Migraine Headache Part 3: Preventive Therapies

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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.

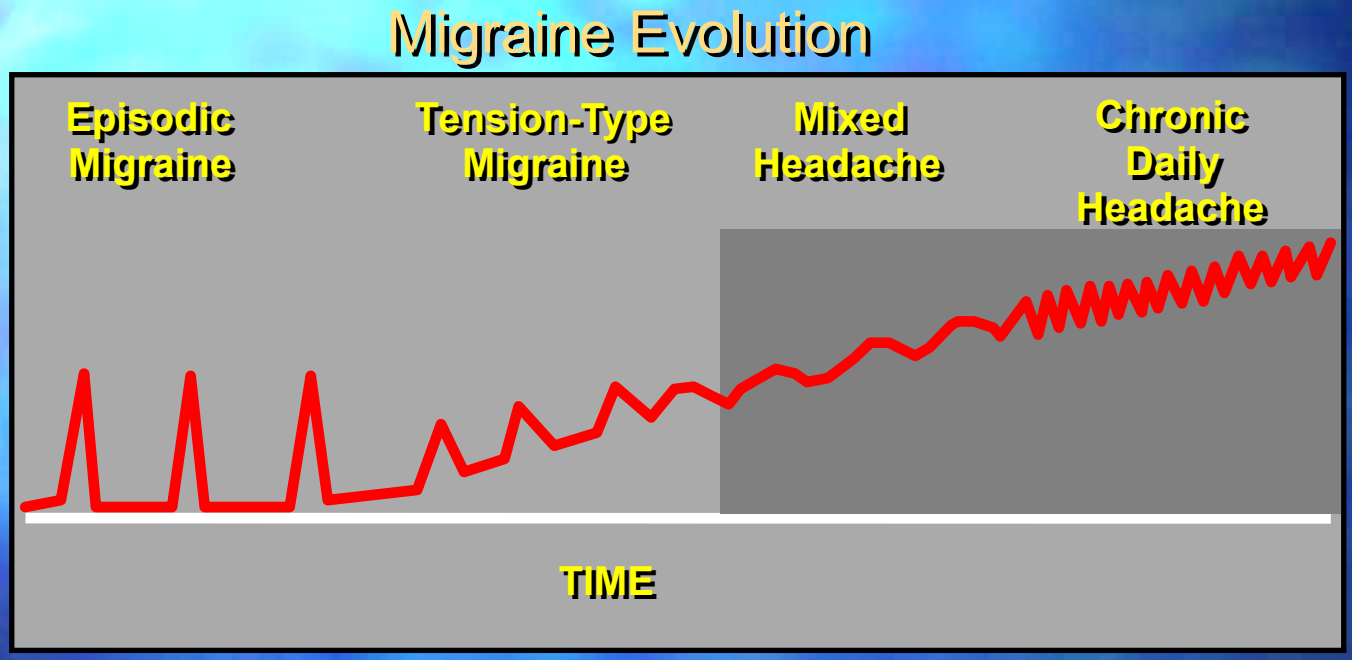
Discuss the safe and effective use of pharmacologic and non-pharmacologic therapies for alleviating migraine attacks.

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.

Migraine Transformation



Raskin NH. Tension Headache. In. Raskin NH, ed. Headache. 2nd ed. New York, NY Churchill Livingstone Inc; 1988:224.

Need multiple approaches to manage migraineur

Migraine Can Be Treated With Acute and Preventive Treatment

Acute Treatment

Used to **abort** a migraine attack[1,2]

Potential benefits:

- May provide symptom relief[1,2]

Limitations:

- Adverse events can include tolerability issues[1,2]
- Risk of medication overuse headache (MOH)[3] (*MOH symptoms ~ to TTH (dull, bilateral, non-throbbing, mild-mod*)

Preventive Treatment

Used to **reduce the frequency, duration, or severity** of attacks[3]

Potential benefits:

- May reduce frequency in monthly migraine attacks and avoid escalation in use of acute meds[3]
- May reduce overall cost associated with migraine treatment[3]

Limitations:

- Often associated with issues of patient adherence[3] (70% after 6 mo of therapy)
- Side effects can lead to discontinuation by up to 40%[4,5]

Individuals with migraine who have frequent and/or severe attacks may require both acute and preventive treatment approaches[1,2]

1. Silberstein SD. *Neurology*. 2000;55:754-762. 2. Marmura MJ, et al. *Headache*. 2015;55:3-20. 3. American Headache Society. *Headache*. 2019;59:1-18. 4. D'Amico D, Tepper SJ. *Neuropsychiatr Dis Treat*. 2008;4:1155-1167. 5. Vecesi L, et al. *Exp Opin Drug Saf*. 2015;14:667-681.

Preventive Treatments Are Recommended for Individuals With More Severe Migraine Presentation

Preventive pharmacological treatments are recommended for patients with migraine, who:[1]

- Have ≥ 4 migraine headache days per month
- Continue to suffer significant disruption to daily routines despite acute tmt
- Suffer attacks that cause functional disability on ≥ 2 days per month, which optimized acute therapy does not prevent (patients must also be willing to take daily medication)
- Overuse acute medications
- Have a contraindication to, have previously failed, or have experienced adverse events with acute medication

1. American Headache Society. *Headache*. 2019;59:1-18.

Preventive Strategies

- Choose treatment from first line agents on the basis of concurrent conditions, side effects, and if an agent has failed, choose another
- Start with low doses and increase (2-4 wk intervals) if needed based on headache diary
- Give adequate time for doses to work (6-12 weeks)
- Use monotherapy if possible
- Educate patient about goals, use, and side effects
- Prescribe medications for acute migraine attacks
- Monitor goals: Frequency, duration, severity, improved response to acute tmt, reduced disability, improved QoL

Evidence-based guideline:
EM (episodic migraine: 4-14 HA days/mo) prevention

Level A: established efficacy

- Antiepileptic drugs
  - Divalproex sodium
  - Sodium valproate
  - Topiramate
- Beta-blockers
  - Metoprolol, Propranolol, Timolol
- Triptans (MRM*)
  - Frovatriptan

Level B: probably effective

- Antidepressants
  - Amitriptyline
  - Venlafaxine
- Beta-blockers
  - Atenolol, Nadolol
- Triptans (MRM*)
  - Naratriptan
  - Zolmitriptan

MRM: menstrually-related migraine

Silberstein et al, *Neurology* 2012;78:1337-45

Preventive Medications Used in the Treatment of Migraine

FDA-approved for prevention of EM &/or CM

- Valproate, Topiramate
- Propranolol, Timolol
- Amitriptyline
- Onabotulinumtoxin A (Botox) injections only for chronic migraine (CM) (≥ 15 HA days/mo)
- Erenumab-aooe (Aimovig) injection EM & CM
- Fremanezumab-vfrm (Ajovy) injection EM & CM
- Galcanezumab-gnlm (Emgality) injection EM, CM & Cluster
- Eptinezumab (Vypeti) intravenous EM & CM

Other drugs commonly used in prevention

- Tricyclic antidepressants (imipramine, nortriptyline)
- Beta antagonists (atenolol, metoprolol)
- Calcium channel antagonists (verapamil – cluster headaches)
- Antiepileptics (gabapentin)

EM Episodic Migraine
CM Chronic Migraine

Compare/Contrast Common ADEs of Oral Prevention Therapies

- **Divalproex Sodium**
  - Nausea, weakness, somnolence, *weight gain, hair loss, tremor*
  - *teratogenicity,* thrombocytopenia
- **Topiramate**
  - Somnolence, weight loss (loss of appetite, change in taste), *psychomotor slowing, difficulty concentrating*
  - *Teratogenicity*, risk of kidney stones, decreased sweating in extreme temps
- **Beta-blockers (lower BP/HR)**
  - Fatigue, *exercise intolerance*, cold extremities, dizziness, vivid dreams, *depression*
  - Contraindications include asthma/COPD, Raynaud's, & not to start in smokers or those >60yo - associated CV risk/stroke
- **Antidepressants**
  - Sedation, *weight gain, anticholinergic effects*, monitor BP and for serotonin syndrome

Onabotulinumtoxin Type A (Botox)

Approved for ***chronic migraine headache*** *(15 or more headaches per month, lasting ≥ 4 hours/day)*

- **small doses injected in the head / neck every 3 months. In clinic administration; 31 IM injections; 155 units, 7 key muscle groups, ~ 15 min**
- **$150-$1200 for each treatment depending on insurance**
- **Major side effects: sore neck (9%), droopy eyelid (4%) (dependent upon injection placement), lasts 1-2 weeks.**

Effect on migraine frequency or severity usually obvious by 1 month; about 2 fewer migraines/mo compared to placebo; some waning in 3rd month. Max benefit in up to 6 months. Can be combined with oral agents.

Anti-CGRP Monoclonal Antibodies

Effective for EM & CM prevention (erenumab, frenezumab, galcanezumab, eptinezumab) and episodic cluster headache (galcanezumab)

Place in therapy: Indications for initiating treatment with anti-CGRP mAbs in patients ≥18 yo with

- 4-14 migraines (with or without aura)/mo
  - Inability to tolerate or inadequate response to a 6-week trial of at least 2 oral prevention meds
- Chronic migraine
  - EITHER inability to respond or tolerate 6 weeks orals OR 2 quarterly injections of onabotulinumtoxinA

AHS Consensus Statement 2018: *Headache* 2018: 0:1-18.

FDA-Approved CGRP-Targeted mAbs

mAb (Targets)	Route of Admin	Soln	Rec Dose mg	Frequency
Erenumab-aooe (CGRP receptor)	SC prefilled single-dose auto-injector	70mg/ml 140mg/ml	70 or 140	Monthly
Fremanezumab-vfrm (α-CGRP, β-CGRP)	SC single-dose prefilled syringe	225/1.5ml	225 675	Monthly Quarterly
Galcanezumab-gnlm (α-CGRP, β-CGRP)	SC via single-use prefilled pen or syringe	120mg/ml	240 120	Loading dose Monthly
Eptinezumab-jjmr (α-CGRP, β-CGRP)	30-min IV infusion in 100mL NS	100mg/ml	100 or 300	Quarterly

CGRP-Antagonists

Efficacy: decrease migraine frequency by about 50% in half of patients; prevent ~2 more episodic migraines / mo vs placebo

Cautions: unknown if cardiovascular risk with long-term use

Little evidence to guide use in specific populations (children, elderly, women during PG/lactation)

Adverse effects: injection site irritation (all), constipation (erenumab)

Cost: ~$6900/year (~$575 per month)

Can be combined with oral agents

Goadsby, P J, et al. *NEJM.* 2017;377(22):2123-2132.
Tepper S, et al. *Lancet Neurol.* 2017;16(6):425-434.
Silberstein, S D, et al. *NEJM.* 2017;377(22):2113-2122.

Erenumab long-term data

3-Year Open-Label Erenumab and Cardio- and Cerebrovascular Event Rate

	Erenumab 70 mg (n = 383) n (r)	Erenumab 140 mg (n = 250) n (r)	Erenumab 70/140 mg (n = 383) n (r)
Cardiovascular AEs	2 (0.3)	0 (0.0)	2 (0.2)
Ischemic heart disease	2 (0.3)	0 (0.0)	2 (0.2)
Cardiac disorders	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial ischemia	1 (0.1)	0 (0.0)	1 (0.1)
Investigations	1 (0.1)	0 (0.0)	1 (0.1)
↑ blood creatine phosphokinase MB	1 (0.1)	0 (0.0)	1 (0.1)
Cerebrovascular AEs	0 (0.0)	0 (0.0)	0 (0.0)

Ashina M, et al. *Cephalalgia*. 2019:333102419854082.

CGRP Physiology and Clinical Implications

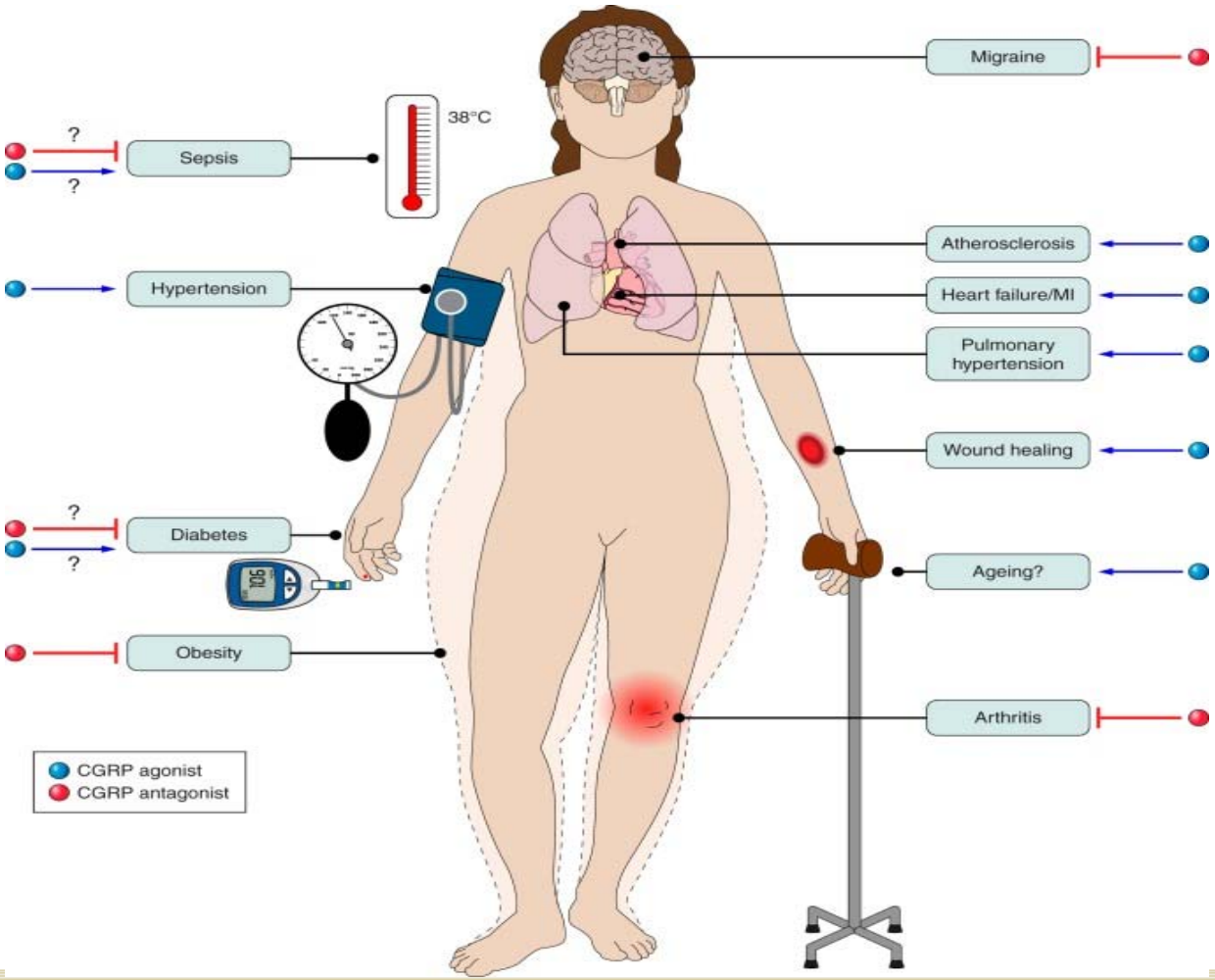
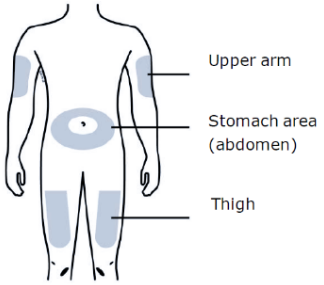


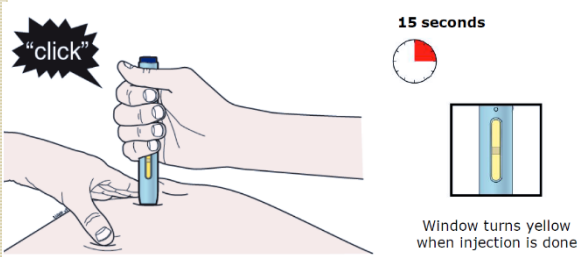
Figure 6 in Physiol Rev 2014; 1099-1142.
Russell et al CGRP: Physiology and Pathophysiology

Aimovig (erenumab) Autoinjector



Remove from refrigerator 30 min before use
Clean injection site area

Pull off white cap (wait no longer than 5 min)
Pinch or stretch skin and push injector firmly
Then click purple button



Hold in place for count of 15 seconds
and sound of second click
Medication window should be yellow

Discard in Sharps container

Ajovy (fremanezumab) Prefilled Syringe

Remove 225mg/1.5ml syringe from frig 30 min before use

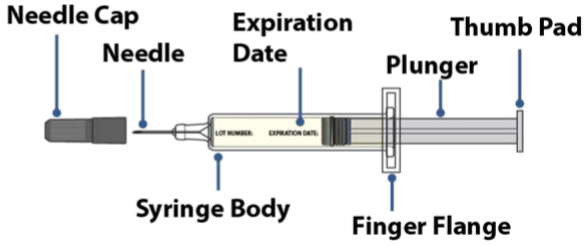
Clean injection site area (SQ: belly, thigh, upper arm)

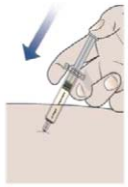
Pull off cap and pinch skin

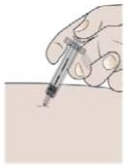
Inject syringe and push plunger down until completed

Remove needle from skin and discard in Sharps

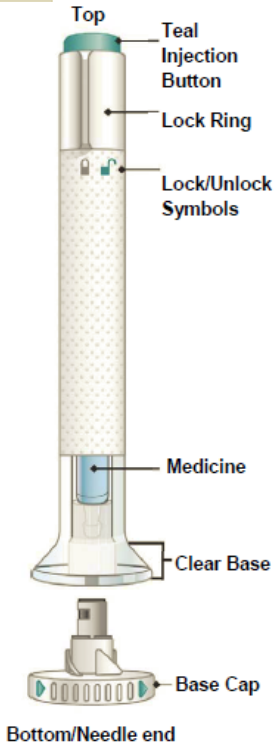
Apply cotton gauze with pressure to injection site



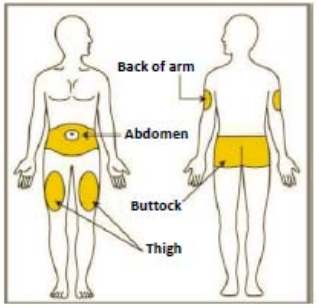


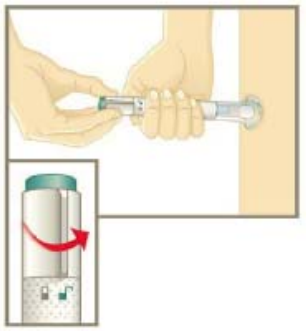


Emgality (galcanezumab) Prefilled Pen



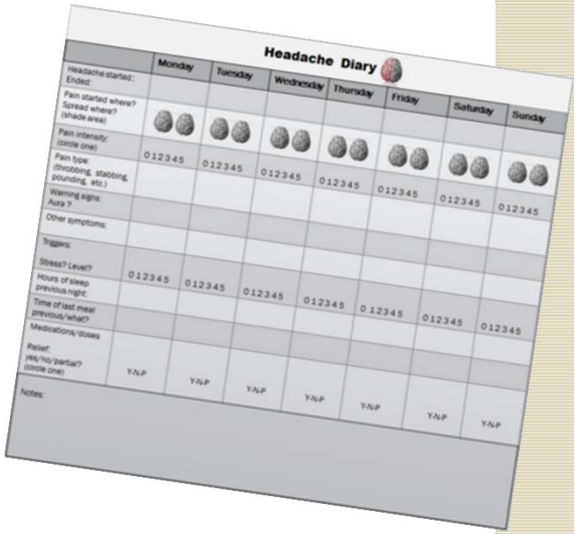
- Remove from refrigerator for 30 min
- Clean injection site area
- Uncap the pen while it is still locked
- Place and hold base flat against skin and turn lock ring to the unlock position
- Press and hold teal injection button (click) for 10 seconds and 2nd loud click
- Remove and dispose in Sharps container





Evidence of treatment benefits for reauthorization after initial use:

- Reduction in mean monthly HA days of ≥ 50% relative to pre-treatment
- Clinically meaningful improvement in ANY of the outcome measures:
  - MIDAS reduction (≥5 points for 11-20 baseline OR ≥30% when baseline >20 points)
  - MPFID reduction of ≥ 5 points
  - HIT-6 reduction of ≥ 5 points



AHS Consensus Statement 2018: *Headache* 2018: 0:1-18.

Which drug options are appropriate?

- Four years later (29yo, 1 child), and frequency of migraines has increased to 3-4 a month.
- Triptan provides good relief
- Desires prevention therapy
- Hopes to have another child

A. *Antiepileptic – VPA, TOP*

B. *Antidepressant – TCA, SNRI*

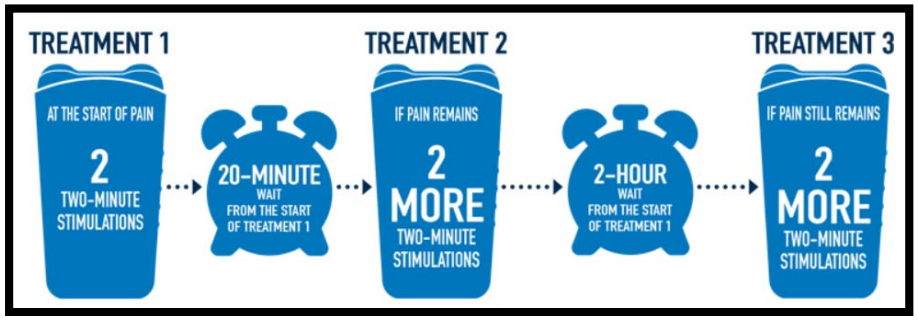
C. *Beta-Blocker - Prop, Metop*

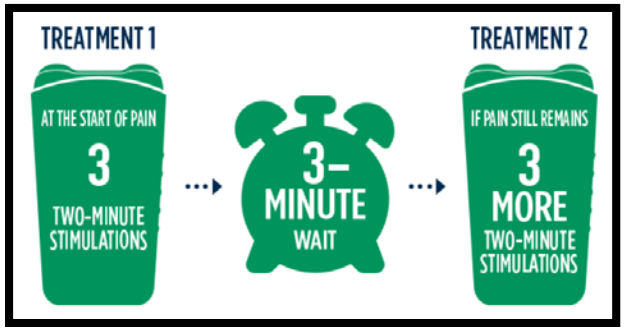
D. *Botox or Anti-CGRP mAb*

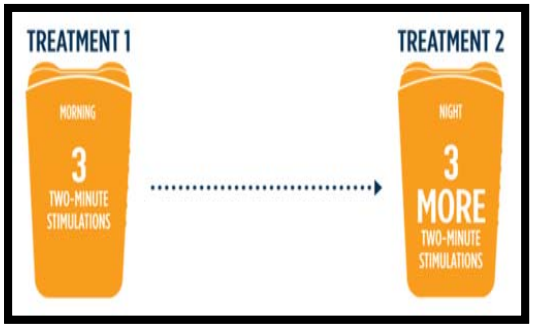
gammaCore nVNS:

FDA-approved noninvasive vagus nerve stimulator

Migraine HA Tmt & Cluster HA Tmt & Prevention







https://gammacore.com/for-migraine/...dosing

gammaCore nVGS directions for use

Practice finding vagus nerve (pulse point in neck)
Apply pea-size amount of gel to each stimulator surface
Turn it on, place with even pressure
Adjust intensity level (1-40; 15-25)
until droop of outer lip area & pull
Will shut off in 2 minutes
Side effect:
application site discomfort

Gammacore.com
ElectroCore LLC

Migraine Counseling Pearls: Abortive & Prevention Therapy

- **Assess Migraine History:**
  - Symptoms
  - Frequency
  - Severity (pain scale)
  - Duration
  - Rate of HA recurrence
  - What relieves or improves HA symptoms?
- **Medication Use:**
  - When to initiate treatment
  - Efficacy of med(s)
  - Incidence and tolerance of side effects
  - Use of adjunct therapies (including acute/rescue med)
- **Lifestyle Changes:**
  - Triggers and trigger reduction
  - Headache diary
  - Sleep/diet/exercise habits

Four Main Points:

1. Discuss when prevention agents are indicated
2. Compare/contrast prevention treatment options (route of administration, time to benefit, side effects, contraindications)
3. Based on a patient scenario, recommend an appropriate prevention treatment option.
4. Describe ways to monitor prevention therapy.

You do NOT need to know doses, just administration guidelines

Migraine Websites

https://www.ninds.nih.gov/Disorders/All-Disorders/Migraine-Information-Page
National Institute of Neurological Disorders and Stroke

http://www.migraineresourcenetwork.com
Migraine Resource Network

http://americanheadachesociety.org/
American Headache Society

http://www.relieve-migraine-headache.com/support-files/headache-diary.pdf
Migraine Diary example

http://www.americanmigrainefoundation.org
American Migraine Foundation