Pharmacology II Review

- Local Anesthetics (LA)
  - Site of action at the sodium channel of the nerve cell membrane
    - Na\(^+\) channels found distributed over entire unmyelinated nerve cell membrane
    - Na\(^+\) channels found at the nodes of Ranvier in myelinated nerves
  - Local must gain access to the intracellular portion of the Na\(^+\) channel
    - Inactivation or “H” gate
      - LA must be ionized to interact with H gate
      - Renders Na\(^+\) channel inactive
        - Blocks influx of Na\(^+\)
        - Threshold potential not reached
        - Action potential prevented
          - Loss of sensation, motor activity
  - Nerve type sensitivity to LA confusing
    - Differences noted in VITRO
      - Most sensitive to the effects of LA – Type A
      - Most resistant to the effects of LA – Type C
        - Based on the concept of “conduction safety”
          - The margin of safety for transmission is greater in small, slow fibers than in large fast fibers
  - Progression of blockade of fibers (noted clinically (in VIVO))
    - Type B, lightly myelinated (autonomic) fibers most susceptible to the effects of LA
      - “ATP, TP, MVP”
        - Autonomic, Temperature, Pain, Touch, Pressure, Motor, Vibratory, Proprioception
  - Structure of LA

![Diagram of LA structure]
LA divided into 2 families based on intermediate linkage

- **Esters**
  - procaine (prototype for esters)
  - tetracaine
  - 2-chloroprocaine
  - benzocaine
  - cocaine

  - **Metabolism of ester LA**
    - ester hydrolysis via plasma cholinesterase
      - cocaine primarily undergoes N-methylation in the liver; secondary metabolism via ester hydrolysis
        - noted for its vasoconstricting capability
      - metabolism yields para-amino benzoic acid (PABA)
      - may cause allergic reactions

- **Amides**
  - lidocaine (prototype for amides)
  - mepivacaine
  - prilocaine
  - bupivacaine
  - ropivacaine
  - levobupivacaine
  - etidocaine
  - dibucaine

  - **Metabolism of amide LA**
    - Hepatic (microsomal enzymes)
      - slower than ester hydrolysis
      - may lead to accumulation of LA and resultant toxic effects
      - addition of vasoconstrictor (epinephrine) slows vascular/systemic absorption
    - speed of absorption of LA directly related to site of injection
      - tracheal > intrapleural > intercostal > caudal > epidural > brachial (or other major nerve) plexus > intradermal > spinal
Pharmacokinetics/dynamics of LA
- Depend on 3 attributes of the LA
  - pKa
    - the pH at which the drug exists 50:50 in the ionized:unionized form
    - responsible for onset of the LA
      - Quicker onset – pKa closer to physiologic pH
        - lidocaine (7.9)
        - mepivacaine (7.6)
        - chloroprocaine*
          - *pKa 8.7 – onset rapid due to high concentration (2-3%) and intrinsic lipid solubility of drug
      - Onset time may be shortened by carbonation (alkalinization) of LA with bicarbonate
        - May also reduce pain on injection
        - May ppt in solution (bupivacaine)
  - Slower onset – pKa farther from physiologic pH
    - procaine (8.9)
    - tetracaine (8.5)
- bupivacaine (8.1)
- ropivacaine (8.1)
  - Onset may be delayed if injected into acidotic environment
- lipid solubility
  - relates to potency of the LA
  - also related to duration of action (DOA) of the LA
- protein binding
  - relates to DOA of the LA
  - Short acting agent chlorprocaine has virtually no protein binding
  - Intermediate acting agents: “LMP” (lidocaine, mepivacaine, prilocaine)
  - Long acting agents: “you can BET on them” (bupivacaine, etidocaine, tetracaine)
- The majority of LAs have the capability to cause methemoglobinemia
  - Prilocaine
    - Metabolite ortho-toluidine, an oxidizing compound
  - Benzocaine
- Lidocaine blunts the ventilatory drive to hypoxemia

- Coagulation Cascade

\[ \text{Intrinsic Pathway} \]

\[ \text{Extrinsic Pathway} \]

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Anticoagulants

Heparin

- **Mechanism of action**
  - Forms complex with antithrombin III allowing inhibition of Factor X and thrombin
  - Metabolized by hepatic heparinase
    - Half-life is dose dependent:
      - 100U/kg – 1 hour
      - 400U/kg – 2.5 hours
      - 800U/kg – 5 hours
    - Low molecular weight heparins (i.e. Lovenox) have a longer half-life
  - Coagulation tests affected -> ACT, APTT
  - Heparin resistance
    - Antithrombin III (AT3) deficiency (may be 2º previous heparin therapy)
      - Resistance is managed by increasing heparin dose, change from porcine to bovine heparin and/or administration of recombinant antithrombin III

- **Complications of heparin therapy**
  - Hemorrhage
    - *The most common serious side effect of heparin therapy*
  - Hypotension
  - Allergic reactions
  - HIT-heparin-induced thrombocytopenia – an allergic reaction to heparin with **triad of signs**:
    - Thrombocytopenia
    - Heparin resistance
    - Thrombus formation
  - Treatment ⇒ discontinue heparin therapy

- **Reversal of heparin**
  - Protamine sulfate
    - Binds to heparin; forms inactive salt
    - May **increase** bleeding if given alone or with larger reversal doses
    - May ppt allergic (anaphylactoid) rxns
- Caution in pts who have received protamine-containing insulin preparations, those with fish allergy, post-vasectomy pts

- **Low-molecular weight heparin**
  - Enoxaparin (Lovenox)
    - Onset 20-30 min after subcutaneous dose, peak effect 3-5º
    - *Effects for up to 12º from anti-factor Xa activity*
    - May be administered IV or SQ
    - Prophylaxis for DVT/PE in pts undergoing major abdominal surgery, total joint surgery
    - Treatment of DVT/PE in conjunction with coumadin
    - Use in pts with unstable angina, non-Q wave MI, acute ST elevated MI (STEMI), coronary stents in conjunction with aspirin, atrial fibrillation
    - *Enoxaparin should be held at least 10-12º before neuraxial anesthesia; 24º if higher doses are used*

- **Oral anticoagulants**
  - Warfarin (Coumadin)
    - Reduced amount and activity of vitamin K dependent factors: II, VII, IX, X, protein C and protein S
    - Effects take days to appear as existing factor levels are reduced
    - Factor VII affected first – shortest half-life
    - Bleeding is the major side effect; is also teratogenic
    - *Immediate reversal of anticoagulant effect with FFP*
    - Intravenous vitamin K is also effective, but requires hours (up to 24) for effect

- **Thrombolytics**
  - Act as plasminogen activators
    - Convert the endogenous proenzyme plasminogen to the fibrinolytic enzyme plasmin (fibrinolysin)
  - Goal of fibrinolytic therapy is to restore circulation through a previously occluded artery or vein (most commonly coronary)
    - Streptokinase
    - Alteplase (recombinant tissue plasminogen activator)

- **Thrombin Inhibitors**
  - Inhibit free and clot-bound thrombin
  - Presence of AT3 not necessary
- Not associated with HIT
- Recombinant hirudin
  - Naturally occurring hirudin found in leech saliva
- Bivalirudin
- Desirudin
- Dabagtripiban
  - Binds only to the active site of thrombin, but blocks thrombin activity
  - Has almost minimal of protein binding and therefore a very dependable profile
  - Also has some antiplatelet activity
  - *No known reversal agent and even FFP may not reverse anticoagulation
  - Monitor activity with APTT
- Elimination half-life: 7-9 hours
- **Factor Xa Inhibitors**
  - Rivaroxaban
    - Competitively binds with Factor Xa
    - Both PT & PTT elevated
      - Usefulness of these coagulation studies in assessing anticoagulation is unknown
    - Elimination half-life: 6-7 hours
    - *No known reversal agent and even FFP may not reverse anticoagulation
- **Fibrinolysis Inhibitors**
  - Aminocaproic acid (Amicar)
  - Tranexamic acid
- **Adenosine Diphosphate inhibitors**
  - Inhibit platelet aggregation via differing mechanisms
    - Aspirin
      - Inhibits thromboxane synthesis by interfering with cyclooxygenase 1 and 2
        - Platelets deactivated for the remainder of their lifespan
          - D/C 7-10 days pre-op
    - Clopidogrel (Plavix)
    - Ticlodipine (Ticlid)
      - Prodrugs which are converted to active metabolites
      - Block ADP receptors on platelet surface
Dipyramidole
- Inhibits platelet aggregation
- Given in combination with warfarin

Dextran
- Prolongs bleeding time and polymerization of fibrin and platelet function
- May incite allergic reactions (large molecule)

Insulin, Oral Hypoglycemics and Hormones as Drugs
- Synthesized by the β cells of the islets of Langerhans of the pancreas
- Binds to plasma membrane insulin receptors
  - Translocate glucose transporters
    - Facilitate glucose diffusion into cells
    - Shift intracellular glucose metabolism toward storage as glycogen
    - Stimulate cellular uptake of amino acids, phosphate, K, Mg
    - Stimulate protein synthesis/inhibition of proteolysis
    - Regulate gene expression via insulin regulation in target DNA molecules
- Number of insulin receptors appears to be inversely proportional to plasma concentration of insulin

Insulin preparations
- Onsets, peaks, DOAs
Oral hypoglycemics

- Sulfonylureas
  - increase release of insulin from pancreas
  - side effect hypoglycemia
    - Glyburide
    - Glipizide
    - Chlorpropamide

- Meglitinides
  - increase release of insulin from pancreas
    - quicker onset and shorter DOA than sulfonylureas
      - Repaglinide

- α-glucosidase inhibitors
  - block starch digesting enzymes
    - decrease carbohydrate digestion and absorption of disaccharides
      - Acarbose
      - Miglitol

- Biguanides
  - Metformin
    - Decrease blood glucose concentrations
      - Decrease excessive hepatic and renal glucose production by inhibiting gluconeogenesis
    - Do not cause hypoglycemia
    - Decrease plasma concentrations of triglycerides, cholesterol
    - Common side effect GI sx (diarrhea, nausea, anorexia)
    - Should be given with caution in pts with hepatic disease, renal disease and dehydration; hold 24 hours pre-op or before pt receives contrast
    - MALA – metformin-associated lactic acidosis
      - Rare; may be fatal

- Thiazolidinediones (TZDs)
  - decrease hepatic glucose release and increase insulin sensitivity
  - Decrease insulin resistance in Type II DM pts
    - Rosiglitazone

Hormones as Drugs

- Preparations that contain synthetic hormones identical to those secreted endogenously by endocrine glands may be administered as drugs
Anterior Pituitary Hormones

- Growth hormone (GH)
  - tx for hypopituitary dwarfism
- Octreotide
  - somatostatin analog that inhibits release of GH
  - tx for acromegaly
  - tx for acute carcinoid crisis
    - bolus may result in bradycardia, 2nd and 3rd degree heart block
- Gonadotropins
  - tx of infertility & cryptorchism
- ACTH
  - stimulates corticosteroid secretion from adrenal cortex

Thyroid Gland Hormones

- Levothyroxine
  - Most frequently administered drug for the tx of diseases requiring thyroid hormone replacement
- Calcitonin
  - decreases plasma calcium [ ] as a reflection of decreased osteoclast activity & bone resorption (Paget’s disease)

Antithyroid Drugs

- Propylthiouracil
- Methimazole
  - interfere with incorporation of iodine into tyrosine residues of thyroglobulin
  - most common side effect -> urticarial/papular skin rash; granulocytopenia, agranulocytosis (rare)
- Iodide
  - paradoxical tx for hyperthyroidism by antagonizing ability of TSH & cAMP to stimulate hormone release
    - inhibits release of TH within 24 hrs
  - Radioactive iodine (^{131}I)
    - tx of hyperthyroidism in elderly, pts with cardiac disease
    - rapidly trapped by thyroid gland cells
      - & emission of destructive B rays exclusively destroys thyroid cells with minimal damage to surrounding tissue

Ovarian Hormones

- Estrogen
• Tx of sx of menopause; utilized as contraceptive in conjunction with progestin
  ◆ Protective against the development of osteoporosis
  ◆ May cause retention of sodium & water
  ◆ HTN occurs in ~ 5% of pts
  ◆ Most frequent side effect -> nausea

- Antiestrogens
  • Bind to estrogen receptors
    ◆ Clomiphene
    ◆ Tamoxifen
      ▶ Administered for 5 years to post-menopausal women with breast CA characterized by (+) estrogen receptors
      ▶ Causes endometrial stimulation and “hot flashes”

- Antiprogestins
  • Inhibit the hormonal effects of progesterone
    ◆ Most effective/safest means of medical abortion

- Oral Contraceptives
  • Commonly a combination of estrogen and a progestin
    ◆ Side effects from mild to serious; mostly due to effects of estrogen
      ▶ Increased incidence of thromboembolism
        ▶ Increases in certain clotting factors
        ▶ Increase in plt aggregation
        ▶ Sx of early pregnancy (n/v, wt gain, breast discomfort)
        ▶ HTN (5%)
          • From estrogen-induced increases in plasma [ ] of renin and angiotensin (↑ Na+/H₂O retention)

- Androgens
  • Administered to males to stimulate development & maintenance of secondary sexual characteristics
  • Enhance erythropoiesis via renal production of erythropoietin
  • ↑ 2,3 DPG levels
  • Danazol
    ◆ preferred androgen for tx of hereditary angioedema (HAE)
  • Finasteride
    ◆ Tx of BPH
Corticosteroids

- Classified according to the potencies to evoke the distal renal tubular reabsorption of sodium in exchange for potassium
  - mineralocorticoid effect
- Antiinflammatory properties
  - glucocorticoid effect
    - Permissive/protective effects critical to maintenance of homeostasis
      - Basal glucocorticoids prepare individual to respond to stress
      - Protective
        - Inhibition of inflammation
        - ↑ WBC count
        - immunosuppression
        - ↑ blood glucose
- Multiple clinical applications for use
  - Immunosuppression
    - Auto-immune diseases
  - Anti-inflammatory
    - Ocular, skin, joint
  - Anti-emetic
  - Post-op analgesia
  - Cerebral edema
- Multiple side effects
  - suppression of HPA axis
    - *need to administer stress-dose steroids to steroid dependent pts intra-op*
      - adrenal medulla response to stress dependent on presence of cortisol
  - electrolyte and metabolic changes
  - osteoporosis
  - PUD
  - CNS disturbances
  - Inhibition of normal growth
  - weight gain
  - skeletal muscle wasting
• fragile integument
• immunosuppression
  ◆ leads to opportunistic infections (bacterial and fungal)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Relative Effects of Commonly Used Corticosteroids</th>
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<tbody>
<tr>
<td>Corticosteroid</td>
<td>Sodium Retention</td>
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<tr>
<td>Hydrocortisone</td>
<td>2</td>
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<tr>
<td>Prednisone</td>
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</tr>
<tr>
<td>Prednisolone</td>
<td>0.8</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>0.5</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0</td>
</tr>
</tbody>
</table>

> Non-steroidal immunosuppressants
  • Tacrolimus
  • Cyclosporine
    ◆ Selectively inhibits helper T lymphocyte-mediated immune responses
    ◆ Mainstay as an anti-rejection agent following organ transplantation
    ◆ Narrow therapeutic range
    ◆ Many side effects
      ◆ Renal tubular atrophy -> nephrotoxicity
        ➢ Most important adverse effect (25-38% of pts)
      ◆ HTN
      ◆ Hepato-cellular dysfunction
      ◆ Gingival hyperplasia
      ◆ Seizures
        ➢ Reports of sz activity in pts receiving ketamine
      ◆ Tremors
      ◆ Limb paresthesias (50% occurrence)
      ◆ Hyperglycemia
      ◆ Allergic reactions
      ◆ Augmentation of NDMR blockade

> Posterior Pituitary Hormones
  • Arginine vasopressin (AVP)
    ◆ Formerly known as ADH
• Target sites – renal collecting ducts
  ♦ Preservation of euvolemia by secretion of AVP
    ➢ Cell membranes of collecting ducts increase permeability to H₂O; reabsorption into the interstitium occurs
  ♦ Non-renal activity
    ➢ Intense vasoconstriction
      ▪ May be infused for severe hypotension associated with hemorrhagic or septic shock
      ▪ ACLS protocol during refractory cardiac arrest as an alternative to epinephrine
        • 40U IVP X 1
  ♦ Other uses
    ➢ Tx of diabetes insipidus
    ➢ Tx of esophageal varices
• Oxytocin
  • Utilized as a uterotonic to stimulate/sustain contractions during labor
  • Given post-delivery to enhance uterine tone
  • Side effects
    ♦ Hypotension with reflex tachycardia
    ♦ Flushing
    ♦ H₂O intoxication (rare)
• Desmopressin (DDAVP)
  • A synthetic analogue of AVP
    ♦ Intense antidiuretic effects
      ➢ Intranasal DDAVP tx of choice for DI
    ♦ Causes the release of factors from endothelial cells
      ➢ VonWillebrand
        ▪ Confers hemostatic activity; pre-op prophylaxis for pts with VW dz
      ➢ Tissue plasminogen activator
      ➢ Prostaglandins
➢ Chymopapain
  ▪ Proteolytic enzyme used in tx of herniated lumbar intervertebral disc disease, dissolves the proteoglycan portion of nucleus pulposus
  ▪ Associated with mild to severe allergic reactions
  • Contraindicated for use in pts with papaya allergy
Antidysrhythmics

Amiodarone
- Analog of thyroid hormone
- Mechanism of action unknown
- Effective in treating almost all arrhythmias including:
  - supraventricular dysrhythmias, ventricular tachydysrhythmias (V-fib and V-tach)
- Prevents recurrence of atrial fibrillation
- Improves response to defibrillation

Adenosine
- Interacts with specific adenosine receptors
- Shortens action potential duration, causes hyperpolarization
- Effects blocked by methylxanthines (i.e. caffeine)
- Effective for reentrant supraventricular tachycardias
- Very short half-life – 12 seconds
- Quickly metabolized by vascular endothelial cells
- Dose 6 mg rapid IV push, may increase to 12 mg IV

**Magnesium**
- May interfere with Ca^{++} influx
- Effective in treating digitalis induced arrhythmias
- Possibly effective in treating Torsades de pointes

**Cardiac glycosides**
- Digitalis (Digoxin)
  - Increases vagal activity
  - Inhibits Na^{+}, K^{+}-ATPase that increases intracellular calcium
  - Causes hyperpolarization, shortening of atrial action potential, decreased phase 4 slope
  - ECG effects: prolonged PR interval, T-wave flattening/inversion
  - Effective in treating: a-fib, a-flutter by reducing AV conduction
  - Digoxin toxicity includes complete heart block, CNS depression
  - *Digoxin toxicity enhanced by hypokalemia*

**Calcium Channel Blockers**
- Calcium channels are pores in cardiac and smooth muscle membranes
- Calcium enters cell through voltage-dependent channels
- CCBs interfere with influx of Ca^{2+} during Phase 2 (A.K.A. plateau) of the cardiac action potential
  - Reduction of intracellular calcium ⇒ myocardial depression, depression of automaticity, depression of AV node conduction, vasodilation
- Effects of all CCBs may be reversed with the administration of CaCl or Ca gluconate
- 3 classes
  - Phenylalkylamines
    - Verapamil
      - *Effective in the treatment of supraventricular tachydysrhythmias, HTN and angina pectoris*
      - Major depressant effect on the AV node
      - Negative chronotropy on SA node
Negative ionotropy on cardiac muscle
Moderate vasodilatory effect on coronaries and systemic arteries
Should not be administered to pts in CHF, with AV node block, severe bradycardia
May accentuate conduction through aberrant pathway(s) in WPW pts and ppt ventricular dysrhythmias

- Dihydropyrimidines
  - Nifedipine
    - Produces marked vasodilation of coronaries and peripheral vessels
    - Lacks effects on the conduction system
    - Produces minimal depression of myocardial contractility
    - Useful in the tx of angina pectoris
  - Nicardipine
    - Greatest vasodilatory effects of all of the CCBs
    - Produces the greatest coronary artery vasodilation
    - Tx of HTN and angina pectoris
    - May be utilized as a tocolytic
      - Devoid of side effects associated with use of the β₂ agonists
  - Nimodipine
    - Highly lipid soluble; crosses the BBB
    - Specifically acts on the cerebral vasculature
      - Useful in the tx of post CVA, cerebral aneurysm clipping/coiling, subarachnoid hemorrhage, post traumatic brain injury-induced cerebral vasospasm
- Amlodipine
  - PO only
  - Minimal detrimental effects on myocardial contractility
  - Anti-ischemic effects rival that of β-blockers in pts with ACS
  - Used in the tx of essential HTN

- Benzothiazepines
  - Diltiazem
    - Similar to verapamil
    - Produces moderate depression of AV node conduction
    - Useful in the tx of supraventricular tachydysrhythmias, chronic control of essential HTN
Used in the tx of rapid ventricular response to A-fib

### Diuretics

- **5 major classifications:**
  - Thiazide diuretics
  - Utilized primarily in the tx of HTN as an adjunct to β-blockers and/or ACE inhibitors; mild CHF
    - Hydrochlorothiazide (HCTZ) (prototype for class)
      - **Functions**
        - Inhibits reabsorption of \( \text{Na}^+ / \text{Cl}^- \) at the distal tubule
        - Increases \( \text{K}^+ \) excretion
        - Possesses mild vasodilatory properties
        - **May cause a hypochloremic, hypokalemic metabolic alkalosis**
  - Loop diuretics
    - Furosemide (Lasix) (prototype for class)
    - Ethacrynic acid (Bumex)
      - Utilized to treat HTN with reduced renal function, moderate to severe CHF, acute pulmonary edema, acute/chronic renal failure, hyperkalemia
      - **Functions**
        - Act principally on the loop of Henle
        - Inhibits reabsorption of \( \text{Na}^+ , \text{Cl}^- \)
        - Increases \( \text{K}^+ \) excretion; may cause hypokalemia
        - *May be ototoxic*
        - *May prolong activity of NDMRs*
        - *May ppt lithium toxicity*
  - Osmotic diuretics
    - Mannitol (prototype for class)
      - Utilized for treatment of acute renal failure, reduction of IOP, ICP, preservation of renal function pre X-clamping of aorta, renal artery
      - Recently shown to be more efficacious in preserving overall renal function vs. renal-dose dopamine
      - **Functions**
        - ↑ renal medullary blood flow
        - ↑ osmolarity of renal tubule fluid
- Transient ↑ in COP
- Draws interstitial fluid into the intravascular space
- **May precipitate acute pulmonary edema in pts with a hx of CHF**

**Aldosterone antagonists**
- Spironolactone (Aldactone) (prototype for class)
  - Utilized for treatment of renal insufficiency concomitant with hepatic failure, CHF concomitant with hypokalemia
  - Functions
    - Blocks effects of aldosterone on the renal tubules
    - Spares K⁺

**Carbonic anhydrase inhibitors**
- Acetazolamide (prototype for class)
  - Treatment of glaucoma (gtts), reduction of CSF production, prevention of altitude sickness
  - Functions
    - Inhibition of carbonic anhydrase (an enzyme of the brush border) @ proximal tubule
    - Increases Na⁺, HCO₃⁻ excretion
    - Alkalinizes tubular urine

**Psychotropics**
- All of these agents are thought to exert their effects by altering the concentrations of available central and peripheral neurotransmitters, primarily norepinephrine, dopamine, and serotonin
- Drug interactions common with many other drugs including anesthetic agents, sedatives, opioids, indirect-acting sympathomimetics
- Many side effects noted with use
Schizophrenia
Phenothiazines
Thioxanthenes
Butyrophenones

Mania
(Also psychosis)
Lithium
Antipsychotics
2nd generation antipsychotics

Depression
Tricyclic amines
MAOIs
SSRIs

- **Classifications:**
  - **Phenothiazines and thioxanthenes**
    - A.K.A. “major tranquilizers”; usually prescribed for management of psychotic symptoms
    - Most likely exert their effects by antagonism of dopamine as a neurotransmitter in the basal ganglia and limbic portions of the forebrain
    - Capable of producing extrapyramidal symptoms due to central dopaminergic receptor blockade; causing ↑ [ ] of Ach in the basal ganglia
    - Improve mood/behavior without excessive sedation
    - High therapeutic index
    - Do not produce physical dependence
    - Many interactions with other agents
    - *May produce orthostatic hypotension*
    - *May PPT neuroleptic malignant syndrome*
    - Avoid use in Parkinsonian pts
      - Chlorpromazine (Thorazine)
      - Promethazine (Phenergan)
  - **Butyrophenones**
    - May reduce anxiety accompanying psychosis
    - Pharmacologically resemble the phenothiazines
    - Block dopamine on postsynaptic sites
- Significant extrapyramidal symptoms associated with use
  - May lead to tardive dyskinesia
- Exhibit potent antiemetic properties (see antiemetics)
- Undergo hepatic metabolism
  - Haloperidol (Haldol) (Prototype for this class)
  - Droperidol (Inapsine)
    - Most commonly utilized as an antiemetic
    - Used as an adjunct in neurolept anesthesia
    - Increases action of fentanyl (no increase in ventilatory depression)
    - May produce orthostatic hypotension
    - May produce dysphoria; produces extrapyramidal symptoms in 1/100 pts
    - Contraindicated in Parkinsonian patients
    - Reports of development of ventricular arrhythmias (i.e. Torsades) noted with use
    - Causes severe hypertension in patients with pheochromocytoma
    - Recommended dose < 1 mg, monitor ECG for 2 hours

- 2nd generation antipsychotics
  - Risperidone (Risperdal)
    - Has antiadrenergic, antiserotonergic & antihistaminergic actions
    - Used to treat schizoaffective disorders, bipolar disease & autism
    - Dopamine receptor specificity – sparing of extrapyramidal tract
      - Results in a lower incidence of extrapyramidal side-effects

- Lithium
  - An alkali metal used for the treatment of mania and manic episodes of bipolar disorder
    - No known physiologic role
    - No known receptor site
    - Does not bind to plasma proteins
    - Normally undetectable in the plasma
    - No effect on non-manic individuals
    - Same group on periodic table as Na⁺, K⁺
Mechanism of action thought to be related to its inhibition of adenylate cyclase and the stabilization of dopamine and beta-adrenergic receptors

Li acts as an imperfect Na\(^+\) ion substitute at the cellular level

Therapeutic level 0.8 – 1.5 mEq/L

Na\(^+\) retention with peripheral edema (noted in initial phases of treatment)

Nephrogenic diabetes insipidus (DI)
- Inhibition of ADH activity on renal adenylate cyclase causing reduced H2O reabsorption across tubules

Li prolongs depolarizing and non-depolarizing muscle blockade

Li lowers the MAC requirement

Reports of irreversible encephalopathy in patients receiving Li concomitantly with Haldol; maybe prudent to avoid droperidol

Diuretics (especially furosemide) may precipitate lithium toxicity from increased excretion of Na\(^+\) with H\(_2\)O

**Tricyclic antidepressants**
- These agents potentiate the action of biogenic amines, particularly NE and serotonin by interfering with their reuptake into adrenergic nerve endings, both centrally and peripherally
  - Amitryptiline
  - Desipramine
  - Clomipramine
  - Nortriptyline
  - Imipramine

**Extreme** hypertension may be noted after the administration of pressors—use only direct acting sympathomimetics

Increased incidence of cardiac dysrhythmias (ST, VT, VF); increased if pancuronium co-administered
- Should avoid ketamine and meperidine as well

Avoid centrally acting anticholinergics; may lead to post-op delerium/confusion

Use direct-acting antihypertensives (i.e. phentolamine, sodium nitroprusside)

Tricyclics augment the analgesic and ventilatory depressant effects of the opioids and depressant effects of the sedative/hypnotics; necessary to reduce usual dosages
- Also utilized in the tx of chronic pain syndromes, migraine
- Extremely dangerous in case of OD

**Monoamine oxidase inhibitors (MAOIs)**
- Form stable and irreversible complexes with the enzyme monoamine oxidase
  - Phenelzine
  - ranylcypromine
  - Selegiline (selective MAO-B inhibitor)
- Biogenic amine concentrations build up in brain, intestines, heart, and blood of patients treated with MAOIs
- Increases in cerebral amines thought to underlie the antidepressant effects of the MAOIs
- MAOIs may cause hypotensive effects due to the production of a false neurotransmitter, octopamine, which builds up in adrenergic nerve endings
  - Only mild vasoconstricting capability

- MANY side effects
  - Anticholinergic effects such as blurred vision, dry mouth
  - Sedation
  - Orthostatic hypotension due to build up of octopamine
  - No ECG or EEG changes noted as with tricyclic amines
  - *Interactions with foods high in tyramine or medications with SNS activity; may see severe hypertension (excess tyramine triggers further release of NE and serotonin)*
  - Use only direct-acting sympathomimetics when treating hypotension
  - Treat hypertension with direct acting vasodilators
  - MAOIs should be D/C’d 2 weeks prior to elective surgery if possible
  - MAC is increased
  - Do not co-administer meperidine with MAOIs
    - MAOIs inhibit deamination of serotonin
    - meperidine inhibits re-uptake of serotonin
    - leads to “serotonin syndrome”

**Serotonin uptake inhibitors (SSRIs)**
- Most broadly prescribed class of drug used for the treatment of depression
♦ Also used to treat OCD, bulimia nervosa, panic disorders, chronic pain syndromes
♦ Inhibit CNS neuronal uptake of serotonin; allows for greater circulating amounts of serotonin
♦ Bind much less potently to muscarinic, histaminergic, and alpha\textsubscript{1} receptors than do other antidepressants
♦ Less side effects noted than with use of tricyclics, MAOIs
  ➢ Fluoxetine
  ➢ Citalopram
  ➢ Paroxetine
  ➢ Sertraline
  ➢ Fluvoxamine
♦ Should not be co-administered with MAOIs
♦ (?) use of meperidine
♦ Caution in pts with impaired hepatic or renal function
♦ Caution in pts with seizure hx
♦ (?) use of ketamine
♦ Safety in pediatric population not established
♦ (?) use of ondansetron, granisetron, etc
♦ Dystonia reported with co-administration of transdermal scopolamine patch
• Benzodiazepenes (see Pharm I review)
  ♦ Primarily utilized as anti-anxiety meds
Antiemetics largely classified by area on CTZ where they exert effects

- **Serotonin (5HT\textsubscript{3}) receptor antagonists**
  - Ondansetron (Zofran)
    - Onset 10-20 mins; DOA 4 hours
  - Granisetron (Kytril)
    - Onset ~ 1 hour; DOA 24 hours
  - Dolasetron (Anzemet)
    - Metabolism via Cytochrome P-450
    - Most common side effect is headache

- **Antihistamines**
  - Reduce the excitability of labyrinth receptors; may prevent n/v secondary to motion
  - Antagonism of histamine receptors in the CTZ adds to antiemetic properties
    - Diphenhydramine (Benadryl)
      - H\textsubscript{1} blocker (also antimuscarinic – see below)
      - May cause sedation
Promethazine (Phenergan)  
Dimenhydrinate (Dramamine)  
Meclizine (Antivert)  
Hydroxyzine (Vistaril)  

**Peripheral muscarinic receptor blockers**  
- May used to prophylax against n/v secondary to:  
  - Unopposed parasympathetic tone seen with regional techniques  
  - Surgeries where vagal stimulation is common  
  - Pts undergoing inner ear surgery  
  - Pts with strong hx of motion sickness  
- Scopolamine (transdermal patch)  
  - May exhibit central actions  
    - causes pupillary dilation; contraindicated for use in pts with narrow-angle glaucoma  
    - common side effect – dry mouth and blurred vision  
- Atropine  
- Glycopyrrolate  
- Diphenhydramine (central action - sedation)  

**Dopamine receptor antagonists**  
- Many potent antiemetic agents have dopaminergic blocking properties  
  - Contraindicated for use in pts with Parkinsonian symptomatology or disease  
  - May PPT acute dystonic reactions  
  - Use with caution in pts who are on psychotropic medications  
  - Butyrophenones  
    - Haloperidol (Haldol)  
    - Droperidol (Inapsine) (see psychotropic meds)  
      - FDA black box warning – may prolong QT interval, ppt Torsades  
      - Unlikely in antiemetic dose of 0.625-1.25 mg IV  
  - Phenothiazines  
    - Prochlorperazine (Compazine)  
    - Chlorpromazine (Thorazine)  
  - Benzamides  
    - Metoclopramide (Reglan)  
      - A gastric prokinetic due to its selective peripheral cholinergic agonism
- Acts as a dopaminergic receptor antagonist
  - Contraindicated for use in Parkinson’s pts, bowel obstruction
- Causes mild alpha blockade
- May cause intense abdominal cramping in the awake pt
- Increases upper GI motility enhancing gastric emptying
- Relaxes the pylorus, duodenum
- Increases motility of the small intestine
- Increases lower esophageal tone
- *Has no effect on gastric acidity or H⁺ ion secretion*
- *May interfere with plasma cholinesterase*
- Dose 10-20 mg IV
  - Onset ~ 10 mins; DOA 2-4 hours

**Substance P antagonists**
- Antagonizes neurokinin I (NK I) receptors; interferes with interaction of ligand Substance P
- Effects both peripheral and central
- Best utilized prophylactically
- Comparable effects to ondansetron but longer acting & synergistic with other PONV treatments
  - Aprepitant (Emend)
    - PO only; fosaprepitant IV formulation
    - Must be given 4 hours prior to surgery

**Corticosteroids**
- Dexamethasone (Decadron)
- Methylprednisone (Solu-medrol)
  - Activity as antiemetic unknown
  - Dosing controversial; latest meta-analysis supports dexamethasone 4 mg IV as efficacious as 8-12 mg without interference with wound healing
    - May be deleterious to pts undergoing surgery requiring bone fusion
    - Use with caution in pts with increased blood glucose

**Antacids**
- Increase gastric fluid pH causing an increase in gastric motility
- Generally contain Mg, Al, or Ca salts which react with/neutralize HCl
- Divided into two types:
- Particulate – not used for aspiration prophylaxis
- Non-particulate – (A.K.A. clear or soluble antacids)
  - mixes well with gastric contents; less dangerous if aspirated
    - Sodium citrate (Bicitra)
      - Use preoperatively is controversial; some feel that it increases gastric volume and may actually contribute to development of aspiration/PONV
      - Usually given before Cesarean sections, “full stomach” cases (30 cc PO)
      - *May cause hypernatremia after repeated doses

- Histamine and Histamine Receptor Antagonists
  - Histamine
    - A naturally occurring autocoid that produces a variety of physiologic and pathologic responses in different tissues and cells
    - Via G-protein coupled membrane receptors
    - A chemical mediator of inflammation in allergic reactions
    - Basophils and mast cells contain histamine; contents released in various tissues (skin, lungs, GI tract) in response to Ag-Ab reactions or other agents (drugs)
    - Effects mediated by interaction with histamine receptors
      - H₁ – found in conductive tissue of heart, epicardial coronaries, and bronchioles
      - H₂ – found in gastric mucosa (parietal cells), cardiac and bronchial tissue, CNS
      - H₃ – Inhibitory; found in cardiac tissue
  - Pharmacologic effects of histamine
    - Bradycardia \( (H₁) \) vs. increased HR/contractility \( (H₂) \)
    - Coronary artery vasoconstriction \( (H₁) \) vs. vasodilation \( (H₂) \)
    - Dysrhythmias
    - Bronchoconstriction \( (H₁) \) vs. bronchodilation \( (H₂) \)
    - CNS stimulation \( (H₂) \)
    - Increased \( H^+ \) ion secretion by gastric parietal cells \( (H₂) \)
    - Increased capillary permeability \( (H_{1,2}) \)
    - Peripheral vasodilation \( (H_{1,2}) \)
    - Urticarial, pruritis
  - Histamine receptor antagonists
- **H₁**
  - Compete with histamine at H₁ receptors
    - Diphenhydramine (Benadryl)
      - Sedative effect
        - Utilized as a sleep aid
      - Dries mucous membranes
      - Antipruritis
      - Antiemetic (see antiemetics)
        - Dimenhydrinate (Dramamine)
    - Treatment of motion-sickness

- **H₂**
  - Compete with histamine at H₂ receptors blocking acid stimulating effects of histamine, pentagastrin and Ach
  - Do not directly raise pH of gastric secretions
  - Used in the treatment of peptic ulcer disease, upper GI bleeding
  - Largely replaced by proton pump inhibitors (omeprazole, lansoprazole, pantozprazole)
  - Used in aspiration prophylaxis
  - May also be used in prophylaxis against anaphylaxis in highly atopic individuals
    - Administered in conjunction with diphenhydramine (Benadryl \(\Rightarrow\) blocks histamine @ H₁ receptors)
    - Cimetidine (Tagamet)
    - Ranitidine (Zantac)
      - Both Inhibit the cytochrome P-450 system
        - Cause significant prolongation of benzodiazepenes, warfarin, and other agents metabolized by CP450
        - May ↓ serum [ ] of digoxin
        - ↑ duration of depolarizing and non-depolarizing muscle relaxants
        - May cause bronchospasm in asthmatics
    - Famotidine (Pepcid)
- **Herbal Medications**

<table>
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<tr>
<th>CV</th>
<th>CNS</th>
<th>Hepatotoxicity</th>
<th>Hypoglycemia</th>
<th>Coagulopathy (↑bleeding)</th>
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<td>↑stim; ↓BP</td>
<td>↑stim; ↓sedation</td>
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<td>Celery</td>
<td>Chapparal</td>
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<td>Yellow root</td>
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- **Dietary Supplement Health and Education Act of 1994 (DSHEA)**
  - Provides standards requiring good manufacturing practices
  - The manufacturer of a dietary supplement or dietary ingredient is responsible for ensuring that the product is safe before it is marketed
  - FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market

- **Chronic Pain Syndromes/Terminology**

  - Pain is transmitted from the periphery to the cortex via
    - stimulation of nociceptors by trauma
    - secretion of nociceptive substances which activate nerves carrying pain signals
      - Substance P
      - bradykinin
      - histamine
      - serotonin
  - transmission to the spinal cord via
    - A-delta fibers (myelinated)
      - rapid transmission of sharp, well defined pain
- short duration
- secrete neurotransmitter glutamate
  - C fibers (unmyelinated)
    - slow transmission of dull, diffuse pain
    - sustained duration
    - secrete neurotransmitter Substance P

A-delta and C fibers enter into the dorsal horn of the spinal cord
- ascend/descend via Tract of Lissauer
- pass through substantia gelatinosa (A.K.A. Rexed’s lamina II)
- crosses cord via the midline and ascends via lateral spinothalamic tract
- dull pain passes through reticular formation of brain stem and terminates in the thalamus
- sharp pain ascends directly through thalamus to the cortex

**Complex Regional Pain Syndrome (CRPS I)**
- Previously known as reflex sympathetic dystrophy (RSD)
- Pathophysiology unknown, but involves altered peripheral/CNS response thresholds to afferent stimuli
- sympathetic dysfunction may also be present
- no definitive diagnostic test available, diagnosis on clinical basis
- associated with antecedent trauma
- characterized by burning neuropathic pain, allodynia, hyperpathia, decreased range of motion, edema, skin and hair atrophy
- no correlation between severity of injury and severity of symptoms
- Treatment includes sympatholytic medication, sympathetic blocks, neuropathic pain medications, PT

**CRPS II – Causalgia**
- Similar to CRPS I
- Occurs with confirmed nerve injury

**Myofascial pain**
- A.K.A. triggerpoints – very common
- often begins with acute muscle injury
- pain can last for years, described as aching muscular pain with tender areas
- compression of the “triggerpoint” produces severe pain
- thought to be secondary to reflex muscle spasms → muscle fatigue → muscle ischemia
- Treatment includes injections of local anesthetic are both diagnostic & therapeutic
- Depo-steroids may also be beneficial
- Stretching exercises may help prevent recurrence

- **Radiculopathy**
  - Lower back and cervical pain most common complaint at pain clinics
  - Radicular pain from nerve root irritation is sharp, aching and may “shoot” to distribution of nerve root
  - Sensory loss, weakness, hyporeflexia may be present
  - Must rule out other causes of root compression: spinal stenosis, tumor, herpes zoster, arachnoiditis
  - Treatment initially via conservative therapy – bed rest, analgesics, local heat, support
    - Epidural steroids - effective in 2/3 of patients
    - Surgical decompression

- **Chronic pain**
  - Pain which outlasts the normal healing period
  - Usually > 3-6 months in duration

- **Neuroplasticity**
  - Refers to changes in neural pathways and synapses which result from inciting events such as bodily injury leading to chronic pain
    - Refutes the formerly-held position that the brain is a static organ

- **“Wind-up”**
  - The perceived increase in pain intensity over time when a given painful stimulus is given repeatedly above a critical rate
  - Caused by repeated stimulation of Type C fibers
    - Leads to progressively increasing electrical response in spinal neurons