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

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

<table>
<tr><th colspan="2">FIORICET</th></tr>
<tr><td>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</td><td>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.</td></tr>
<tr><td>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</td><td>Pharmacokinetics
Absorption/Distribution:

Metabolism and excretion:
CYP450:
Excretion:
½ life:
Renal ½ life:</td></tr>
<tr><td colspan="2">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</td></tr>
</table>

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-HT1D)

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

<table>
<tr><th colspan="2">ERGOTAMINE/CAFFEINE</th></tr>
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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)

</td><td>

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-HT2B receptor agonist leading to hypertensive effects and weak serotonergic effects

</td></tr>
<tr><td colspan="2">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

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<table>
<tr><th colspan="2">SUMATRIPTAN/IMITREX</th></tr>
<tr><td>5-HT1 agonist
• Mechanism of Action:
>> activates vascular serotonin 5-HT1 receptors, producing vasoconstriction (selective serotonin agonist)</td><td>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</td></tr>
<tr><td>Metabolism and Excretion:
liver extensively
CYP450: unknown
Excretion:
urine 60% feces 40%
half-life:
2.5h</td><td>• Dosing information
• INTIAL: 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</td></tr>
<tr><td colspan="2">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)</td></tr>
</table>

How to determine if Prophylaxis Therapy is warranted

1. more than 2 migraines per month
2. 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

<table>
<tr><th colspan="2">TOPAMAX /TOPIRAMATE</th></tr>
<tr><td>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</td><td>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)</td></tr>
<tr><td>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.</td><td>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)</td></tr>
<tr><td colspan="2">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</td></tr>
</table>

- 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/