HEADACHE
**HEADACHE**

- Caused by **pain referred to the scalp**, termed headache

**Statistics:**
- 3% of clinic patients (family practice, general practice, & internal medicine) list headaches as their chief complaint
- #5 emergency department chief complaint in the U.S.

**PATHOPHYSIOLOGY**

- Caused by either:
  - Involuntary muscle contraction = spasm of the scalp, neck, &/or shoulder
  - Pressure &/or inflammation of the tissues innervated by trigeminal nerve, supplying touch, pain, & temperature sensation to the:
    - Facial skin
    - Oral, nasal, & orbital membranes
    - Teeth
    - Temporomandibular joint–TMJ
    - Anterior 2/3ds of the tongue
    - External surface of the tympanic membrane
  - Although the cerebrum is not innervated by pain receptors, the surrounding meninges & vasculature (including the dural venous sinuses) are

  ... → **Trigeminal nucleus caudalis** mediated cerebrovascular dysregulation via perivascular trigeminal neuron release of vasoactive calcitonin gene related peptide–CGRP, serotonin, & substance P →
  - Extracranial vasodilation & inflammation →
    - **Throbbing headache**
  - Intracranial vasoconstriction → transient neuronal ischemia† → dysfunction → early disease sensory symptoms, termed **aura**, which may preceed headache by ≤ 1 hour
    - Occipital lobes → visual dysfunction →
- Flashing lights
- Changing object size &/or distance
- Photophobia

○ Parietal lobe → sensory dysfunction →
  - Paresthesias
○ Brain stem &/or cerebellum → vertiginous dysfunction →
  - Dizziness
  - Vertigo
○ Hypothalamus →
  - Nausea ± vomiting
  ...
  ...w/ subsequent intracranial vascular smooth muscle fatigue →
  • ↓↓ Vascular tone = flaccidity, w/ vascular pulsatile stretching →
  ○ Throbbing headache

† Neuronal ischemia rarely →
  • Cerebrovascular accident syndrome &/or seizure

---

**PRECIPITATING FACTORS**

General:
- Emotional &/or physical stress via upper body skeletal muscle tension
- Bright lights
- Strong odors
- Dietary
  - Caffeine, esp. withdrawal
  - Citrus fruits
  - Ethanol
  - Monosodium glutamate–MSG, being a flavor enhancer
  - Nitrates &/or nitrites, used in processed meats
  - Phenylethylamine: Chocolate, wine
  - Tyramine: Cheese, sour cream, yogurt, nuts
  - Fresh baked yeast products
- Hormone fluctuations
Menstruation
Perimenopause & menopause

**Medications**
- β receptor agonists
- Decongestants
- Estrogen containing medications: Oral contraceptives, hormone replacement therapy–HRT

**Extracranial:**
- Poor vision
- Nasopharyngeal &/or paranasal sinus mucosal inflammation
  - Allergy &/or infection→
    - Rhinitis, sinusitis, &/or pharyngitis
- Temporal arteritis
- Irradiation

**Intracranial:**
- ↑Intracranial pressure
  - Inflammation
    - Encephalitis
    - Meningitis
    - Subarachnoid hemorrhage
  - Tumor
    - Abscess
    - Neoplasm
    - Intracerebral, epidural, &/or subdural hemorrhage
  - Hydrocephalus
  - Hypertensive encephalopathy
  - Idiopathic intracranial hypertension = Pseudotumor cerebri
- ↓Intracranial pressure
  - Cerebrospinal fluid (removal of ≥ 20mL)→
    - Non–nervous tissue tugging
- Meningeal irritants
  - Ethanol
  - Constipation mediated colonic toxin absorption
- Nerve impingement
Trigeminal neuralgia

**DIAGNOSIS/ RISK FACTORS**

- **Tension headache**—most common
  - **Bilateral**—90%, mild–moderate dull headache, lasting hours–days w/ varying frequency. Auras being unusual—10%

- **Migraine headache**
  - **Unilateral**—80%, excruciating, *throbbing headache* (including the peri/ retro–orbital areas), lasting several hours to days w/ varying frequency
  - Termed ‘complicated’ if accompanied by a stereotypical *neurologic deficit*, which may last hours
  - Usually accompanied by an *aura*—60%
    - A spreading *scintillating scotoma*—20% (formations of dazzling zig–zag lines) in the visual field, being *pathognomonic for migraine headache*
    - Nausea ± vomiting
    - Sensitivity to light = photosensitivity → avoidance of light = photophobia
    - Sensitivity to sound = phonosensitivity → avoidance of loud sounds = phonophobia
    - Sensitivity to movement

Risk factors:
- **Gender**: ♀ 3X ♂, affecting 15% of ♀ vs. 5% of ♂
- **Genetic**: Family history

- **Cluster headache**
  - **Unilateral**, excruciating headache in the periorbital &/or retro–orbital areas, being both:
    - **Paroxysmal**: Lasting ≤ 1 hour
    - **Periodic**: Occurring over the course of several weeks–months, termed *clusters*
  - Usually accompanied by *ipsilateral*:
    - Ophthalmologic: *Conjunctival inflammation = injection, tear*
production = lacrimation, ↓pupil size = miosis, &/or drooping eyelid = ptosis
– Nasal congestion ± coryza
– Forehead & facial sweating
Risk factors:
  • Gender: ♂ 10X ♀

• Trigeminal neuralgia
  ◦ Unilateral, excruciating electric shock–like pain, lasting seconds to hours
    – Forehead via the ophthalmic branch = V1
    – Midface via the maxillary branch = V2
    – Mandibular area via the mandibular branch = V3
    … usually due to a tortuous vessel compressing the trigeminal nerve root as it enters the brain stem
  ◦ Many patients describe a facial ‘trigger area’ that may incite an attack via touch or even wind
Prognosis:
  • May spontaneously remit @ 6–12 months

• Idiopathic intracranial hypertension = pseudotumor cerebri
  ◦ Idiopathic ↑intracranial pressure→
    – Headaches
    – Visual changes
Risk factors:
  • Gender: Obese young ♀
  • Tetracycline antibiotics
Opthalmoscopy:
  • Being that the dura mater of the brain extends as a sheath around the optic nerve, connecting w/ the sclera of the eye, intracranial pressure is transmitted through the optic nerve into the eye, w/ the ophthalmologic exam in a patient w/ ↑intracranial pressure possibly showing papilledema, identified via:
    ◦ Congestion &/or hemorrhage of the peripapillary veins→
      – Loss of normal venous pulsation, being the earliest sign
- Blurring of the normally sharp optic disk margins
- Bulging of the optic disk

**Eye disease headache**
- **Poor vision** →
  - ↑Ciliary muscle contraction ± ↑contraction of facial &/or extraocular muscles, which, when prolonged → retro-orbital headache
- ↑**Eye irradiation via light rays** (esp. ultraviolet light as by watching the sun) →
  - Conjunctival irritation → surface &/or retro-orbital headache

**Ethanol headache**
- ↑↑Alcohol consumption = binge →
  - Meningeal irritation → headache, termed “hangover”

**Constipation headache**
- Constipation →
  - ↑Absorbed colonic toxins → meningeal irritation → headache

**TREATMENT**

- Being that all headache types may respond to the following medications, a response cannot be used to differentiate among the various etiologies

**TENSION HEADACHE**
- Avoidance of precipitating factors

---

**ACETAMINOPHEN**

<table>
<thead>
<tr>
<th>M/♀: Dose (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LK/ P: 650mg PO/ PR or 1g IV q6hours prn (4g/24hours)</td>
</tr>
</tbody>
</table>

**Mechanism:**
- Reversible inhibition of the cyclooxygenase–COX 1 enzyme in the central nervous system → peripheral tissues →
  - Predominantly ↓central nervous system prostaglandin synthesis →
- ↓Pain
- ↓Temperature (antipyretic)
  ...w/ minimal effects on inflammatory cell mediated inflammation

**Background physiology:**
- Presynaptic neuronal mediated prostaglandins are released in response to afferent signals, indicating peripheral inflammation→
  - Enhanced sensitivity of pain neurons (but not direct excitement)→
    - Pain
- Interleukin–IL1→
  - ↑Hypothalamic prostaglandin production→
    - Fever

**Side effects:**

**Gastrointestinal**
- **Hepatitis**

  **Mechanism:**
  - 90% of Acetaminophen undergoes either hepatocyte mediated:
    - Glucuronidation→
      - Nontoxic glucoronides
    - Sulfation→
      - Nontoxic sulfates
  - 10% of Acetaminophen undergoes hepatocyte mediated oxidation by the cytochrome P450 enzyme complex→
    - A potentially toxic reactive electrophilic compound, which then undergoes either:
      - Conjugation w/ cellular glutathione→nontoxic compound
      - Reaction w/ cellular proteins→cellular toxicity ± death→**hepatitis**
  - Normally, glutathione depletion occurs w/ ingestion of >10g of Acetaminophen. However, any substance which ↑cytochrome P450 function (such as ethanol) causes relatively more Acetaminophen to be diverted to the formation of the toxic compound→
    - More rapid hepatocyte depletion of glutathione→Cell toxicity at lower ingested Acetaminophen doses

**Contraindications:**
- **Do not administer Acetaminophen to chronic heavy ethanol drinkers**
Nonsteroidal Anti-Inflammatory Drugs—NSAIDs

*One cannot predict which NSAID a patient will respond to*

<table>
<thead>
<tr>
<th>Generic</th>
<th>M/♀: Start (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>L/P in 1st &amp; 2nd, U in 3rd trimester: 600mg PO/IV q8hours (3.2g/24hours)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>L/P in 1st &amp; 2nd, U in 3rd trimester: 50mg PO/PR q8hours</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>L/P in 1st &amp; 2nd, U in 3rd trimester: 15mg IM/IV q6hours (30mg q6hours X 5days†)</td>
</tr>
</tbody>
</table>
| Naproxen | L/P in 1st & 2nd, U in 3rd trimester: 375mg PO q12hours
  •XR form: 750mg PO q24hours |

†Due to potency

**Ketorolac specific dose adjustment to max of 60mg/24hours:**

- Age ≥65 years
- <50kg weight
- Renal failure

**Mechanism:**

- Aspirin & other anti-inflammatory medications→
  - Respectively to irreversible & reversible inhibition of both cyclooxygenase enzymes (COX-1 & COX-2), being responsible for the production of neural & inflammatory cell prostaglandins respectively→
    - ↓Pain
    - ↓Temperature (antipyretic)
    - ↓Inflammation

**Background pathophysiology:**

- Inflammatory cell mediated prostaglandins are released at sites of inflammation (in addition to other inflammatory cytokines)→
  - Leukocyte migration
  - Vasodilation→↑blood flow→
    - Erythema, edema, warmth, &/or tenderness/ pain via enhanced neuronal sensitivity
- Interleukin-1 IL1→
  - ↑Hypothalamic prostaglandin production→
    - Fever

**In Brief:**
• Cyclooxygenase COX–1 enzymes are found in most cells of the body, being responsible for normal physiologic processes

• Cyclooxygenase COX–2 enzymes are responsible for the production of inflammatory cell prostaglandins

Side effects:

Cardiovascular

• ↓ Production of vasodilatory prostaglandins →
  ◦ Hypertension, w/ an average rise of 5 mmHg

Gastrointestinal

• Inhibition of the cyclooxygenase COX–1 enzyme → ↑ peptic inflammatory disease risk → upper gastrointestinal hemorrhage – 2% via:
  ◦ ↓ Gastric mucosal prostaglandin synthesis →
    – ↓ Epithelial cell proliferation
    – ↓ Mucosal blood flow → ↓ bicarbonate delivery to the mucosa
    – ↓ Mucus & bicarbonate secretion from gastric mucosal cells

Indications for peptic inflammatory disease prophylaxis:

• Prophylaxis w/ proton pump inhibitors – PPI’s, histamine 2 selective receptor blockers, or Misoprostol in patients w/ any of the following:
  ◦ Age > 60 years w/ a history of peptic inflammatory disease
  ◦ Anticipated therapy > 3 months
  ◦ Concurrent glucocorticoid use
  ◦ Moderate to high dose NSAID use

Genitourinary

• Patients w/ pre–existing bilateral ↓ renal perfusion, not necessarily failure:
  ◦ Heart failure
  ◦ Bilateral renal artery stenosis
  ◦ Hypovolemia
  ◦ Renal failure
  … rely more on the compensatory production of vasodilatory prostaglandins →
  • Afferent arteriole dilation →
    ◦ Maintained glomerular filtration rate – GFR, whereas NSAIDs →
      – ↓ Prostaglandin production, which may → renal failure

Pulmonary

• Inhibition of both cyclooxygenase enzymes (COX–1 & COX–2) → ↑ Lipoxygenase activity →
Leukotriene synthesis → symptomatic asthma within 2 hours of ingestion in 5% of Asthmatics

Maternofetal
Fetal effects:
• Constriction ± closure of the ductus arteriosus (during the 3rd trimester) →
  ○ Pulmonary hypertension
• Necrotizing enterocolitis
• Nephropathy →
  ○ ↓ Amniotic fluid formation →
    – Oligohydramnios

Interactions:
• ↓ Tissue prostaglandin synthesis →
  ○ ↓ Effectiveness of loop & thiazide diuretics (both diuretic & peripheral vascular effects)

MIGRAINE / CLUSTER HEADACHE
• Same as Tension headache w/ the addition of the following:
• Overuse of the Triptans or Ergot alkaloids (≥ 2 days/ week X > 3 months) may →
  ○ Medication overuse headache, occurring ≥ 15 days/ month

ANTIEMETIC MEDICATIONS
• Although used for nausea/ vomiting, these medications often times relieve the underlying headache as well, the mechanism of which is thought to be due to dopamine receptor antagonism in the trigeminal nucleus caudalis

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Dose (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide (Reglan)</td>
<td>K/ P: 10mg PO/ IM/ IV (15mg q6hours)</td>
</tr>
<tr>
<td>Prochlorperazine (Compazine)</td>
<td>LK/ ?: 5mg PO/ IM/ IV (10mg q6hours)</td>
</tr>
</tbody>
</table>

Metoclopramide additional mechanism:
• ↑ Gastric motility →
  ○ ↑ Gastric emptying, thus facilitating the absorption of PO medications, especially as a migrainemay cause gastric stasis, in addition to nausea ± vomiting

Side effects:
  Neurologic
• Dopamine receptor blockade→
  ○ **Extrapyramidal dysfunction**, esp. w/ IV administration→
    – **Secondary Parkinson’s disease**, esp. motor restlessness, termed
      **akathisia**→ difficulty remaining in a sitting posture (treat w/ Diphenhy-
      dramine)

**Prochlorperazine specific:**

**Cardiovascular**
• Dysrhythmias
• Hypotension w/ IV administration

**Mucocutaneous**
• Gynecomastia, being the ↑ development of male mammary glands

**Neurologic**
• Anticholinergic effects
• Sedation
• Seizures

**Hematologic**
• Leukopenia
• Thrombocytopenia

**Contraindications:**
• Parkinson’s disease/ syndrome

---

**SEROTONIN (5-HT\textsubscript{1B/1D}) RECEPTOR AGONISTS aka ‘Triptans’**
• One cannot predict which ‘Triptan’ a patient will respond to

<table>
<thead>
<tr>
<th><strong>Generic</strong> (Trade)</th>
<th><strong>M/♀: Start (Max)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Almotriptan</strong> (Axert)</td>
<td>LK/♀: 12.5mg PO q2hours prn (25mg/ 24hours)</td>
</tr>
<tr>
<td><strong>Eletriptan</strong> (Relpax)</td>
<td>LK/♀: 20–40mg PO q2hours prn (80mg/ 24hours)</td>
</tr>
<tr>
<td><strong>Frovatriptan</strong> (Frova)</td>
<td>LK/♀: 2.5mg PO q2hours prn (7.5mg/ 24hours)</td>
</tr>
<tr>
<td><strong>Naratriptan</strong> (Amerge)</td>
<td>KL/♀: 2.5mg PO q4hours prn (5mg/ 24hours)</td>
</tr>
<tr>
<td><strong>Rizatriptan</strong> (Maxalt)</td>
<td>LK/♀: 5–10mg PO q2hours prn (30mg/ 24hours)</td>
</tr>
</tbody>
</table>
  • Dissolving form: Same dosing
| **Sumatriptan** (Imitrex) | K/♀: 50–100mg PO q2hours prn (200mg/ 24hours) |
  • SC form: 6mg q1hour prn (12mg/ 24hours) |
  • Intranasal form: 5–20mg q2hours prn (40mg/ 24hours) |
<table>
<thead>
<tr>
<th><strong>Zolmitriptan</strong> (Zomig)</th>
<th>L/ ?: 2.5–5mg PO q2hours prn (10mg/ 24hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dissolving form</td>
<td>2.5mg PO q2hours prn (10mg/ 24hours)</td>
</tr>
<tr>
<td>• Intranasal form</td>
<td>5mg q2hours prn (10mg/ 24hours)</td>
</tr>
</tbody>
</table>

**Onset:**
- PO form: 30–60minutes, except Frovatriptan & Naratriptan requiring ~2hours
- Intranasal & SC forms: 10minutes

**Mechanism:**
- ↓Trigeminal nucleus caudalis release of calcitonin gene related peptide–CGRP & substance P (in addition to serotonin antagonism)→
  - ↓Cerebrovascular dysregulation via:
    - ↓Extracranial vasodilation & inflammation
    - ↓Intracranial vasoconstriction

**Outcomes:**
- 30% of patients experience a recurrence within 24hours, usually responding to a second dose

**Side effects:**

**Cardiovascular**
- • Vasoconstriction→
  - ○ Hypertension

**Gastrointestinal**
- • Nausea ± vomiting

**Mucocutaneous**
- • Cutaneous flushing reaction

**Musculoskeletal**
- • Neck, throat, jaw, &/or chest pain, pressure, &/or stiffness

**Neurologic**
- • Dizziness
  - • Paresthesias via tingling &/or sensations of warmth in the head, neck, chest, & limbs

**Interactions:**
- • **Serotonin syndrome**, being an idiosyncratic, life threatening complication of combining ≥ 2 serotonergic medications, esp. a **monoamine oxidase inhibitor** w/ another serotonergic medication:
  - ○ Any other antidepressant, esp. selective serotonin reuptake inhibitors
○ Opiates, esp. Dextromethorphan & Meperidine
○ Amphetamine–like: Phentermine
○ Antibiotics: Linezolid
○ Antihistamines: Chlorpheniramine
○ Antipsychotics: Risperidone
○ CNS stimulants: Methylphenidate
○ Illicit drugs: Cocaine, Lysergic acid diethylamide–LSD, Methylenedioxymethamphetamine–MDMA or Ecstasy
○ Other: Buspirone, Lithium, Sibutramine

...Being an idiosyncratic, life threatening complication→
  • Autonomic nervous system dysfunction→
    ○ Diaphoresis
    ○ Dysrhythmia
    ○ Fever→
      – Hyperthermia
    ○ Hypertension or hypotension
    ○ Tachycardia
  • Somatic nervous system dysfunction→
    ○ Hyperreflexia
    ○ Shivering
    ○ Tremor
  • Altered mental status
  • Diarrhea
  • Disseminated intravascular coagulation–DIC
  • Dyspnea
  • Renal failure
  • Seizures

Contraindications:
  • Uncontrolled hypertension
  • Coronary artery disease
  • Cerebrovascular disease
  • Concurrent use of Ergotamine preparations (within 24 hours), as the combination→
    ○ Significant vasoconstriction

ERGOT ALKALOIDS: Triptans are preferred, due to the following disadvantages:
  • Erratic pharmacokinetics
- Lack of evidence regarding effective doses
- Relatively more potent & sustained vasoconstrictor effects

<table>
<thead>
<tr>
<th><strong>Generic</strong> (Trade)</th>
<th><strong>M/ ♀: Dose (Max)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydroergotamine</td>
<td>(DHE) L/ U: 1mg qhour prn SC/ IM/ IV (3mg/ 24hours or 6mg/ week)</td>
</tr>
<tr>
<td>• Intranasal form (Migranal)</td>
<td>0.5mg each nostril q15min prn (3mg/ 24hours or 4mg/ week)</td>
</tr>
<tr>
<td>Ergotamine/ caffeine (Cafergot)</td>
<td>ML/ U: 2 tabs PO (1mg/ 100mg tabs), then 1 tab q30minutes prn (6tabs/ 24hours or 10/ week)</td>
</tr>
<tr>
<td>• Rectal form</td>
<td>2mg/ 100mg q1hour prn (2supp/ 24hours or 5/ week)</td>
</tr>
</tbody>
</table>

**Side effects:**

**General**
- Cardiac valve, pleural, pericardial, &/or retroperitoneal fibrosis w/ chronic use

**Gastrointestinal**
- Nausea ± vomiting

**Contraindications:**
- Renal failure
- Hepatic failure
- Uncontrolled hypertension
- Coronary artery disease
- Cerebrovascular disease
- Concurrent use of 5–HT1 receptor agonists (within 24hours), as the combination →
  - Significant vasoconstriction

---

**MAGNESIUM SULFATE**

<table>
<thead>
<tr>
<th><strong>M/ ♀: Dose</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>K/ S: 2g IV infusion over 20minutes</td>
</tr>
</tbody>
</table>

**Mechanism:**
- Vascular & organ smooth muscle relaxation →
  - Vasodilation
SUPPLEMENTAL CLUSTER HEADACHE TREATMENT
• 100% Oxygen via a non-rebreathing face mask @ 7–10L/minute X 15 minutes
Outcomes:
• Improvement in 60% of patients via cerebral vasoconstriction

TRIGEMINAL NEURALGIA

ANTISEIZURE MEDICATIONS
• Being that many antiseizure medications have a relatively narrow therapeutic window between the effective dose & toxicity (unlike other medications), substitution of trade to generic versions should be undertaken w/ caution. If possible, generic refills should come from the same manufacturer

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀ Start (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>(Tegretol)</td>
</tr>
<tr>
<td>100mg PO q12h, then titrate q2days by 200mg/24h prnpain (1.2g/24h)</td>
<td></td>
</tr>
</tbody>
</table>

• The anti–seizure therapeutic plasma level is 4–12μg/ mL

Side effects: Withdrawal from anti–seizure medications should be done gradually in order to prevent rebound ↑seizure frequency &/or severity

General
• Fever
• ↑Weight

Cardiovascular
• Heart block

Gastrointestinal
• Diarrhea
• Nausea ± vomiting
• Hepatitis

Mucocutaneous
•Dermatitis, including Erythema multiforme, & its severe variants:
  ○Toxic epidermal necrolysis–TEN
  ○Stevens–Johnson syndrome–SJS

Carbamazepine specific screening:
  •HLA–B*1502 genotyping in Asians, in whom:
    ○This allele occurs almost exclusively
    ○Carbamazepine mediated SJS occurs 10X relative to other ethnic groups
    ...being highly associated w/ ↑Carbamazepine mediated SJS risk

Musculoskeletal
  •Hepatic enzyme inducing antiseizure medications likely→
    ○Osteoporosis, w/ the recommendation of concurrent Vitamin D & calcium supplemen-tation

Neurologic
  •Aseptic meningitis
  •Altered mental status
  •Double vision = diplopia
  •Headache
  •Incoordination = ataxia
  •↓Neuropathic pain
  •Sedation

Hematologic
  •Agranulocytosis (1/ 200,000)
  •Aplastic anemia (1/ 500,000)
  •Benign leukopenia
  •Hyponatremia
    •Pseudolymphoma: A benign lymphocytic skin infiltrate that mimics cutaneous lymphoma, usually resolving within several months after discontinuation
    •Thrombocytopenia, w/ ↑doses

Overdose:
  **Pulmonary**
    •Respiratory depression

Interactions:
  •Hepatic enzyme inducing antiseizure medications→↑hepatic clearance of:
    ○Antiretroviral medications
    ○Chemotherapeutic medications
- Immunosuppressive medications (ex: glucocorticoids, Cyclosporine)
- Oral contraceptive pills. Therefore, ♀s taking these medications should use preparations containing ≥ 50μg of ethinyl estradiol to ↓ pregnancy risk

**Monitoring:**
- Plasma medication levels should be checked @:
  - Baseline, after initiating treatment, & until therapeutic levels are reached & sustained
  - Addition of a potential interacting medication
  - Change in gastrointestinal, hepatic, or renal function
  - Occurrence of side effects
  - Pregnancy, which ↑ the clearance of many antiseizure medications

## SECOND LINE

### TRICYCLIC ANTIDEPRESSANTS—TCAs

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/ ♀: Start (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine (Norpramine)</td>
<td>L/ ?: 25mg PO qhs (300mg/ 24hours)</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor)</td>
<td>L/ U: 25mg PO qhs (150mg qhs)</td>
</tr>
</tbody>
</table>

**Mechanism:**
- Inhibit the presynaptic reuptake of Norepinephrine > Serotonin→
- ↑ Synaptic cleft concentrations

## THIRD LINE

- Glycerol injection into the region of the ipsilateral trigeminal nerve root
- Microvascular nerve root decompression via posterior fossa craniotomy

## IDIOPATHIC INTRACRANIAL HYPERTENSION

- Weight loss if obese
- **Lumbar puncture,** w/ normalization of cerebrospinal fluid pressure (<18 cm = 180 mmH2O in the lateral decubitus position)

  **Procedure:**
  - Performed through the L3–L4/ L4–L5 interspace (typically found via an imaginary line connecting the iliac crests) as the
spinal cord ends at ~L1–L2
  ◦ Basic testing requires <10mL of cerebrospinal fluid, w/ more required for additional tests (likely safe maximum being 20mL)

Side effects:
  • **Post–lumbar puncture headache 10–30%**
    ◦ Cerebrospinal fluid aspiration w/ continued leak via the lumbar puncture dural rent →
      ↓Cerebrospinal fluid, **w/ loss of ≥20mL** → ↓intracranial pressure → non–nervous tissue tugging → **upright postural headache**, **w/ usual onset within 48 hours ± tinnitus &/or ↓hearing. Relieved upon recumbency, w/ resolution occurring gradually over hours to 2 weeks**
    **Note:** The adult cerebrospinal fluid volume is ~150mL, w/ production being 450mL/24 hours (0.3mL/min)
  • Cerebral venous thrombosis–rare, not being postural

Prevention of headache:
  • Use the smallest gauge needle practical, while aligning the bevel parallel to the dural fibers which run longitudinally, in order to separate, not cut, the fibers
  • The following have not been shown to be risk factors:
    ◦ Position or hydration before, during, or after the procedure

Treatment of headache:

<table>
<thead>
<tr>
<th>METHYLXANTHINES</th>
<th>M/♀: Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caffeine (Vivarin)</strong></td>
<td>L/♀: 500mg PO q4hours prn, being absorbed within 15–45min</td>
</tr>
<tr>
<td><strong>Caffeine sodium benzoate</strong></td>
<td>500mg IM/IV q4hours prn</td>
</tr>
</tbody>
</table>

Mechanism:
  • Methylxanthines →
    ◦ Adenosine receptor antagonism →
      • Cerebral vasoconstriction
• For severe &/or prolonged headaches, ask an anesthesiologist to place an **epidural blood patch**, consisting of 20mL of autologous venous blood injected into the epidural space previously punctured→
  ◦ Immediate relief in 95% of patients

**Contraindications:**
• Infection involving the path of the spinal needle
  ◦ Cellulitis
  ◦ Epidural abscess
• Coagulopathy (INR > 1.3 &/or PTT > 35seconds) &/or thrombocytopenia (< 50,000/ μL)→
• ↑ Intracranial pressure due to a localized lesion
  ◦ Abscess
  ◦ Localized edema
  ◦ Localized hemorrhage
  ◦ Neoplasm
  … which may→
  • **Focal neurologic deficits**

<table>
<thead>
<tr>
<th>CARBONIC ANHYDRASE INHIBITORS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic</strong> (Trade)</td>
</tr>
<tr>
<td><strong>Acetazolamide</strong> (Diamox)</td>
</tr>
</tbody>
</table>

**Mechanism:**
• ↓ Choroid plexus mediated cerebrospinal fluid formation→
  ◦ ↓ Intracranial & intraocular pressures
• ↓ Ciliary epithelium mediated aqueous humor formation→
  ◦ ↓ Intraocular pressure

**Side effects:**
**General**
• Anorexia
**Gastrointestinal**
• Diarrhea
• Metallic taste

Hematologic
• ↓Renal tubular bicarbonate ion reabsorption →
  ◦ Hypokalemic, hyperchloremic, non-anion gap metabolic acidemia

Contraindications:
• Sulfa allergy, due to a sulfa component

Note:
• If signs &/or symptoms remit, discontinue Acetazolamide
• If signs &/or symptoms persist, perform serial lumbar punctures as above w/ continuation of Acetazolamide
• If signs &/or symptoms persist despite serial lumbar punctures, consider surgical treatment (lumboperitoneal cerebrospinal fluid shunting vs. optic nerve sheath fenestration) in order to prevent ischemic optic neuropathy →
  ◦ Blindness

PROPHYLAXIS

MIGRAINE / CLUSTER HEADACHE
• All migraine headache medications are considered of equal efficacy, but differ greatly in their side effect profile. A patient may need to try several classes of medication in order to find the one that works best for their biology, w/ the least & most tolerable side effects. If there is an inadequate response to the maximum tolerable dose of the initial medication @ 2–3months, then switch to another

Migraine headache indications:
• ≥ 2 episodes/ month
• Headache refractory to abortive treatment
• Abortive medication intolerance &/or contraindications
• Predictable pattern of occurrence
  …w/ 65% of patients experiencing a 50%↓ in frequency

Cluster headache indications:
• Onset of a cluster headache episode, & continued for several weeks if episodic, or indefinitely if non-episodic (near daily)
**β1 SELECTIVE RECEPTOR BLOCKERS** (Cardiorenal selective): Being less selective w/ ↑dosage

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Start (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol (Tenormin)</td>
<td>K/ U: 25mg PO q24hours (100mg/ 24hours)</td>
</tr>
<tr>
<td>Metoprolol (Lopressor)</td>
<td>L/♀: 25mg PO q12hours (225mg q12hours)</td>
</tr>
<tr>
<td>•XR form (Toprol XL)</td>
<td>50mg PO q24hours (400mg q24hours)</td>
</tr>
</tbody>
</table>

**Mechanism:**
- Competitive antagonist of the β1 ± β2 receptor
  - ↓Sinoatrial & atrioventricular node conduction (β1) ➔
  - ↓Pulse
  - Anti-dysrhythmic via nodal effects (β1)
  - ↓Cardiac muscle contractile strength (β1)
  - ↓Juxtaglomerular cell renin release (β1) ➔
    - ↓Angiotensin 1, angiotensin 2, & aldosterone formation
  - ↓Cardiovascular remodeling
  - ↑Vascular/ organ smooth muscle contraction (β2) via relatively ↑α1 receptor stimulation = ‘unopposed α effect’ ➔
    - Vasoconstriction
    - Bronchoconstriction
    - Uterine contraction
  - ↓Tremor (β2)
  - ↓Hepatocyte glycogenolysis (β2)
- ↓Extrathyroidal tetraiodothyronine–T4 (also termed thyroxine) conversion to the more metabolically active triiodothyronine–T3 form

**Side effects:** Most patients w/ chronic obstructive pulmonary disease–COPD (including asthma), diabetes, &/or peripheral vascular disease can be safely treated w/ **cardioselective β1 receptor blockers**, as they have ↓peripheral effects

**General**
- Fatigue
- Malaise

**Cardiovascular**
- Bradycardia ± heart block
- Hypotension
  - Orthostatic hypotension
  - Pelvic hypotension† ➔
- Impotence, being the inability to achieve &/or maintain an erection. However, Nebivolol may actually improve impotence

  • Initial worsening of systolic heart failure
  • Worsening symptoms of peripheral vascular disease
    ◦ Impotence
    ◦ Intermittent claudication
    ◦ Raynaud’s phenomenon

**Pulmonary**
  • Bronchoconstriction

**Endocrine**
  • Hyperglycemia
  • May block catecholamine mediated:
    ◦ Physiologic reversal of hypoglycemia via:
      – ↓ Hepatocyte gluconeogenesis & glycogenolysis
    ◦ ↓ Hypoglycemic symptoms, termed hypoglycemic unawareness →
      – ↓ Tachycardia as a warning sign

**Gastrointestinal**
  • Diarrhea
  • Nausea ± vomiting
  • Gastroesophageal reflux

**Mucocutaneous**
  • Hair thinning

**Neurologic:** β receptor blockers w/ ↓ lipid solubility (Atenolol) cross the blood brain barrier less readily, but have not been shown to cause fewer neurologic side effects
  • Sedation
  • Sleep alterations
  • ↓ Libido →
    ◦ Impotence

**Psychiatric**
  • Depression

**Hematologic**
  • Hyperkalemia
  • ↓ High density lipoprotein–HDL levels
  • ↑ Triglycerides

**Contraindications:**
  **Cardiovascular**
Acutely decompensated heart failure
• Hypotension
• Pulse <50bpm
• Atrioventricular heart block of any degree
• Wolf Parkinson White–WPW syndrome

Pulmonary
• Moderate to severe chronic obstructive pulmonary disease–COPD, including asthma

Caution:
• In certain hyper-catecholamine states, a hyper-vasoconstrictive state may develop due to vascular smooth muscle contraction via β2 receptor blockade in the setting of α1 receptor stimulation, termed the ‘unopposed α effect’→
  • Vasoconstriction→
    – Myocardial ischemic syndrome
    – Cerebrovascular accident syndrome
    – Peripheral vascular ischemic syndrome
    …for which Carvedilol & Labetalol may be used due to their α1 blocking property, & Nebivolol due to its nitric oxide mediated vasodilating property

Hypercatecholamine states:
• Amphetamine use
• Cocaine use→
  • Varying ischemic syndrome onset per administration route, & may occur @ minutes to days (usually within 3 hours)
• Clonidine withdrawal
• Monoamine oxidase inhibitor–MAOi mediated tyramine effect
• Pheochromocytoma

<table>
<thead>
<tr>
<th>CALCIUM CHANNEL BLOCKERS: Non–dihydropyridines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic</strong></td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>• XR form</td>
</tr>
<tr>
<td>• Calan XR form</td>
</tr>
<tr>
<td>• Veleran XR form</td>
</tr>
<tr>
<td>• Covera XR form</td>
</tr>
</tbody>
</table>
Mechanism:

• Block voltage dependent calcium ion channels in smooth & cardiac muscle →
  ◦ ↓ Calcium influx →
  – ↓ Sinoatrial & atrioventricular node conduction (non–dihydropyridines) → ↓ pulse
  – Anti–dysrhythmic via nodal effects (mainly non–dihydropyridines)
  – ↓ Cardiac muscle contractile strength (mainly non–dihydropyridines)
  – Vasodilation: Arterial > venous (mainly dihydropyridines)

Side effects:

Cardiovascular
  • Bradycardia ± heart block
  • Edema
  • Flushing
  • Hypotension

Gastrointestinal
  • Constipation, esp. Verapamil
  • Nausea ± vomiting

Mucocutaneous
  • Gingival hyperplasia

Neurologic
  • Dizziness
  • Headache

Contraindications:
  • Wolf Parkinson White–WPW syndrome

SECOND LINE

TRICYCLIC ANTIDEPRESSANTS–TCAs

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Start (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine (Norpramine)</td>
<td>L/ ?: 25mg PO qhs (300mg/ 24hours)</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor)</td>
<td>L/ U: 25mg PO qhs (150mg qhs)</td>
</tr>
</tbody>
</table>

Mechanism:

• Inhibit the presynaptic reuptake of Norepinephrine > Serotonin →
  ◦ ↑ Synaptic cleft concentrations

Side effects:

General
  • ↑ Appetite →
Cardiovascular
  • Dysrhythmias, esp. w/ a QRS complex > 0.10sec
  • Ventricular dysrhythmias occur w/ a QRS complex > 0.16sec

Neurologic
  • ↑Neuropathic pain
  • Precipitation of manic episodes
  • Seizures
  • Sexual dysfunction—20%
    • Consider adding Bupropion, which may →
      – Reversal of other antidepressant mediated sexual dysfunction
  • Tremor

Other receptor antagonism mediated side effects:
  • Anticholinergic → see below
  • Antihistamine →
    • Sedation
  • Anti α1 →
    • Erectile dysfunction
    • Orthostatic hypotension
    • Sedation

Antidote:
  • Gastric lavage & activated charcoal
  • Plasma alkalization via:
    • Sodium bicarbonate (MK, ♂♀):
      1mEq/ kg IV push (1 ampule = ~50mEq), then 0.5mEq/ kg IV q10minutes prn in order to achieve a plasma pH of 7.50–7.55, followed by either:
        • 150mEq/ 1L of 5% Dextrose water (D5W) IV, in order to achieve an isoosmolar solution
        • 75mEq/ 1L of 1/2 normal saline IV, in order to achieve an isoosmolar solution
      ...@ 150–200mL/ hour to maintain adequate pH values

Indications:
  • QRS complex duration > 0.10sec
Goal:
  • QRS complex duration < 0.10sec
Mechanism:
- ↑ Intravascular volume
- Plasma alkalization
  - Myocardial stabilization
Side effects:
- May exacerbate volume overload due to sodium content

Contraindications:
- Suicidal ideation
- Previous suicide attempt
...as overdose, via ingestion of ≥ 2 weeks supply, may be fatal

THIRD LINE

ANTISEIZURE MEDICATIONS
- Being that many antiseizure medications have a relatively narrow therapeutic window between the effective dose & toxicity (unlike other medications), substitution of trade to generic versions should be undertaken w/ caution. If possible, generic refills should come from the same manufacturer

<table>
<thead>
<tr>
<th>Generic (Trade)</th>
<th>M/♀: Start (Max)</th>
<th>K/♀: 25mg PO q12hours (200mg PO q12hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate (Topamax)</td>
<td>L/ U</td>
<td>500mg PO q24hours (1g/24hours)</td>
</tr>
<tr>
<td>Valproic acid (Depakote)</td>
<td>XR form</td>
<td></td>
</tr>
</tbody>
</table>

Side effects: Withdrawal from anti-seizure medications should be done gradually in order to prevent rebound ↑ seizure frequency &/or severity

Mucocutaneous
- Dermatitis, including Erythema multiforme, & its severe variants:
  - Toxic epidermal necrolysis—TEN
  - Stevens–Johnson syndrome—SJS

Neurologic
- Altered mental status
- Double vision = diplopia
- Headache
- Incoordination = ataxia
- ↓ Neuropathic pain
- Sedation
Maternofetal
  • Teratogenic during the 1st trimester ➔
    ○ Fetal malformation
    ○ Fetal death

Overdose:
  **Pulmonary**
  • Respiratory depression

**Topiramate specific:**
  **General**
  • **Heat stroke:** ↑Core body (rectal) temperature, usually being ≥ 107.6°F = 42°C, being termed hyperthermia ➔
    ○ Systemic enzymatic dysfunction ➔ cell dysfunction & death
  • ↓Weight

**Genitourinary**
  • Nephrolithiasis—1.5%

**Musculoskeletal**
  • **Osteoporosis**, w/ the recommendation of concurrent Vitamin D & calcium supplementation

**Ophthalmologic**
  • Acute = narrow = closed (iridocorneal) angle glaucoma—rare, being a MEDICAL EMERGENCY, as blindness may occur within hours to days (usually @ ≤ 1month)

**Hematologic**
  • Metabolic acidemia—3%

**Valproic acid specific:**
  **General**
  • ↑Weight

**Gastrointestinal**
  • Diarrhea
  • Nausea ± vomiting
  • Hepatitis—rare
  • Pancreatitis—rare

**Genitourinary**
  • Altered menstrual hemorrhage, being either ↑ or ↓
  • Polycystic ovary syndrome
<table>
<thead>
<tr>
<th><strong>Mucocutaneous</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alopecia</td>
</tr>
<tr>
<td>• Hirsutism</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Neurologic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Secondary Parkinson’s disease, w/ effects being reversible after discontinuation</td>
</tr>
<tr>
<td>• Tremor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Hematologic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↑ Ammonia levels</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Maternofetal</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• ↑ Relative risk of cognitive deficits in children exposed in utero (relative to other antiseizure medications), being dose dependent</td>
</tr>
</tbody>
</table>

**Monitoring:**

- Plasma medication levels should be checked @:
  - After initiating treatment
  - Addition of a potential interacting medication
  - Change in gastrointestinal, hepatic, or renal function
  - Occurrence of side effects
  - Pregnancy, which ↑ the clearance of many antiseizure medications

**Topiramate specific interactions:**

- A hepatic enzyme inducing antiseizure medication → ↑ hepatic clearance of:
  - Antiretroviral medications
  - Chemotherapeutic medications
  - Immunosuppressive medications (ex: glucocorticoids, Cyclosporine)
  - Oral contraceptive pills. Therefore, ♀s taking these medications should use preparations containing ≥ 50μg of ethinyl estradiol to ↓ pregnancy risk