Headache Board Review:
Pharmacology of Drugs, Guidelines and Evidence-Based Medicine

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Disclosures:

• Dr. Marmura has royalty payments from Cambridge, Devos Medical, and Medlink Neurology. He receives salary support from Teva for work as a principal investigator in clinical trials and has received compensation for consultations from Teva and Supernus.

• This talk discusses therapeutic treatments for headache, many of which are off-label. He will discuss which are FDA-approved and which are not during this lecture.
Objectives:

• Summarize the mechanism of action for known preventive and acute pharmacologic treatments for headache.
• Differentiate medications which have the greatest evidence for effectiveness in headache based on published trials from treatments with no proven efficacy.
• Summarize recent guidelines for acute and preventive migraine treatment.
Key points:

• Know general principles for treating acute migraine/cluster and preventing attacks
• Know mechanisms of action
• Know common and serious adverse events of essential medications
• Know evidence basis for commonly used medications
• Open-label studies/case reports are low yield
Preventive Treatment
Why use preventatives?

- Too many headaches
- Too severe
- Too many acute medications (MOH)
- Too sick to take medications (contraindications)
- Too disabled
- Too little warning or severe for acute treatment to work
- Too much to do (patient preference)
- Too much aura (i.e. hemiplegic migraine)
- Too scary

PREVENTIVES ARE GENERALLY UNDERUTILIZED

Types of preventive treatment

• **Pre-emptive**
  For a known trigger – e.g. exercise, sexual activity.
  Treat prior to exposure or activity.

• **Short term prophylaxis**
  For time-limited exposure such as peri-menstrual.

• **Chronic prevention (main focus)**
  Treat on a regular basis for a long period of time.
Potential mechanisms of action of migraine preventives

- Inhibiting cortical spreading depression (CSD)
- Inhibiting peripheral/central sensitization
- Blocking neurogenic inflammation (release of inflammatory cytokines such as CGRP)
- Enhancing anti-nociception
- Modulating autonomic nervous system tone
- Gap junction inhibition (to prevent CSD)
Level of Evidence

- **Level A**: Established as effective (or ineffective) for acute migraine (supported by at least two Class I studies).

- **Level B**: Probably effective (or ineffective) for acute migraine (supported by one Class I study or two Class II studies).

- **Level C**: Possibly effective (or ineffective) for acute migraine (supported by one Class II study or two Class III studies).

- **Level U**: Evidence is conflicting or inadequate to support or refute the use of the medication(s) for acute migraine.

# Preventive Guidelines (Episodic Migraine)

## Table 1: Classification of migraine preventive therapies (available in the United States)

<table>
<thead>
<tr>
<th>Level A: Medications with established efficacy (≥2 Class I trials)</th>
<th>Level B: Medications are probably effective (1 Class I or 2 Class II studies)</th>
<th>Level C: Medications are possibly effective (1 Class II study)</th>
<th>Level U: Inadequate or conflicting data to support or refute medication use</th>
<th>Other: Medications that are established as possibly or probably ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiepileptic drugs</td>
<td>Antidepressants/SSRI/SSNRI/TCA</td>
<td>ACE inhibitors</td>
<td>Carbamic anhydride inhibitor</td>
<td>Established as not effective</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Amitriptyline</td>
<td>Angiotensin receptor blockers</td>
<td>Acetazolamide</td>
<td>Antiepileptic drugs</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>Venlafaxine</td>
<td>Candesartan</td>
<td>Antithrombotics</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Topiramate</td>
<td>β-Blockers</td>
<td>α-Agonists</td>
<td>Atenocoumarin</td>
<td>Possibly not effective</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Nadolol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Guanfacine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Pimobendan</td>
<td>Possibly not effective</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Triptans (MRM&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>Antiepileptic drugs</td>
<td>Antidepressants/SSRI/SSNRI</td>
<td>Acebutolol&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Timolol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Naratriptan&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Carbamazepine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Fluoxetine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Clonazepam&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triptans (MRM&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>Zolmitriptan&lt;sup&gt;b&lt;/sup&gt;</td>
<td>β-Blockers</td>
<td>Fluoxetine</td>
<td>Naxebutol&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>FrovatRIPTAN&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Nebivolol</td>
<td>Antiepileptic drugs</td>
<td>Oxicarbazepine</td>
<td>Telmisartan</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>TCAs</td>
<td>Cypohostidine</td>
<td>Protriptyline&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>Bisoprolol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Bisoprolol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Bisoprolol&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Ca++ blockers</td>
<td>Nicardipine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Nicardipine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Nicardipine&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Diltiazem</td>
<td>Diltiazem</td>
<td>Diltiazem</td>
<td></td>
</tr>
<tr>
<td>Direct vascular smooth muscle relaxants</td>
<td>Cyclandelate</td>
<td>Cyclandelate</td>
<td>Cyclandelate</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACE = angiotensin-converting-enzyme; MRM = menstrually related migraine; SSRI = selective serotonin–norepinephrine reuptake inhibitor; SSNRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

<sup>a</sup> Classification based on original guideline and new evidence not found for this report.

<sup>b</sup> For short-term prophylaxis of MRM.

*Neurology.* 2012 Apr 24;78(17):1337-45
# β receptor antagonists

## Non-selective

- * Propranolol (inderal)  120 - 400 mg/d
- * Timolol (blocadren)  20 - 40 mg/d
- Nadolol (corgard)  40 - 160 mg/d

## β₁ selective

- Metoprolol (lopressor)  50 - 200 mg/d
- Atenolol (tenormin)  25 – 100 mg/d

* FDA approved
Reduction in cortical excitability

Treatment with beta-blockers in patients with migraine increases phosphene thresholds with transcranial magnetic stimulation

β receptor antagonists: AEs

**CV:** hypotension, bradycardia, fatigue
decreased exercise tolerance,
may worsen PVD and Raynaud disease

**CNS:** drowsiness, nightmares, insomnia, depression (?)

**Other:** masking symptoms of hypoglycemia
rebound hypertension or tachycardia

**Potential uses:** Hypertension, tachycardia, POTS, anxiety, essential tremor

Recent data suggests depression-β-blocker link unlikely

Ranchord A. American Heart Journal 2016
Antidepressants (none are Level A)

• Monoamine reuptake inhibitors
  – non-selective (TCAs). Amitriptyline up to 75 mg
  – selective serotonin reuptake inhibitors (SSRIs) fluoxetine effective (chronic daily headache)
  – serotonin and norepinephrine (SNRIs). Venlafaxine 150 mg

• Monoamine oxidase inhibitors (MAOIs)

• Anti-depressants do not work in HA by treating masked depression
Antidepressants

- **TCAs**
  - amitriptyline has been consistently shown as effective
  - as effective as propranolol and superior to placebo
  - benefit is independent of antidepressant effect
  - other TCAs: little evidence in migraine (nortriptyline is effective for neuropathic pain)

- **SSRIs**
  - fluoxetine may be effective (chronic daily headache)

- **SNRIs**
  - venlafaxine: migraine prevention dose 150 mg or greater
Tricyclic antidepressants - AEs

- **Anti cholinergic-related** – dry mouth, constipation, tachycardia, palpitations, blurry vision (poor accommodation), urinary retention, confusion.

- **Anti-adrenergic (α₁)-related** – orthostatic hypotension

- **Serotonergic** – nausea, sweating

- **Anti histamine (H₁)-related** – drowsiness, fatigue

- **Na channel effect-related** – cardiac conduction delay.

- **Other** – Weight gain, lowered seizure threshold, sexual dysfunction, mania.
Calcium Channel Antagonists

**Drugs**

- **Verapamil** (unknown effectiveness in migraine) - 240 to 620mg/d
- **Flunarizine** (probably effective in migraine) - 5 to 10mg/d

**AEs**

- **Verapamil** - constipation, AV block, CHF
- **Flunarizine** - weight gain, somnolence, dizziness, hypotension, extrapyramidal reactions

**Contraindications**

- CHF, heart block, hypotension, sick sinus syndrome
Topiramamide:

Broad spectrum anticonvulsant used in migraine
- Antagonist of AMPA/kainate subtype of glutamate receptors
  (Main reason for effectiveness in migraine/epilepsy?)
- Augments the GABA$_A_1$ receptor (Less sedating than most anxiolytics)
- Blocks voltage-dependent calcium and sodium channels
- Inhibits carbonic anhydrase isoenzymes II and IV. (metabolic acidosis, paresthesias)
- May inhibit protein kinase activity (? weight regulation / glucose homeostasis)
- Possible serotonin activity on 5-HT$_{2C}$ receptor (cause of weight loss?)

Dose: 25-1000 mg/day given QD-BID. Available as extended release.

Effective for migraine, chronic migraine, cluster headache

AEs: weight loss, tingling, concentration /memory / language impairment, decrease sex hormone levels (>200 mg), pallinopsia, kidney stones, acute angle closure glaucoma

Gryder DS J Neurosci. 2003; O'Neil PM Obesity 2012
Change from Baseline to Double-Blind Phase in Average Monthly Migraine Period Rate (+SE)

- Placebo (N=115 and 114)
- TOPAMAX 50 mg/day (N=117 and 117)
- TOPAMAX 100 mg/day (N=125 and 120)
- TOPAMAX 200 mg/day (N=112 and 117)

* p < 0.010, ** p < 0.001
Topiramate for Chronic Migraine

Primary Outcome
Migraine/Migrainous Days

Topiramate 17.1 ± 5.4
Placebo 17.0 ± 5.0

Second Key Outcome
Migraine Days

Topiramate 15.2 ± 6.4
Placebo 15.1 ± 5.8

Mean baseline ± SD

Mean Change From Baseline

-6.4 ± 5.8  -4.7 ± 6.1
-5.6 ± 6.0  -4.1 ± 6.1

P = 0.010  P = 0.032

Headache: The Journal of Head and Face Pain
Divalproex Sodium

• **Drug**
  Valproic acid/sodium valproate (Depakote) 500-3000 mg/d

• **Therapeutic blood level**
  50-120 mcg/ml

• **AEs**
  Nausea, sedation, platelet dysfunction, hair loss, tremor, change in cognition, hepatotoxicity (young children), weight gain, pancreatitis, polycystic ovaries

• **Comments**
  Use in presence of co-morbid mania, epilepsy
  Check LFTs and CBC before and as needed during therapy

*Expert Opin Drug Metab Toxicol. 2010 Apr;6(4):495-504.*
Other Preventive Medications

- Cyproheptadine – serotonin antagonist, antihistamine
  - acts mostly at 5HT-1a and 5HT-2 receptors
  - treats serotonin syndrome
  - may reduce antidepressant effectiveness

- Gabapentin – conflicting evidence, requires higher doses (1800+ mg)

- Candesartan 16 mg – angiotensin receptor blocker

- Vitamins, Minerals, Herbs
  - Riboflavin (B2) 400 mg
  - Co-enzyme Q 10
  - Magnesium, Feverfew, Petadolex (Petasites hybridus)
# Candesartan and Propanolol vs Placebo

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n = 61)</th>
<th>PLA (n = 60)</th>
<th>CAN (n = 56)</th>
<th>PRO (n = 60)</th>
<th>p value PLA vs CAN</th>
<th>p value PLA vs PRO</th>
<th>p value CAN vs PRO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine days per four weeks (primary efficacy variable), mean (95% CI)</td>
<td>4.82 (4.16–5.47)</td>
<td>3.53 (2.98–4.08)</td>
<td>2.95 (2.35–3.55)</td>
<td>2.91 (2.36–3.45)</td>
<td>0.02</td>
<td>0.02</td>
<td>0.88</td>
</tr>
<tr>
<td>Headache days per four weeks, mean (95% CI)</td>
<td>8.21 (7.18–9.24)</td>
<td>5.97 (4.96–6.99)</td>
<td>5.30 (4.24–6.36)</td>
<td>5.75 (4.40–7.09)</td>
<td>0.01</td>
<td>0.16</td>
<td>0.96</td>
</tr>
<tr>
<td>Headache hours per four weeks, mean (95% CI)</td>
<td>59.2 (47.7–70.7)</td>
<td>43.5 (33.7–53.2)</td>
<td>35.1 (26.7–43.5)</td>
<td>41.4 (27.2–55.6)</td>
<td>0.004</td>
<td>0.04</td>
<td>0.96</td>
</tr>
<tr>
<td>Average headache intensity (0–3)*, mean (95% CI)</td>
<td>1.9 (1.8–2.0)</td>
<td>1.8 (1.7–1.9)</td>
<td>1.8 (1.7–1.9)</td>
<td>1.8 (1.6–1.9)</td>
<td>0.05</td>
<td>0.02</td>
<td>0.85</td>
</tr>
<tr>
<td>Average function level during attacks (0–3)*, mean (95% CI)</td>
<td>1.4 (1.3–1.6)</td>
<td>1.4 (1.3–1.5)</td>
<td>1.3 (1.1–1.4)</td>
<td>1.2 (1.1–1.4)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.84</td>
</tr>
<tr>
<td>Triptan doses per four weeks, mean (95% CI)</td>
<td>4.5 (3.6–5.4)</td>
<td>3.5 (2.9–4.2)</td>
<td>2.4 (1.7–3.1)</td>
<td>2.9 (2.1–3.7)</td>
<td>0.001</td>
<td>0.04</td>
<td>0.41</td>
</tr>
<tr>
<td>Analgesics doses per four weeks, mean (95% CI)</td>
<td>7.0 (4.5–9.6)</td>
<td>5.4 (3.3–7.5)</td>
<td>5.0 (3.2–6.8)</td>
<td>3.5 (2.2–4.9)</td>
<td>0.23</td>
<td>0.003</td>
<td>0.01</td>
</tr>
<tr>
<td>Work absence (days per four weeks), mean (95% CI)</td>
<td>0.78 (0.50–1.06)</td>
<td>0.43 (0.27–0.59)</td>
<td>0.39 (0.24–0.53)</td>
<td>0.47 (0.26–0.67)</td>
<td>0.34</td>
<td>0.56</td>
<td>0.97</td>
</tr>
<tr>
<td>Satisfaction with treatment effect*, median (25%–75% percentile)</td>
<td>n.a.</td>
<td>3.0 (3.0–5.0)</td>
<td>5.0 (3.0–6.0)</td>
<td>4.5 (4.0–5.0)</td>
<td>0.001</td>
<td>0.002</td>
<td>0.85</td>
</tr>
<tr>
<td>Lack of discomfort due to AEs*, median (25%–75% percentile)</td>
<td>n.a.</td>
<td>5.0 (4.5–5.0)</td>
<td>4.0 (3.5–5.0)</td>
<td>4.0 (3.0–5.0)</td>
<td>0.001</td>
<td>0.003</td>
<td>0.26</td>
</tr>
<tr>
<td>AEs since last visit (yes/no, %)*</td>
<td>n.a.</td>
<td>20/40, 33</td>
<td>28/28, 50</td>
<td>35/25, 58</td>
<td>0.07</td>
<td>0.006</td>
<td>0.37</td>
</tr>
<tr>
<td>Other illness since last visit (yes/no, %)*</td>
<td>n.a.</td>
<td>31/29, 52</td>
<td>27/29, 48</td>
<td>26/34, 43</td>
<td>0.71</td>
<td>0.36</td>
<td>0.60</td>
</tr>
</tbody>
</table>

*ITT: intention to treat; AEs: adverse events; CAN: candesartan; PLA: placebo; PRO: propranolol; CI: confidence interval; n.a.: not applicable.

None, mild, moderate, severe.

Normal, reduced, markedly reduced, in bed.

From 1: extremely dissatisfied, to 7: extremely satisfied.

From 1: very unpleasant, to 5: not unpleasant at all.
OnabotulinumtoxinA Injection

• Approved: Chronic Migraine (15 or more headache ≥ 4 hours, ≥ 50% migraine/probable migraine
• PREEMPT 1 and 2 trials: 155-195 U every 12 weeks
• Allows for additional injections (follow-the-pain strategy)
• AEs: neck pain, ptosis, weakness
• Mech of action: cleavage of SNAP-25, preventing acetylcholine vesicle binding and release at the motor end plate
• Other possible mechanism of actions in pain/migraine: effects on excitatory neurotransmitter release/fusion, spinal c-Fos expression, CGRP release
Supraorbital transcutaneous stimulator

Prevention of Cluster

• No large clinical trials with high level evidence
• Corticosteroids at cycle onset
• High dose verapamil (240-720 mg)
• Lithium (600-1200 mg)
• Methysergide
• Divalproex sodium
• Topiramate
• Devices (VNS), OnabotulinumtoxinA

Cluster headaches may involve pain around one eye, along with drooping of the lid, tearing and congestion on the same side as the pain.
Sphenopalantine ganglion stimulation for chronic cluster headache:

Schoenen et al Cephalalgia 2013
Vagal Nerve Stimulation—Cluster Headache

Decrease in daily number of attacks and severity for patients after starting treatment with nVNS.

Marin et al., Cephalalgia 2012
Acute Treatment
Principles of Acute Treatment

Evidence-Based Guidelines

• Treat attacks rapidly and consistently without recurrence
• Restore the patient’s ability to function
• Minimize the use of back-up and rescue medications
• Optimize self-care and reduce subsequent use of resources
• Be cost-effective for overall management
• Have minimal or no adverse events
Acute Migraine Treatment: Drug Classes

• **Antiemetics**: medications designed to help relieve nausea and vomiting

• **Analgesics & NSAIDS**: nonspecific pain relievers; often used as first-line therapy (many are available over the counter)

• **Triptans & Ergots**: migraine-specific prescription medications for use by patients with moderate to severe migraines

• **Rescue Therapies**
  - Opioids (narcotic pain relievers)
  - Corticosteroids (steroid hormones)
  - Neuroleptics (anti-psychotics)
Strategies of Acute Care

**Step Care**

- **Stage 1:** OTC analgesic
- **Stage 2:** NSAID
- **Stage 3:** Triptan, DHE, or ergot
- **Stage 4:** Rescue therapy: opioid, corticosteroid, neuroleptic

**Stratified Care**

- **Therapy:** Choose treatment based on attack profile, associated symptoms, and level of disability

- Attack No.
  - 1
  - 2
  - 3
  - 4
  - 5

- Increase Rx
Acute Guidelines for acute migraine:

- **Level A:** All triptans including Sumatriptan/naproxen 85/500 mg, DHE NS/Inhaler, NSAIDs: diclofenac, aspirin, naproxen, ibuprofen, acetaminophen/ aspirin/caffeine 500/500/130 mg, Acetaminophen 1000 mg (for non-incapacitating attacks), Butorphanol nasal spray 1 mg

- **Level B:** Chlorpromazine IV, Droperidol IV, Metoclopramide IV Prochlorperazine, IM/IV DHE, Ketorolac, Codeine/acetaminophen, Tramadol/acetaminophen

Triptans

Serotonin agonists:

• 5HT1B – trigeminal ganglia, vessels (constriction, MMA > MCA)
• 5HT1D - trigeminovascular afferents, PAG
• To a lesser extent… 5HT1F
Triptans: Tolerability

- Similar side effect profiles across triptans
- Most common side effects:
  - Dizziness
  - Somnolence
  - Asthenia/fatigue
  - Paresthesias
  - Warmth/flushing
  - Chest tightness
- Chest pressure/tightness in 2 to 4%
- Most side effects are mild and transient
Triptans: How they Work

- 5 HT1B/D Receptor Agonists
- Designed as cerebral vessel vasoconstrictors
- Block the transmission of trigeminal nerve to the trigeminal nucleus caudalis
- Prevent release of inflammatory neuropeptides
- Inhibitors of neurogenic inflammation

a. Minutes after the onset of migraine, activated meningeal nociceptors enter a new physiological state

b. Systemically administered triptan molecules (green circles) bind to presynaptic 5HT1B/1D receptors on terminals of both the peripheral and central branches of the meningeal nociceptor, resulting in blockade of neuropeptide release.

c. After the establishment of central sensitization, the pain continues to throb and the skin becomes allodynic.

d. Blockade of synaptic transmission provides only partial pain relief terminates the throbbing, but does not resolve the allodynia
### TABLE 5: Serotonin 5-HT\textsubscript{1B/1D} Agonists (Triptans)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Formulations</th>
<th>Doses (mg)</th>
<th>Tmax (hours)</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almotriptan</td>
<td>PO</td>
<td>6.25, 12.5</td>
<td>2.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>PO</td>
<td>20, 40</td>
<td>1.8</td>
<td>5</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>PO</td>
<td>2.5</td>
<td>~2.5</td>
<td>~26</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>PO</td>
<td>1, 2.5</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>PO, tablet or dissolvable (ODT)</td>
<td>5, 10</td>
<td>2-3</td>
<td>2</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>PO</td>
<td>25, 50, 100</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>20</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>4, 6</td>
<td>0.17</td>
<td>2</td>
</tr>
<tr>
<td>Sumatriptan/naproxen</td>
<td>PO</td>
<td>85/500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>PO, tablet or ODT</td>
<td>2.5, 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
New formulations of sumatriptan

Zecuity patch 6.5 mg:
Delivered over 4 hours

Pain freedom 18% vs 9% placebo at 2 hours, p = 0.0092; headache relief 53% vs 29%, p = 0.001
22 mg breath-powered intranasal system

Pain freedom at 2 hours 57% vs 25%, p < 0.05; pain relief 80% vs 44%, p < 0.01
Triptans of Note

- **Fast-acting, Cluster headache**
  - Sumatripan sc >> NS (suma/zolmi)

- **Effectiveness**
  - Rizatriptan, Eletriptan

- **Fewer AEs**
  - Almotriptan, Sumatriptan 25 mg, Naratriptan, ? Sumatriptan transdermal

- **Preventative**
  - Frovatriptan > Naratriptan, Eletriptan

- **Non MAO metabolism**
  - Eletriptan (CYP 3a4), Frovatriptan, Naratriptan
DHE and ergotamines:

• Ergotamines – Dihydroergotamine:
  • $\alpha$-adrenergic activity in addition to 5HT1B/D activity
  • More nausea (especially ergotamines, iv DHE) than triptans
  • Vasoconstrictive
  • May increase blood pressure
  • Work later in attack (status migranosus, infusion therapy)
• DHE – minimal oral absorption (NS, IM, IV)
## Neuroleptics in Migraine

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide</td>
<td>PO, IM, IV</td>
<td>5-20</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>PO</td>
<td>5-10</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>5-10</td>
</tr>
<tr>
<td>Droperidol</td>
<td>IM, IV</td>
<td>0.625-2.5</td>
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<tr>
<td>Chlorpromazine</td>
<td>PO</td>
<td>25-100</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>50-100</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>10-50</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>IM</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>2-5</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>PO</td>
<td>2.5-20</td>
</tr>
</tbody>
</table>
Neuroleptic side effects

- Extrapyramidal, tardive dystonias
- Hyperprolactinemia
- Anticholinergic
- Weight gain, metabolic syndrome
- Sedation
- Hypotension (chlorpromazine)
- QTc prolongation (droperidol, haloperidol, chlorpromazine)
- Lowered seizure threshold

QTc prolongation can predispose the patient to life-threatening arrhythmias
Opioids

- Bind to opioid receptors: mu, kappa, and delta mainly
- Variable evidence for migraine (Butorphanol Level A) but generally not recommended as initial treatment or regular use
- Methadone – also has NMDA antagonism
- Tramadol – low potency mu agonist, has SNRI activity
- Butorphenol - partial agonist and antagonist activity
- Naloxone (for overdose) and naltrexone (used in addiction) are antagonists
- Be familiar with rational use, risk factors for misuse, risk of worsening headache control, dependancy/addiction
Combination medications including barbiturates

- Best evidence for aspirin-acetaminophen-caffeine
- Isomethoptyne-dichoralphenazone-APAP (Midrin), Isomethoptyne-APAP (Migraten): contraindications include glaucoma, renal failure, severe hypertension, heart or renal disease and MAO inhibitors
- Barbiturates: Banned in some countries, high risk of rebound, may be used to self-treat anxiety. May include codeine
NSAIDs in migraine

• May suppress inflammation (mast cell activation, sensitization, fluid extravasation)
• May treating central sensitization by blocking glial production of prostaglandins
• May treat non-traditional migraine symptoms, such as neck pain and sinus pressure
• Easy to combine with other treatments (triptans, antiemetics)
• Adverse events: peptic ulcers or renal disease, may increase the risk of myocardial infarction and stroke (except aspirin, maybe naproxen), inflammatory bowel disease
• Lower risk of medication-overuse?
<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxyn</td>
<td>PO</td>
<td>500-1100</td>
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<tr>
<td>Indomethacin</td>
<td>PO, PR</td>
<td>25-75, 50</td>
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<tr>
<td>Ketoprofen</td>
<td>PO</td>
<td>75-150</td>
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<td>Ibuprofen</td>
<td>PO</td>
<td>200-800</td>
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<td>Piroxicam</td>
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<td>Ketorolac</td>
<td>IM, IV</td>
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<td>Diclofenac</td>
<td>PO</td>
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</tr>
<tr>
<td>Aspirin</td>
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<td>Celecoxib</td>
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<td>400</td>
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<tr>
<td>Tolfenamic acid</td>
<td>PO</td>
<td>200-400</td>
</tr>
<tr>
<td>ASA-acetaminophen-caffeine</td>
<td>PO</td>
<td>250-250-65</td>
</tr>
</tbody>
</table>
Indomethacin:  
Putative mechanisms of action

- Inhibits nitric oxide production.
- Decreases intracranial pressure
- Cox-1 inhibition inhibiting synthesis of prostaglandins
- Structural similarity to serotonin
- Inhibits the metabolism of an active progesterone metabolite
- Can be used for acute migraine or as daily medication for indomethacin-responsive headaches
- Usual dose 50-225 mg
Indomethacin-responsive headache syndromes

Absolute responders
• Hemicrania Continua
• Paroxysmal Hemicrania

Possible responders
• Valsalva-induced headaches (cough headache)
• Primary stabbing headache (ice-pick headache or jabs and jolts syndrome)
• Hypnic headache? Exertional headache?
Treatment of uncommon headache syndromes

• Cluster headache – SC sumatriptan, high-flow oxygen
• Idiopathic Intracranial hypertension – acetazolamide
• SUNA/SUNCT – lamotrigine, IV lidocaine
• Hypnic headache – caffeine
• High-altitude headache – acetazolamide, dexamethasone, NSAIDs
• Trigeminal neuralgia (non-surgical) – carbamazepine, other AEDs, baclofen
Primary endpoints:

**Acute treatment:**
- Two-hour pain relief, two-hour pain freedom most common for oral medication.
- Less common: Time to pain relief/freedom, change in pain intensity, 24-hour sustained relief.
- Nausea/vomiting, photo and phonophobia usually secondary

**Preventive treatment:**
- Reduction in headache days
- Reduction in migraine days
- Frequency of headache episodes
- Reduction in moderate-severe days
- Reduction in acute medication use
General Advice

• Focus on drugs studied in placebo-controlled trials (more than open-label or comparative trials): use guidelines as a reference

• Know commonly used doses, drug interactions, and serious adverse events for major drugs

• Be comfortable with both the “two-for-one” concept and using best drug for the condition in question