risk of these events occurring in the general population.
Differentiating the Triptans

- Meta-analysis using data of 24,089 patients in 53 controlled clinical trials of triptans:
  - All triptans contrasted to sumatriptan 100 mg & were more effective than placebo in relieving pain & symptoms of migraine.
  - Rizatriptan 10 mg and eletriptan 80 mg were significantly more effective than sumatriptan 100 mg in the primary endpoint -pain relief in 2 hours.
  - Sumatriptan - superior to naratriptan 2.5 mg, eletriptan 20 mg, and frovatriptan 2.5 mg. Pain free-rates at 2 h and over 24 h - higher for eletriptan 80 mg, almotriptan 12.5 mg, and rizatriptan 10 mg, compared to sumatriptan 100 mg.
  - Only triptans that presented lower rates of adverse events compared to sumatriptan 100 mg, were naratriptan 2.5 mg and almotriptan 12.5 mg.

Triptans Route of Administration

- Route of administration may play an important role in the onset of action and in the preference patterns of triptans.
- SC delivery of sumatriptan offers the most rapid and complete pain relief of the triptans - as early as 10 - 15 minutes, but is associated with a higher incidence of adverse events.
- Nasal deliveries also yield fast relief.
  - Sumatriptan nasal spray - not as effective as the SC form.
  - Zolmitriptan nasal spray - rapid onset & high response rates.
- All of the triptans available orally, and rizatriptan & zolmitriptan are also available in orally disintegrating tablets.

Triptans and Triptan Fixed-Dose Combination Products

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Form and dose (mg)</th>
</tr>
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<tbody>
<tr>
<td>Almotriptan</td>
<td>Axert®</td>
<td>Oral tablet (6.25 or 12.5)</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Relpax®</td>
<td>Oral tablet (20 or 40)</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Frova®</td>
<td>Oral tablet (2.5)</td>
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<td>Naratriptan</td>
<td>Amerge®</td>
<td>Oral tablet (1 or 2.5)</td>
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<tr>
<td>Rizatriptan</td>
<td>Maxalt®</td>
<td>Oral tablet (5 or 10)</td>
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<tr>
<td>Maxalt-MLT®</td>
<td></td>
<td>Orally disintegrating tablet (5 or 10)</td>
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<tr>
<td>Sumatriptan</td>
<td>Imitrex®</td>
<td>Oral tablet (25, 50, or 100)</td>
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<td>Imitrex®</td>
<td></td>
<td>Nasal spray (5 or 20)</td>
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<td>Imitrex®</td>
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<td>Subcutaneous injection (6 or 8)</td>
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<td>Treximet®</td>
<td>Oral tablet (85/500)</td>
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<td>Zolmitriptan</td>
<td>Zomig®</td>
<td>Oral tablet (2.5 or 5)</td>
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<td>Zomig Nasal Spray®</td>
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<td>Nasal spray (5)</td>
</tr>
<tr>
<td>Zomig-ZMT®</td>
<td></td>
<td>Orally disintegrating tablets (2.5 or 5)</td>
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Current Delivery Options for Migraine Treatment:

- Oral: conventional and rapid-release
  - ODTs can be taken when the patient is nauseated. They will not be absorbed if vomiting occurs soon after ingestion, but can be swallowed without water
- Rectal
- Nasal spray
- Injection – IV, SQ, IM

Specific Drugs with Novel Deliver Forms

- Sumatriptan
  - Needle-free injection (Sumavel®)
  - Epipen-type needle injection (Alsuma®)
- Rapid-dissolution oral tablets (Imitrex®-RT, Imigran® FDT, RRT, RADIS or RECOVERY)
- Soluble oral diclofenac (Cambia®, Volfast®)
- Intranasal ketorolac (Sprix®)
Additional delivery options under investigation:
• Novel rapid-release tablets
• Dissolvable liquid preparations
• Inhalational
• Transdermal

Why so many different dosage forms?
The nausea that accompanies migraine is indicative of gastroparesis. Orally administered drugs are inadequately absorbed by the GI tract. When the oral route is compromised, alternative delivery systems become necessary.

Limitations of the Triptans
• Largely underutilized, esp. by doctors worried about potential constrictive effects.
• 30-40% of patients in clinical trials do not respond to triptans.
• Long term adherence to a specific triptan is very low, due to triptan-specific side effects: chest pain, chest pressure, paresthesia, throat tightness, fatigue, diziness and myalgias.
  ▶ More common with injectable sumatriptan than with oral triptans
  ▶ The incidence of chest symptoms are lower with almotriptan.
  ▶ Newer triptans may have more central side effects: somnolence, dizziness and fatigue.
• Migraine is one of the most common co-morbid conditions for patients with psychiatric disease (depression and anxiety). Concern about the rare potential for serotonin syndrome with triptans and serotoninergic medications has further limited the use of triptans.

Dopamine Antagonists and Prokinetic Agents
• There is some evidence to suggest that dopaminergic system may be activated during the initial phases of migraine.
• The nausea and vomiting associated with migraine may also be due to activation of the dopaminergic system.
• Gastroparesis during acute attacks results in poor absorption. Prokinetic agents such as metoclopramide increase gastric motility and enhance absorption, in addition to being effective antiemetic drugs.
• Antidopaminergic agents used in acute migraine are IV chlorpromazine, IV prochlorperazine, metoclopramide, IV droperidol, and domperidone.

Other Agents for Acute Migraine
• Recent trial reports indicate IV diphenhydramine 50 mg is a useful agent in the ER.
• IV valproate sodium – very rapid effect in resolving a migraine attack – well tolerated & efficacy is comparable to that of DHE.
• IV MgSO4 has also been reported to be effective in relieving the symptoms of acute migraine.
• NSAIDS such as indomethacin reduce neurogenic inflammation in the trigeminal vascular system in experimental animals.
• Diclofenac potassium is as effective as oral ergotamine.
• One report indicated aspirin/metoclopramide – only slightly less effective than oral sumatriptan.
• Naproxen sodium (550 to 750 mg) effective in mild to moderate headache.
• IM ketorolac (60 mg) useful in acute attacks.
COX2 inhibitors may be an option, as they lack GI side effects.

Oral rofecoxib alone shown to be effective in producing pain-free status in 2 hours in 35% of patients with early intervention. (Vioxx – withdrawn from the market)

Combinations of triptans with COX2 inhibitors may enhance efficacy of both.

Opioids have no place in the routine management of acute migraines.

Opioids may be used in a controlled fashion when triptans are totally ineffective or when contraindicated.

Mixing opioids with DHE and triptans may nullify the effect of the later agents.

CGRP = neuropeptide product produced by alternative RNA splicing of the calcitonin gene. CGRP receptors found in areas of the brain associated with migraine.

Stimulation of the trigeminal ganglion can result in elevations of CGRP and substance P

- Only CGRP was significantly elevated in the external jugular veins in patients during an acute attack of migraine.

- Elevated levels of CGRP have been shown to be an early critical part of migraine pathophysiology.

- CGRP is closely involved in the cascade of molecular events leading to migraine painful crisis.

- These observations contributed to the development of CGRP receptor antagonists in the treatment of acute migraine attacks.

The CGRP-RA class is the first migraine specific class of medication that acts through a non-vasoconstrictive and non-serotonergic mechanism of action.

CGRP receptor antagonism began with discovery of high affinity antagonist BIBN4096 (olecegepant). Positive proof of clinical concept was reported with IV administration in spontaneous migraine.

Telcagepant was the first oral formulation of CGRP-RA to reach positive proof of concept, and was tested in an extensive phase 3 program.

Efficacy of telcagepant 300 mg and zolmitriptan 5 mg were similar. Adverse events = 37% for pts taking telcagepant 300 mg, 51% taking zolmitriptan 5 mg, and 32% taking placebo.

To date, five chemically unrelated CGRP receptor antagonists (olecegepant, telcagepant, MK-3207, BMS-922771 and BI 44370 TA) have displayed efficacy in the treatment of migraine.
CGRP Receptor Antagonists (cont.)

- When compared with triptans, CGRP class showed a similar efficacy.
- CGRP-R antagonists clinical trials seem to be discouraging for their forthcoming use in clinical practice.
- While there has been a decade long effort to discover orally available CGRP receptor antagonists, only a number of antagonists have been effective in clinical trials, and none has so far advanced to the market.
- The only CGRP RA still in active clinical trials is BMS-9227711

Latest Migraine Headlines

- Botox could be used as a treatment for migraine sufferers
- Florida Medical School offering inpatient treatments with DHE
- Health Union launches mobile app, Migraine Meter to help patients better monitor and manage migraines
- Two-drug combo helps teens with migraines
- IntelGenx achieves positive pivotal study results for bioequivalent anti-migraine VersaFilm formulation of Maxalt-MLT

Conclusions

- Pathogenesis of migraine is unclear but may be due to primary neural dysfunction originating in the CNS.
- Non-opioid analgesics are effective abortive therapy for mild-to-moderate pain, opioids are reserved for severe migraines unresponsive to other therapies.
- Ergotamine is useful for abortive therapy on a limited basis.
- Triptans are the DOC for abortive therapy of migraines.
- Propranolol, amitriptyline, divalproex sodium, timolol, and topiramate are all effective for preventative therapy.
- The most promising class of drugs in clinical trials for migraine are the CGRP receptor antagonists.