Migraine Headache Part 2: Acute Treatment

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Potential Conflict of Interest Disclosure Statement

My spouse works for Amgen, Inc

I do not receive any direct remuneration or funding from Amgen, Inc

Objectives

Discuss the prevalence of migraine and its debilitating effects.

Explain current thinking regarding the pathophysiology of migraine.

Characterize the symptoms, diagnosis & classification of migraine.

Identify common migraine triggers and aggravating factors.

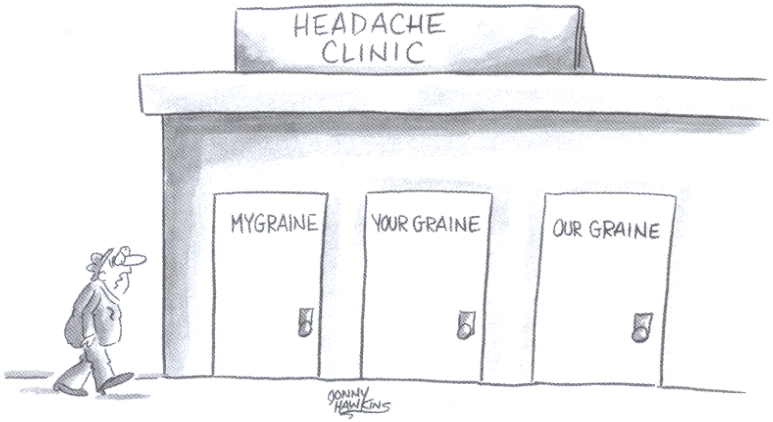
Discuss the safe and effective use of pharmacologic and non-pharmacologic therapies for alleviating migraine attacks.

Compare and contrast pharmacologic treatment therapies (e.g. route of administration, onset of action, time to relief).

Discuss therapeutic strategies for migraine prevention.

Choose an appropriate therapeutic regimen based on an individual migraine patient's history and needs.

Managing the Migraine Patient



Acute/abortive

Symptomatic – N/V

Preventive

Acute Treatment Goals

Rapidly relieve attack

Consistently relieve attack

No recurrence

Restore ability to function

Minimize need for back-up/rescue medications

Optimize self-care

Cost-effective

Minimize or avoid adverse effects

US Headache Consortium: 2000

Non-Pharmacologic Strategies in Headache Management

- Biofeedback
- Progressive relaxation training
- Cool compress
- Rest in a cool, dark, quiet environment
- Hydrate
- Acupuncture
- Headache diary to facilitate identification of specific triggers to avoid

COMPLEMENTARY TREATMENTS

- Level A:

  Standardized Butterbur Extract - Petasites (75mg BID)
- Level B:

  Feverfew

  Magnesium oxide (500mg/d)

  Riboflavin(B2) (400mg/d)
- Level C:

  Coenzyme Q-10 (300mg/d)

Holland et al, *Neurology* 2012;78:1346-53.

Acute Outpatient Migraine Medications

Treatment choice may depend on migraine severity[2,3]

Nonspecific Analgesics:
mild to moderate HA

Acetaminophen/aspirin/caffeine

Aspirin (900-1000mg dose; 24% 2-hr relief)

Ibuprofen

Naproxen

Opiates* (also *RESCUE*)
Butorphanol (nasal spray), tramadol (oral)

Acetaminophen with codeine/hydrocodone/tramadol

NOTE: no butalbital-containing analgesics

Specific:
moderate to severe HA

Triptans

Ergotamine derivatives

*Not recommended as first-line treatment options and AHS recommends against using barbiturates and opioids for the treatment of migraine.

1. Marmura MJ, et al. *Headache*. 2015;55:3-20. 2. American Headache Society. *Headache*. 2019;59:1-18. 3. Silberstein SD. *Neurology*. 2000;55:754-762. 4. Kirthi V, et al. Cochrane Database 2010, Issue 4. Art. No.: CD008041.

Approaches to Acute Migraine in the Emergency Setting

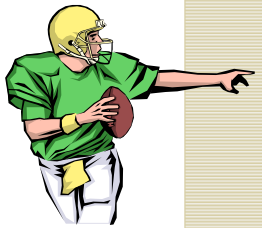
- Sumatriptan 6mg SQ (+/- dexamethasone 10-25mg IV or IM)
- Metoclopramide 10mg (or 20mg single agent) IV*
- Prochlorperazine 10mg IV or IM (+/- diphenhydramine 12.5-25mg IV to prevent akathisia)
- Chlorpromazine range 0.1mg/kg IV to total dose of 25mg IV*
- DHE 45 (1mg IV) with metoclopramide (10mg IV)
- Ketorolac 30mg IV or 60mg IM

NOTE: opioid overuse in US, likely return in 7 days; ondansetron and granisetron not rigorously studied and adverse effect of associated headache

Dihydroergotamine (DHE)

High affinity for serotonin-1 b/d receptors, also interact with alpha adrenergic, beta-adrenergic, dopaminergic, and serotonin-3 receptors

Adverse effects: **N/V**, diarrhea, and vasoconstriction of systemic and coronary arteries



DHE dosage forms: nasal spray and injection

- 1 spray (0.5mg) in each nostril, repeat 15 min later (4 spr to prime)
- 1mg IM, SC, IV at onset, then 1mg at 1hr intervals prn, NTE 3mg IM or SC or 2mg IV or 6mg/wk IM or IV

Most effective at first sign of migraine

Risk of stroke and/or gangrene when taken with certain antibiotic, antiviral and antifungal drugs (CYP3A4 inhibitors)

Classification of 5-HT Receptors

$5\text{-HT}_{1B,1D,1F}$

Neuronal inhibition of central nervous system (CNS) neurons, smooth muscle relaxation, contraction of some vascular smooth muscle

5-HT_2

Neuronal depolarization, vasoconstriction of most blood vessels, bronchoconstriction, contraction of gastrointestinal smooth muscle, platelet aggregation

5-HT_3

Neuronal depolarization leading to activation of autonomic reflexes, neuronal excitation in the CNS, GI symptoms (N&V)

5-HT_1 agonists – Treatment

5-HT_2 antagonists – Prevention

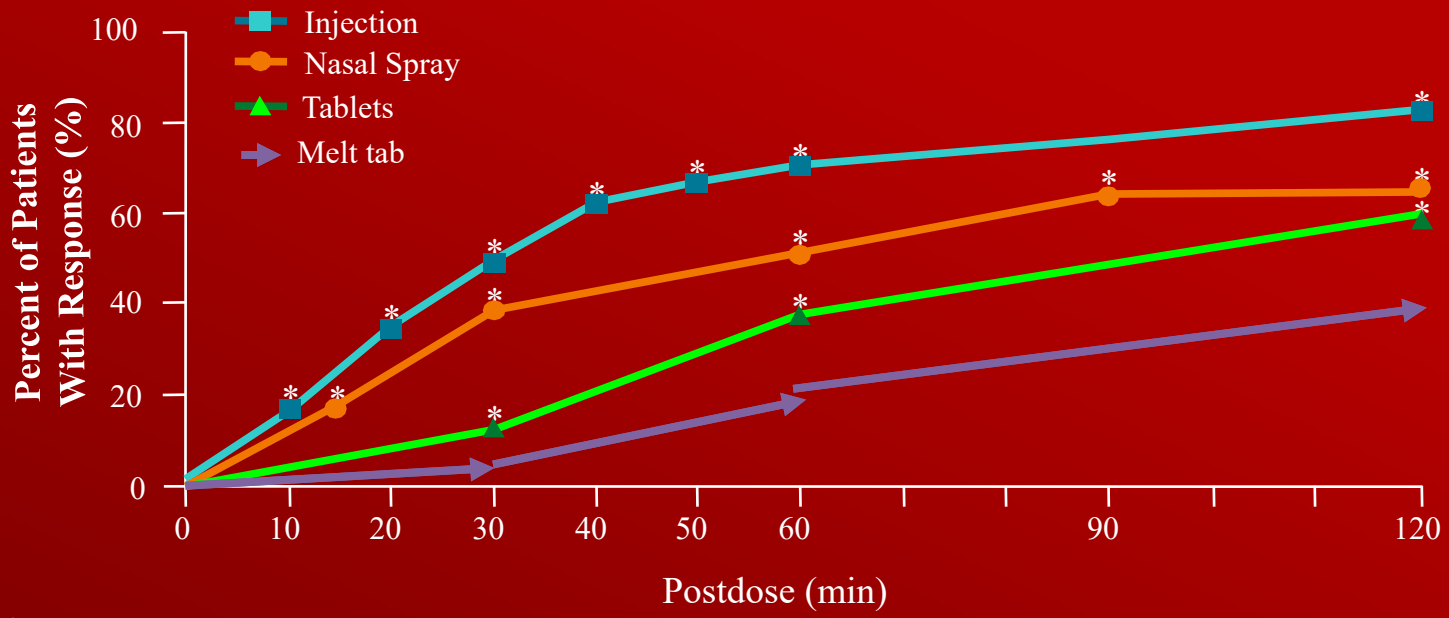
5-HT_3 antagonists – N/V

Triptan (5HT 1B, D, F) Pharmacology

	Drug	$t_{1/2}$ (h)	T_{max} (h) Before Attack	T_{max} (h) During Attack	Bioavail-ability (%)	Cranio-vascular Selectivity	CNS Penetration: Lipophilicity	CNS Penetration: PGP Substrate
B,D	**Sumatriptan**	2	2	2.5	15#	✓	-1.3 (min)	No
B,D	**Zolmitriptan**	3	1.5/3*	2.5	40	✓	-1.0	No
D,F	**Naratriptan**	6	2-3	3-4	70	✓	-0.3	Yes
D	**Rizatriptan**	2	1-1.5/1.6-2.5*	1-1.5	42	✓	-0.7	Yes
D	**Almotriptan**	3.5	1-3	2.6±1.5	70	✓	?	Yes
D	**Frovatriptan**	25	3	3	30	✓	? (low)	?
B,D,F	**Eletriptan**	4	1.5	2.8	50	✓	0.5	Yes
F	**Lasmiditan**	5.7	1.8	2.8	22	Low HR	CNS depression	

*oral/melt #oral – not RT/nasal (SC higher bioavailability)

Speed of Effect – Comparisons Among Formulations



*$P<0.05$.

Pfaffenrath et al. *Headache*. 1998;38:184-190. Peikert et al. *Eur J Neurol*. 1999;6:43-49.
Cady et al. *JAMA*. 1991;265:2831-2835.

Only use 2nd dose if some response to 1st dose

Triptans: Usual Adult Dosage

Almotriptan (Axert) Oral tablet

- 6.25-12.5mg at onset; may repeat after 2 hr, NTE 2 doses in 24 hours

Eletriptan (Relpax) Oral tablet

- 20-40mg at onset, may repeat 2 hr, NTE 80mg in 24 hr

Frovatriptan (Frova) Oral tablet

- 2.5mg at onset, may repeat 2 hr, NTE 7.5mg in 24 hr

Lasmiditan (Reyvow) C-V Oral tab

- 50, 100, or 200mg tab at onset. NTE one dose in 24 hours Do not drive for 8 hrs

Naratriptan (Amerge) Oral tablet

- 1-2.5mg at onset, may repeat 4 hr, NTE 5mg in 24 hr

Rizatriptan (Maxalt, Maxalt MLT)

Oral conventional & disintegrating tabs

- 5 or 10mg at onset; may repeat intervals of at least 2 hr, NTE 3 doses in 24 hr

Sumatriptan (Imitrex)

- **Oral tablet:** 25, 50mg or 100mg at onset; may repeat after 2 hr, NTE 200mg/d
- **Nasal spray:** (5 or) 20mg IN at onset; may repeat after 2hr if needed, NTE 40mg/d
- **Tosymra (w/permeation enhancer)** 10mg IN; may repeat after 1 hr, max of 30mg in 24 hrs.
- **Nasal powder (Onzetra Xsail)** 22mg at onset (11mg capsule in nosepiece: 1 in each nostril); may repeat in 2 hrs, NTE 44mg/day
- **Injection (Imitrex, Sumavel; Zembrace 3mg)** 4mg or 6mg SC at onset; may repeat after 1 hr, NTE 12mg/day

Sumatriptan/naproxen (Treximet) oral tab

- 85mg/500mg tab at onset, may repeat 2 hr. NTE 2 tablets in 24 hr.

Zolmitriptan (Zomig, Zomig ZMT)

- **PO conventional & disintegrating tabs** 2.5-5mg at onset, may repeat 2 hr, NTE 10mg in 24 hr
- **Nasal Spray** 5mg IN at onset, may repeat after 2 hr if needed, NTE 10mg in 24 hr


IMITREX
SUMATRIPTAN SUCCINATE
NDC 0173-0406-00
IMITREX
SUMATRIPTAN SUCCINATE
INJECTION
GlaxoWellcome
0.5 mL
PROFESSIONAL SAMPLES —
NOT FOR SALE

How to use SUMAVEL® DosePro®

STEP 1

Snap the tip off firmly

STEP 2

Flip the green (6mg) or lavender (4mg) lever down to get it ready

STEP 3

Pinch your stomach or thigh and PRESS against your skin to deliver the medicine

What to expect when you use SUMAVEL® DosePro®

Sound

When you break the tip, it may feel and sound like the snapping of a carrot. There is a sound when you deliver the medicine that is similar to the opening of a soda can.

Site Sensation

Needle-free doesn't mean you won't feel anything. Expect to feel something like the snapping of a rubber band against your skin

Site Reactions

You may experience some bleeding, swelling, redness, or bruising at the delivery site. In clinical trials, no one stopped using SUMAVEL® DosePro® because of site reactions

Check the Tip

Make sure the snap-off tip is firmly attached. Don't use it if it's already snapped off or tilted.

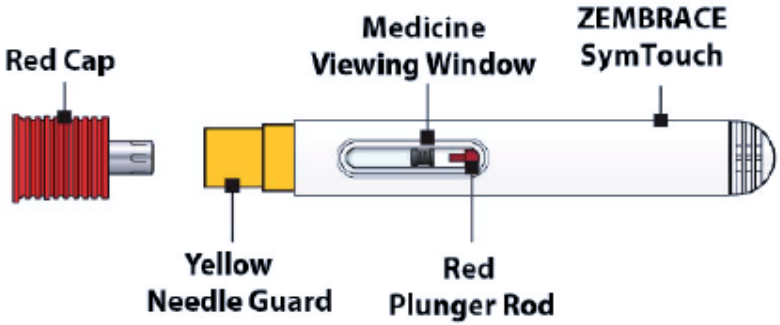
Check the Medication Chamber

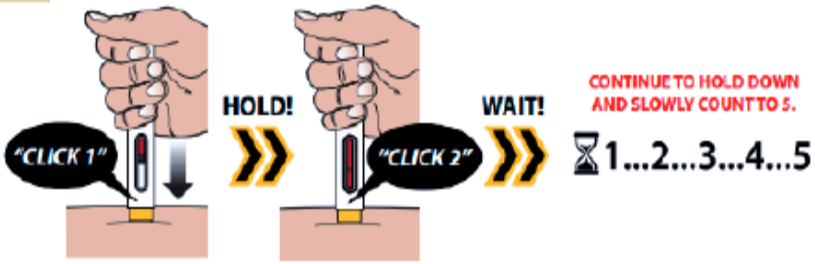
The medicine inside should be colorless or pale yellow. Don't use it if it's dark or cloudy.

Check the Expiration Date

It's printed on both the SUMAVEL® DosePro® label and the carton. Do not use SUMAVEL® DosePro® if the medicine is expired.

Zembrace Symtouch (sumatriptan 3mg) Injection



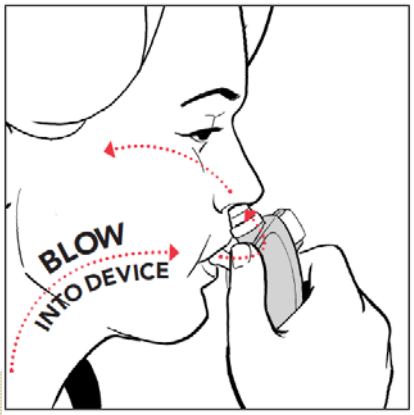


Imitrex 5 or 20mg
Nasal Spray Unit

Tosymra 10mg
Nasal Spray Unit

Zomig 2.5 or 5mg
Nasal Spray Unit

Onzetra Xsail (sumatriptan 11mg) nasal powder



You blow with your mouth into the device to deliver medication into your nose.

Contraindications and Precautions for ALL TRIPTANS

Ischemic heart disease: angina, Hx of MI, documented silent ischemia

Coronary vasospasm (including Prinzmetal's angina)

Multiple risk factors for CAD, unless workup is fully negative

Uncontrolled hypertension

Hypersensitivity

Use within 24hrs of an ergot or another $5HT_1$ agonist

Hemiplegic/basilar migraine

Severe hepatic impairment (& severe renal: naratriptan, almotriptan)

Pregnancy (Category C – compared to nonmigraine cohort, rates of major birth defects, abortions and preeclampsia not increased with exposure to triptans during pregnancy; however, a safe duration and amount of exposure is unclear. Cephalgia 2018 Practice Update O. Khan)

Concurrent administration of MAOIs (or use within 2 weeks)-except eletriptan (3A4), almotriptan, naratriptan, Lasmiditan (2D6)

SSRI precaution (weakness, hyperreflexia, & incoordination in combo)

Triptan Drug Interactions

MAO Inhibitors: avoid within 2 wks of DC MAOI Tx

Exception: eletriptan, frovatriptan, naratriptan, lasmiditan

Ergots: avoid use within 24 hours of triptan therapy

Serotonin Syndrome *potential* with Selective Serotonin Receptor Inhibitors (SSRIs) and SNRIs (St John's Wort)

Oral Contraceptives *potential* increase in triptan conc

Propranolol/Rizatriptan Interaction:

Propranolol can increase plasma concentrations by 70%. Rizatriptan 5mg should be used.

Cimetidine/Zolmitriptan Interaction: Use zolmitriptan 2.5mg

Eletriptan (CYP3A4): Avoid nefazodone, clarithromycin, azoles and grapefruit juice

Common Triptan Side Effects

Tingling

Warmth

Flushing

Chest and neck pressure/discomfort

Dizziness, somnolence

Abnormal taste with nasal formulations

Injection site burning with sumatriptan injection

Patients should report chest pain

Choices for Acute Specific Migraine Treatment

Patient Appropriate for 5-HT_1 Therapy

Max Efficacy & Speed	Speed & Non-Oral	Convenience & Flexibility	Tolerability & Duration
Sumatriptan Injections	Sumatriptan Zolmitriptan Nasal Sprays & Powder	Sumatriptan Zolmitriptan Rizatriptan Almotriptan Eletriptan Tablets	Naratriptan Frovatriptan Tablets

Alternative Options

Lasmiditan C-V
Ubrogepant
Rimegepant

The best triptan is the one that works!

CGRP Antagonists (once daily dosing) for Acute Migraine Treatment

Ubrogepant (UBRELVY)

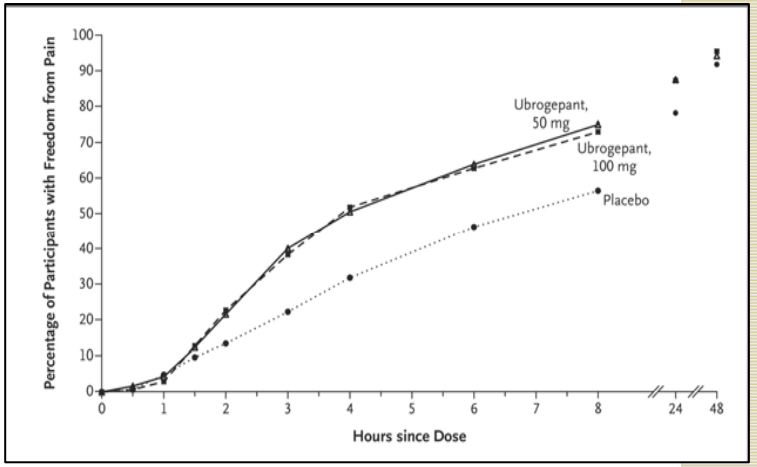
Approved Dec 2019

- Placebo vs 50mg vs 100mg
- Pain free at 2hrs: 12%/19%/21%
- Absence of most bothersome migraine-associated symptom*: 28%/38%/39%
- Side effects: nausea, somnolence, dry mouth

Rimegepant (NURTEC-ODT)

Approved Feb 2020

- Placebo vs 75mg
- Pain free at 2 hrs: 11% vs 22%
- Absence of bothersome symptom*: 27% vs 35%



Dodick DW etal NEJM 2019;381:2230-41.
*bothersome symptom predefined as photophobia, phonophobia or nausea
Croop R et al. Lancet 2019;394:737-45.

Due to short term, single-attack trial designs, long-term data are needed to determine safety and tolerability. Efficacy vs triptans unknown. May be option for patients with CV risk factors.

What specific agent would you recommend?

- Minimal nausea
- Pain score: 7 (moderate)
- Tried naproxen 220mg tablet 2 hours ago – no relief
- Usual HA: 8-24 hrs
- Placebo week of COCs
- Triggers: red wine, stress, barometric pressure changes

Write down the drug and route you would recommend.

Overuse of Acute Medications May Cause Medication Overuse Headache (MOH)

Acute medications are used by ~ 98% of individuals with migraine[1]

Acute medication overuse may lead to development of MOH.[2-4]
~ 50% of patients with ≥ 15 headache days per month for more than 3 months have MOH[5]

The global prevalence ranges from 0.7% to 1.7%[6]

It is important to ensure that patients do not overuse acute medications, as this may lead to the development of MOH[7,8]

MOU, medication overuse.

1. Diamond S, et al. *Headache*. 2007;47:355-363. 2. Kristoffersen ES, Lundqvist C. *Ther Adv Drug Saf*. 2014;5:87-99. 3. Kristoffersen ES, Lundqvist C. *J Pain Res*. 2014;7:367-378. 4. Cupini LM, Calabresi P. *J Headache Pain*. 2005;6:199-202. 5. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211. 6. Evers S, Jensen R. *Eur J Neurol*. 2011;18:1115-1121. 7. American Headache Society. *Headache*. 2019;59:1-18. 8. Marmura MJ, et al. *Headache*. 2015;55:3-20.

Medication Overuse by Drug Class, Presentation & Management

Acute medication overuse is generally defined by the number of days in which a patient uses a particular acute medication per month, and each class has a specific threshold[1]

MOH presents as more tension-type HAs where pain is mild-moderate, dull, non-throbbing, bilateral and usually not associated with migraine-type symptoms.

Non–migraine-specific	**Simple analgesics**	**≥ 15** days per month for > 3 months[1]
	Combination pain relief	**≥ 10** days per month for > 3 months[1]
	Opioids*	**≥ 10** days per month for > 3 months[1]
Migraine-specific	**Triptans and ergotamine derivatives**	**≥ 10** days per month for > 3 months[1]

Management:
Limit weekly use +/- withdraw the offending agent.
Refer to HA specialist to detoxify.

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
2. Marmura MJ, et al. *Headache*. 2015;55:3-20. 3. Data on file, Amgen; [Study 20170150, AMG 334].

Devices for the Acute Treatment of Migraine

External vagal nerve stimulator[1]

- Vagus nerve stimulation applied on the side of the neck for the acute treatment of pain associated with migraine

External trigeminal nerve stimulator[2]

- Trigeminal nerve stimulation applied on the forehead for the acute treatment of pain associated with migraine

Trunk and limb electrical stimulator[3]

- Electrical stimulation is applied anywhere on the body (excluding head or neck) via electrodes placed on the skin and may be provided transcutaneously or percutaneously

Transcranial magnetic stimulator[4]

- A single pulse of magnetic energy is delivered to the back of the head to induce an electrical current in the occipital cortex to cease or lessen the effects of migraine

1. Gammacore Sapphire 510(k) summary. Electrocore. 2018. 2. Cefaly Technologies. TENS device 510(k) Summary. 2012. 3. Nerivio Migra De Novo summary. Theranica. 2019. 4. TMS device. 510(k) FDA Approval Letter. eNeura Therapeutics. May 21, 2014

Summary for Acute Treatment

Use migraine-specific agents (triptans, DHE, ergots) in patients with moderate-severe migraine and those whose migraines respond poorly to NSAIDs or combination analgesics

Use a non-oral route for early or significant N/V

Consider self-administered rescue medication for severe or unresponsive migraine

Guard against medication overuse headache

Educate patients!