Acute and Preventive Treatments for Headache

Evidence based Review

Rashmi Halker Singh MD FAHS
Mayo Clinic, Phoenix AZ

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

Lipton RB. Headache. 2001; Lipton RB. Neurology. 2002

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.

Gronseth et al. AAN Clinical Practice Guidelines Manual 2011 Edition.

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 (corgard)	40 - 160 mg/d

β_1 selective

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

* FDA approved

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

Ranchord A. American Heart Journal 2016

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 $GABA_{A1}$ 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 $5\text{-}HT_{2C}$ receptor (cause of weight loss?)

Gryder DS J Neurosci. 2003; O'Neil PM Obesity 2012

Topiramate: AE

- **General**: Weight loss
- **Neurological**: Tingling, concentration /memory / language impairment,
- **Endo**: Decrease sex hormone levels (>200 mg),
- **Optho**: 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.

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

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 (α_1)-related** – orthostatic hypotension
- **Serotonergic** – nausea, sweating
- **Anti histamine (H_1)-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 5HT-1a and 5HT-2 receptors
  - treats serotonin syndrome/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
  - Evidence- Equals propranolol as migraine preventive
  - Dose- 16mg daily
  - AE- Dizziness
- **Vitamins, Minerals, Herbs**
  - Riboflavin (B2) 400 mg
  - Co- enzyme Q 10
  - Magnesium, Feverfew, Petadolex (Petasites hybridus)

Lars J Stovner et al. Cephalalgia 2013;0333102413515348

Prevention of Cluster Headache

Guidelines; Effective

- Level A
  - Suboccipital steroid injections
- Level B
  - Civamide 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%
  - Candasartan 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)

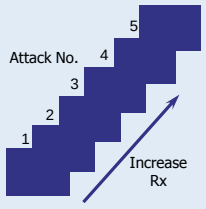
Acute Treatment Migraine

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

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

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)

6

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 & Prochlorperazine
- Anti-dopamine: IV Chlorpromazine & Droperidol
- IM/IV DHE
- Ketorolac
- Codeine/acetaminophen, Tramadol/acetaminophen

Marmura MJ et al. Headache. 2015 Jan;55(1):3-20.

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 (Naritriptan) to 26 hrs (Frovatriptan)

- Oral: Naratriptan 1mg/2.5mg, Frovatriptan 2.5mg

Triptans of Note

Fast-acting, Cluster headache	• Sumatripan sc >> Nasal (suma/zolmi)
Effectiveness	• Rizatriptan, Eletriptan
Fewer AEs	• Almotriptan, Sumatriptan 25 mg, Naratriptan
Preventative	• Frovatriptan > Naratriptan, Eletriptan
Non MAO metabolism	• Eletriptan (CYP 3a4), Frovatriptan, Naratriptan

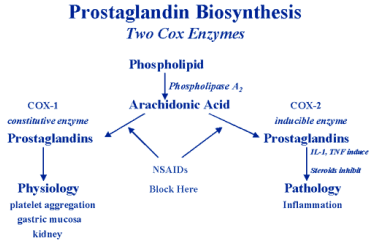
DHE

- 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



Drug	Route	Dose (mg)
Naproxyn	PO	500-1100
Indomethacin	PO, PR	25-75 , 50
Ketoprofen	PO	75-150
Ibuprofen	PO	200-800
Piroxicam	SL	40
Ketorolac*	IM, IV, NS	30-60 , 15-60
Diclofenac*	PO, IM	50-100
Aspirin	PO	650-1000
Celecoxib	PO	400
Tolfenamic acid	PO	200-400
ASA-acetominophen-caffeine	PO	250-250-65

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

Medication	Route	Dose (mg)
Metoclopramide	PO, IM, IV	5-20
Prochlorperazine	PO	5-10
	PR	25
	IV	5-10
Droperidol	IM, IV	0.625-2.5
Chlorpromazine	PO	25-100
	PR	50-100
	IV	10-50
Haloperidol	IM	5
	IV	2-5
Olanzepine	PO	2.5-20

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
- Isometheptene-dichoralphenazone-APAP (Midrin), Isometheptene-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

48

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

Robbins MS. Headache 2016

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