Acute and Preventive Treatments for Headache
Evidence based Review

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Acknowledgements

• Drs. Jessica Ailani and Michael Marmura, slides updated from previous lectures.

Disclosures

• Honoraria from Allergan and Amgen for advisory board, Current Neurology and Neuroscience Reports for editing Headache section
• This talk discusses therapeutic treatments for headache, many of which are off-label. It will be discussed which are FDA-approved and which are not during this lecture.
Objectives

• Describe the mechanism of action for currently utilized preventive and acute pharmacologic treatments for headache.
• Differentiate best evidence medications in headache from treatments with no proven efficacy
• Summarize guidelines for acute and preventive migraine and cluster treatment.

Key points for the boards

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

**PREVENTIVES ARE GENERALLY UNDER-UTILIZED**

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**
  Treat on a regular basis for a long period of time.

Potential Mechanisms of Action

- 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 disease state (supported by at least two Class I studies).

• **Level B**: Probably effective (or ineffective) for disease state (supported by one Class I study or two Class II studies).

• **Level C**: Possibly effective (or ineffective) for disease state (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 disease state.

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**FDA Approved Preventives for Migraine**

**β receptor antagonists**

*Disease State*: Migraine, Chronic Migraine

**Non-selective**

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

**β₁ selective**

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

* FDA approved

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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 other uses: Hypertension, tachycardia, POTS, anxiety, essential tremor

Topiramate

Disease State: Migraine, Chronic Migraine, Cluster headache

Dose: 25-100 mg/day given QD-BID. Available as extended release

Mechanism of Action
• Antagonist of AMPA/kainate subtype of glutamate receptors (Main reason for effectiveness in migraine/epilepsy?)
• Augments the GABA_A 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?)

Topiramate: AE

• General: Weight loss
• Neurological: Tingling, concentration/memory/language impairment
• Endo: Decrease sex hormone levels (>200 mg),
• Ophth: Pallinopsia, acute angle closure glaucoma
• Nephro: Kidney stones
**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.*

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**Onabotulinum toxin A for Chronic Migraine**

- **Disease State:** Chronic Migraine
- **Dose:** PREEMPT 1 and 2 trials: 155-195 U every 12 weeks
  - Allows for additional injections (follow-the-pain strategy)
- **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
- **AEs:** neck pain, ptosis, weakness

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**CGRP Monoclonal Antibodies**

- **Monoclonal antibodies against CGRP receptor vs. CGRP**
  - Remove excess CGRP released from perivascular trigeminal nerve endings
  - Receptor ab block receptor from signaling transmission

- **Erenumab- R mab**- SQ - Migraine/Chronic Migraine – monthly
- **Galcanezumab- mab – SQ** - Migraine/Chronic Migraine – monthly
- **Fremanezumab- mab – SQ** - Migraine/Chronic Migraine - monthly/Q12 weeks
- **Eptinezumab – mab – IV**- Migraine/Chronic Migraine - monthly/Q12 weeks
Aimovig (Erenumab) Phase 3 Data

- Migraine (ARISE)
  - 70mg vs. placebo
  - Treatment Q month for 12 weeks
  - Reduction in number of migraine days/month: 2.9 vs. 1.8 (placebo)

- Chronic Migraine (STRIVE)
  - 70mg vs. 140mg vs. placebo
  - Treatment Q month for 24 weeks
  - Reduction in migraine days/month: 3.2 vs. 3.7 vs. 1.8 (placebo)

- AE: Injection site pain, URI, Nausea

Dodick, DW. Cephalalgia 2018
Goadsby PJ. NEJM 2017

Other Preventives for Migraine

Antidepressants

- Monoamine reuptake inhibitors
  - Non-selective (TCAs)
    - Amitriptyline most studied
  - Serotonin and norepinephrine (SNRIs)
    - Venlafaxine 150 mg
    - Duloxetine 60mg

- Monoamine oxidase inhibitors (MAOIs)

- None FDA approved for migraine
Antidepressant AE’s

• **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
• **Med specific** - elevated BP in venlafaxine, elevated LFT’s in duloxetine, cardiac conduction delay in TCA’s
• **Other** - Weight gain, lowered seizure threshold, sexual dysfunction, mania, suicide

Calcium Channel Antagonist

• **Verapamil**
  • Efficacy - Level U
  • Dose - 240-620mg daily
  • AE - constipation, AV block, CHF

• **Flunarazine**
  • Efficacy - Level B
  • Dose - 5-10mg daily
  • AE - weight gain, somnolence, dizziness, hypotension, extrapyramidal reactions
• **Contraindications:** CHF, heart block, hypotension, sick sinus syndrome

Other Preventive Medications

• **Cyproheptadine**
  • Mechanism - Serotonin antagonist - mostly at SHT-1a and SHT-2 receptors
  • Igts prostaglandin synthesis, may reduce antidepressant effectiveness
  • AE - Dry mouth, dizziness

• **Gabapentin**
  • Efficacy - conflicting evidence
  • Dose - 1800mg
  • AE - somnolence, weight gain, edema, dizziness

• **Candesartan**
  • Type of med - angiotensin receptor blocker
  • Efficacy - Equals propranolol as migraine preventive
  • Dose - 16mg daily
  • AE - Dizziness

• **Vitamins, Minerals, Herbs**
  • Riboflavin (B2) 400 mg
  • Co-enzyme Q10
  • Magnesium, Feverfew, Petadolex (Petasites hybridus)
Prevention of Cluster Headache

Guidelines; Effective

• Level A
  • Suboccipital steroid injections

• Level B
  • Cimamide ns (not used in US)

• Level C
  • Lithium 900mg daily
  • Verapamil 360mg daily
  • Warfarin to INR 1.5-1.9
  • Melatonin 10mg daily

• Level U
  • Frovatriptan 5mg daily
  • Capsaicin IN
  • Nitrate tolerance
  • Prednisone 20mg QOD

Robbins MS. Headache 2016

Guidelines; Ineffective

• Level B
  • Sodium Valproate 1000-2000mg
  • Sumatriptan 100mg tid
  • DBS in refractory CCH

• Level C
  • Cimetidine/chlorpheniramine 800-2000/16-20
  • Misoprostol 300 micrograms
  • Hyperbaric Oxygen 100%
  • Candesartan 32mg

Robbins MS. Headache 2016
Clinical Practice

- Corticosteroids at cycle onset
- High dose verapamil (240-720 mg/day)
- Lithium (600-1200 mg)
- Gabapentin (1800mg)
- Methysergide
- Divalproex sodium
- Topiramate
- Devices (VNS)

Acute Treatment
Migraine

Principles of Acute Treatment

- 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
Strategies of Acute Care

<table>
<thead>
<tr>
<th>Step Care</th>
<th>Stratified Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attack No.</td>
<td>Therapy: Choose treatment based on attack profile, associated symptoms, and level of disability</td>
</tr>
<tr>
<td>1</td>
<td>Stage 1: OTC analgesic</td>
</tr>
<tr>
<td>2</td>
<td>Stage 2: NSAID</td>
</tr>
<tr>
<td>3</td>
<td>Stage 3: Triptan, DHE, or ergot</td>
</tr>
<tr>
<td>4</td>
<td>Stage 4: Rescue therapy: opioid, corticosteroid, neuroleptic</td>
</tr>
<tr>
<td>5</td>
<td>Increase Rx</td>
</tr>
</tbody>
</table>

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)

Acute Guidelines for acute migraine

- **Level A**:
  - All triptans
  - 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**:
  - Anti-emetics: IV Metoclopramide & Promethazine
  - Anti-dopamine: IV Chlorpromazine & Droperidol
  - IM/IV DHE
  - Ketorolac
  - Codeine/acetaminophen, Tramadol/acetaminophen

Triptans: Mechanism of action

- 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

Triptans: AE

- 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

Fast Acting
Half life between 1.8 (suma nasal)-5hrs (eletriptan)

- Oral: Sumatriptan 25mg/50mg/100mg, Sumatriptan 85mg/naproxen 500mg, Rizatriptan 5mg/10mg/MLT, Zolmitriptan 2.5mg/5mg/ODT, Almotriptan 6.25mg/12.5mg, Eletriptan 20mg/40mg
- Nasal: Sumatriptan 20mg, Sumatriptan 22mg, Zolmitriptan 2.5mg/5mg
- SQ: Sumatriptan
Triptans

Long Acting
Half life between 6 (Naratriptan) to 26 hrs (Frovatriptan)
• Oral: Naratriptan 1mg/2.5mg, Frovatriptan 2.5mg

Triptans of Note

Fast-acting, Cluster headache
• Sumatriptan sc >> Nasal (suma/zolm)

Effectiveness
• Rizatriptan, Eletriptan

Fewer AEs
• Almotriptan, Sumatriptan 25 mg, Naratriptan

Preventative
• Frovatriptan > Naratriptan, Eletriptan

Non MAO metabolism
• Eletriptan (CYP 3A4), Frovatriptan, Naratriptan

DHE
• α-adrenergic activity in addition to 5HT1B/D activity
• More nausea than triptans
• Vasoconstrictive
• May increase blood pressure
• Work later in attack (status migranosus, infusion therapy)
• DHE – minimal oral absorption (NS, IM, IV)
NSAIDs

- May suppress inflammation (mast cell activation, sensitization, fluid extravasation)
- May treat 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, inflammatory bowel disease
- Lower risk of medication-overuse?

**Mechanism of Action**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>PO</td>
<td>500-1100</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>PO, PR</td>
<td>25-75, 50</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>PO</td>
<td>75-150</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>PO</td>
<td>200-800</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>SL</td>
<td>40</td>
</tr>
<tr>
<td>Kеторолак*</td>
<td>IM, IV, NS</td>
<td>30-60, 15-60</td>
</tr>
<tr>
<td>Диклофенак*</td>
<td>PO, IM</td>
<td>50-100</td>
</tr>
<tr>
<td>Аспирин</td>
<td>PO</td>
<td>650-1000</td>
</tr>
<tr>
<td>Целекоксиб</td>
<td>PO</td>
<td>400</td>
</tr>
<tr>
<td>Толфенамид</td>
<td>PO</td>
<td>200-400</td>
</tr>
<tr>
<td>АСА-асетаминофен-кофеин</td>
<td>PO</td>
<td>250-250-65</td>
</tr>
</tbody>
</table>
Indomethacin

- 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?

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>
</tr>
<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

Opioids

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

Combination medications including barbiturates

- Best evidence for aspirin-acetaminophen-caffeine
- Isomethptene-dichoralphenazone-APAP (Midrin), Isomethptene-APAP (Migraten)
  - Contraindications: 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
Acute Treatment of Cluster Headache; Guidelines

• Level A
  • Oxygen
  • Sumatriptan 6mg SQ
  • Zolmitriptan 5mg NS

• Level B
  • SPG stimulation in CCH
  • Sumatriptan 20mg NS
  • Zolmitriptan 5mg and 10mg oral

• Level C
  • Cocaine/Lidocaine NS
  • Octreotide SQ

Treatment of uncommon headache syndromes

• 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

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