

LECTURE NOTES
N513:ADVANCED PHARMACOTHERAPEUTICS
HEADACHES

1. Headaches

- a. one of the most common complaints for primary care
- b. can range from mild to severe, be acute or chronic, and may last hours to days in duration
- c. most common headaches seen in primary care are the primary and secondary headaches
 - i. The practitioner must first rule out a secondary headache (or more serious cause of headache pain) and then accurately diagnose and treat the type of primary headache

Headaches Requiring Further Testing • Headache onset after age 50 • Sudden-onset headache • Accelerating headache pattern • Headache with fever and stiff neck • Abnormal results on the neurologic examination	Types of Headaches: Primary • Migraine • Tension-type headache (TTH) • Trigeminal autonomic cephalalgias (TACs) • Cluster headache
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1. Causes of Tension Headaches

- a. Stress
- b. Sleep dysregulation, fatigue
- c. Sunlight
- d. Anxiety
- e. Temperature
- f. Activity
- g. Traveling; reading

2. Adjuncts to Pharmacotherapy for Headaches

- a. Relaxation therapy
- b. Biofeedback
- c. Self-hypnosis
- d. Cognitive therapy
- e. Manual therapy (massage)

3. Goals of Drug Therapy for Tension Headaches

1. Reduce severity & frequency of headaches, thereby improving the patient's quality of life and ability to function
2. Select appropriate analgesic agents that will have the fewest side effects
3. Consider prophylactic therapy in addition to abortive analgesic agents for patients with more than two significant headaches per week

4. Therapy for Tension Headaches

- a. First line:
 - i. Aspirin (maximum dose of 650 mg)
 - ii. Acetaminophen (maximum daily dose of 3,250 mg)
 - iii. should be used no more than 2 days a week.
- b. Second line:
 - i. NSAIDs, caffeine-containing analgesics available OTC
- c. Third line:
 - i. butalbital-containing compounds (Fioricet or Fiorinal) may be used in patients without specific risk factors for these medications
 - ii. should never be used more than 3 days per month

ACETAMINOPHEN, NSAIDS, AND ASPIRIN

Aspirin/NSAIDS

1. alleviate mild to moderate tension headaches
2. Very effective
3. used as first-line therapy
4. Single dose ibuprofen; naproxen or aspirin
5. Diclofenac 2nd option

Acetaminophen

1. 1,000 mg dose can be very effective in treating mild to moderate tension headaches
2. Should be used in pregnant patients
3. Abortive Agents for Headaches
4. OTC agents containing acetaminophen, aspirin, and caffeine (such as Excedrin Extra Strength)

BUTALBITAL/ACETAMINOPHEN/CAFFEINE (FIORICET AND OTHERS)

1. Butalbital/aspirin/caffeine (Fiorinal and others)
 - a. Combination acetaminophen/narcotic products such as Vicodin and Percocet are not recommended

FIORICET	
butalbital/apap/caffeine barbiturate Mechanism of Action exact mechanism of action unknown, produces analgesia and anti-pyretic effects butalbital produces sedation caffeine produces cerebral vasoconstriction Cautions w/ Use: • Agranulocytosis/thrombocytopenia • respiratory depression • hepatotoxicity • hypersensitivity rxn/anaphylaxis/skin rxn	Dosage forms: • 50 mg/300 mg/40 mg • Max: 6 caps/day, do not exceed • 300 mg/day butalbital taper dose gradually to D/C if long-term use Interaction Characteristics: • Major CYP inducer • CNS depression • thyroid hormone clearance will be increased As always with any APAP containing medication the limits are to be discussed to maintain non-toxic levels.
Baseline/Monitoring Parameters • Cr at baseline • then if severe renal dz or in pts 65 yo and older, cont. periodically • LFTs if severe hepatic dz With chronic use dependency, abuse withdrawal sx if abrupt D/C and analgesic-assoc. nephropathy are possible	Pharmacokinetics Absorption/Distribution: Metabolism and excretion: CYP450: Excretion: ½ life: Renal ½ life:
Important precautions and contraindications • BBW: Associated with hepatotoxicity • CrCl<50; elderly patients, hx of drug use/abuse or alcohol use; porphyria Special populations Beers/STOPSTART • Avoid due to cognitive effects Pregnancy • Not recommended Children • Available in ped iatric doses	

PROPHYLAXIS OF TENSION HEADACHES

WHEN >>> More Than Two Headaches/Week

1. First line:
 - a. Amitriptyline
2. Second line:
 - a. Venlafaxine (Effexor/SNRI) @ 150 mg
 - b. Mirtazapine (Remeron, a tetracyclic antidepressant) at 30 mg
3. Tricyclic antidepressants (TCAs)
 - a. such as imipramine, doxepin, and protriptyline

MIGRAINE PHARMACOTHERAPY

Characteristics of Migraine Headaches • Recurrent headache; attacks lasting 4–72 hours • Unilateral location • Pulsating quality • Moderate or severe intensity • Aggravation by routine physical activity • Association with nausea and/or photophobia and phonophobia	Pathophysiology • Inherited susceptibility to brain excitability, intracranial blood vessel dilatation, and central sensitization of the trigeminovascular system • Serotonin • Changes in serotonin cause release of vasoactive neurotransmitters. • Causes inflammatory response • Excitatory serotonin receptors (5-HT₂) activated • Serotonin receptor agonists: abort migraines by stimulating inhibitory serotonin receptors (5-HT₁, 5-HT_{1D})
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Triggers: Migraine Headaches (list examples)

Psychological:

Medications:

Dietary factors:

Environmental, mechanical factors:

Lifestyle factors:

Hormonal factors:

G.O.T (GOALS OF TREATMENT)

1. Reduce the attack severity, frequency, & duration
2. Improve responsiveness to treatment of acute attacks
3. Improve function and reduce disability
4. Prevent progression or transformation of episodic migraine to chronic migraine

DRUGS FOR MIGRAINE TREATMENT

Abortive	Prophylactic
• Aspirin/NSAIDs • Triptans • Ergot derivatives • Barbiturates/opioids • Steroids	• Beta-blockers • Antidepressants • Anticonvulsants • Calcium channel blockers • CGRP's

Recommended Order of Treatment of Migraine Headaches

1. First line:
 - a. NSAIDs (oral) or aspirin
2. Second line:
 - a. Triptans
3. Third line:
 - a. Triptans plus an NSAID
4. CGRP's
 - a. Nurtec
5. Infrequent headache:
 - a. Ergotamine 1–2 mg
 - b. Dihydroergotamine 2 mg nasal spray

Migraine: Ergots

Vasoconstrictors

1. Ergotamine
 - a. Tablets/Suppositories
 - b. Adverse drug reactions (ADRs):
 - i. drug-rebound HA, vasoconstrictor effects, pregnancy category X
2. Dihydroergotamine (DHE)
 - a. Safer than ergotamine
 - b. Given intramuscular(IM) or intranasal
 - c. Pretreatment with antiemetic
3. Migraine: Triptans
 - a. Serotonin receptor agonists
 - i. Differ slightly in response
 - ii. Taken at onset of migraine
 - b. **Contraindications**
 - i. **Coronary artery disease , uncontrolled hypertension (HTN), pregnancy**
 - c. Drug interactions
 - i. Ergotamine, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors
 - d. First tier
 - i. Sumatriptan 50–100 mg
 - ii. Almotriptan 12.5 mg
 - iii. Rizatriptan 10 mg
 - iv. Eletriptan 40 mg
 - v. Zolmitriptan 2.5 mg
 - e. Slower effect/better tolerability:
 - i. naratriptan 2.5 mg
 - ii. frovatriptan 2.5 mg
4. Adjunctive agent: Anti-emetics
 - a. Nausea and vomiting common in migraine
 - b. Co-administered with abortive medication
 - c. Metoclopramide (Reglan)
 - i. boxed warning for use in children 2 years and younger and for its injectable formulation
 - d. Phenothiazines (Compazine)
 - i. boxed warning for use in older patients with dementia-related psychosis who are being treated with antipsychotics
 - e. Can augment pain-relieving properties of analgesics by decreasing gastric emptying and improving absorption
 - f. Can be sedating and have numerous other potential side effects, including neurologic and bone marrow effects

ERGOTAMINE/CAFFEINE	
• Mechanism of Action >> ergotamine stimulates alpha adrenergic receptors ○ producing peripheral vasoconstriction and decreased blood flow ○ exhibits serotonin antagonistic properties • caffeine enhances vasoconstrictive effects • Metabolism: ○ liver extensively (ergo) ○ CYP450: 3A4 substrate; 3A4 inhibitor • Excretion: ○ for ergotamine: bile 90% • Half-life: 2h (ergo) 3-7h (caffeine)	• Initial dosing: ○ 1-2 tabs PO q30min prn • Max dosing: ○ 6 mg/day, 10 mg/wk. (ergo) Monitoring Parameters >> Cr at baseline Interaction characteristics: • Caffeine is CYP1A2 substrate/CYP1A2 inhibitor leading to moderate hypertensive effects • Ergot alkaloid: STRONG CYP3A4 substrate/Potent 5-HT_{2B} receptor agonist leading to hypertensive effects and weak serotonergic effects
IMPORTANT PRECAUTIONS AND CONTRAINDICATIONS • BBW: peripheral ischemia/strong CYP3A4 Inhibitor. Avoid w/ protease inhibitors/macrolide abx >> risk of vasospasm leading to cerebral or peripheral ischemia. • CYP drugs avoid use with: zileuton; fluoxetine, fluvoxamine, nefazodone; clarithromycin, erythromycin, metronidazole, telithromycin; clotrimazole, fluconazole, itraconazole, ketoconazole; indinavir, nelfinavir, ritonavir, saquinavir. • Avoid grapefruit/juice SPECIAL POPULATIONS • Beers/STOPSTART ○ Avoid due to cognitive effects • Pregnancy ○ Not recommended/contraindicated (ergo)/ caffeine >200mg day review risk/benefit. • Children ○ NOT available in pediatric doses	

SUMATRIPTAN/IMITREX	
5-HT ₁ agonist Mechanism of Action: >> activates vascular serotonin 5-HT₁ receptors, producing vasoconstriction (selective serotonin agonist)	Baseline/Monitoring Parameters - BP at baseline - cardiovascular eval. at baseline - periodically during long-term tx if risk factors Interaction Characteristics: - Can cause CNS depression - hypertensive effects - lowers seizure threshold - Strong serotonergic effects
Metabolism and Excretion: liver extensively CYP450: unknown Excretion: urine 60% feces 40% half-life: 2.5h	- Dosing information - INITIAL: 25-100 mg PO x1 - Max: 200 mg/24h - may repeat dose x1 after 2h - may follow initial 4-6 mg SC dose after 1h w/ 25-100 mg PO q2h x1-2 doses - MAX: up to 100 mg/24h PO
IMPORTANT PRECAUTIONS AND CONTRAINDICATIONS - BBW: none. - Avoid within 14 days of MAO inhibitor - Do not use if using another HA medicine within 24 hours. SPECIAL POPULATIONS - Beers/STOPSTART - None - Pregnancy/Lactation - Risk benefit stratification no known teratogenicity. - Children - Available in pediatric doses (OFF LABEL age 6 years and above/see medication dosing online resource)	

How to determine if Prophylaxis Therapy is warranted

- more than 2 migraines per month
- 50% reduction in migraines is GOAL

3. 4 weeks minimum time to work
4. HA diary used to track effectiveness

Medications

- Beta blockers (propranolol, timolol)
- Antidepressants (amitriptyline, venlafaxine)
- Antiepileptic drugs (divalproex sodium, sodium valproate, and topiramate)

Beta Blockers: Migraine Prevention

Propranolol

- Start at 60 to 80 mg/day
- slowly increase MAX 240 mg/day
- Start children at 0.5 mg/kg/day and increase to 2 to 4 mg/kg/day.
- Perform 3-month trial.
- Reassess every 6 months
- Taper off slowly
- ADRs are fatigue, lethargy, depression
- Failure to respond does not predict response to another beta blocker.

Tricyclic Antidepressants: Migraine Prevention

- Amitriptyline (Elavil) Nortriptyline (Pamelor)
- Work on serotonin receptors
- Lower doses than for depression
- ADRs: drowsiness, weight gain, constipation

Antiepileptics: Migraine Prophylaxis

- Divalproex (Depakote)
- Decreases the number and intensity of migraine
- Baseline laboratory values and close monitoring
- Pregnancy category D

Gapapentin (Neurontin)

- Started low and titrated up over 4 weeks to target dose
- Well-tolerated

Other Migraine Prophylactic Drugs

NSAIDs

Naproxen twice daily
May be effective for menstrual migraines

Started a week before menses and continued for a week after

Calcium channel blockers

Verapamil

Patients with HTN who cannot tolerate beta blockers

Angiotensin-converting enzyme (ACE) inhibitors

Lisinopril and candesartan

Botulinum toxin

TOPAMAX /TOPIRAMATE	
carbonic anhydrase inhibitor Mechanism of Action - exact mechanism of action unknown - blocks voltage-dependent sodium channels - augments GABA activity - antagonizes glutamate receptors - inhibits carbonic anhydrase	Metabolism: liver minimally CYP450: 3A4 substrate & inducer (minor)/ CYP 2C19 weak inhibitor Excretion: urine 70% and is primarily unchanged Half-life: 21h 56h (ER form)
Dosing Initial: 25 mg PO qhs x1wk incr. by 25 mg/day per wk. Max: 200 mg/day taper dose gradually to D/C Renal - Doing adjustments needed - CrCl 10-70: 50% dose dec. - CrCl <10: 75% dose dec.	Baseline Parameters - Cr at baseline - bicarbonate at baseline, then periodically - s/sx depression, behavior changes, suicidality Alert practitioner if vision changes/loss, SI and depression, mood changes, kidney stones, weak bones (children/long term)
IMPORTANT PRECAUTIONS AND CONTRAINDICATIONS - BBW: none. - Avoid use in patients attempting reproduction/use effective contraception SPECIAL POPULATIONS - Beers/STOPSTART - None - Pregnancy/Lactation - Risk benefit stratification/ risk of teratogenicity. - Children	

- Available in pediatric doses 12 years and older (See medication dosing online resource)

Complementary and alternative medicine

Feverfew:

Butterbur

Magnesium

high-dose riboflavin (vitamin B2)

coenzyme Q10

<https://americanmigrainefoundation.org/resource-library/headache-prevention-complementary-alternative-medicine/>