

# FINAL CHEAT SHEET AND REFRESHER

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## 1. Clinical Pharmacokinetics & Drug Monitoring (~10-15%)

1. **Therapeutic drug monitoring (TDM)** – drugs requiring monitoring: **vancomycin, aminoglycosides, digoxin, lithium, phenytoin**
  2. **Loading dose formula:**  $LD = (\text{Target concentration} \times V_d) / F$
  3. **Maintenance dose formula:**  $MD = (CL \times C_{ss} \times \tau) / F$
  4. **Half-life calculation:**  $t_{1/2} = (0.693 \times V_d) / CL$
  5. **First-order vs zero-order kinetics** – phenytoin follows **Michaelis-Menten kinetics (nonlinear saturation)**
  6. **AUC (area under the curve) and bioavailability (F)** –  $F = \text{AUC(oral)} / \text{AUC(IV)}$
  7. **Volume of distribution (Vd):** Drugs with **high Vd** distribute into tissues (lipophilic, e.g., diazepam)
  8. **Clearance (CL) equation:**  $CL = (\text{Rate of elimination}) / (\text{Plasma concentration})$
  9. **Steady-state concentration (C<sub>ss</sub>):** Achieved in **4–5 half-lives**
  10. **Renal vs hepatic clearance:** Creatinine clearance estimation (**Cockcroft-Gault formula**)
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## **2. Infectious Diseases & Antibiotics (~10-15%)**

1. **Penicillins: Gram-positive coverage**, no activity against **MRSA**, **atypicals**
  2. **Cephalosporin generations:**
    1. **1st gen (cefazolin)** – Gram-positive
    2. **3rd gen (ceftriaxone, ceftazidime)** – expanded Gram-negative
    3. **5th gen (ceftaroline)** – **MRSA**
  3. **Aminoglycosides (gentamicin, amikacin, tobramycin): Concentration-dependent killing (Peak:MIC)**
  4. **Vancomycin: Red man syndrome, TDM required, nephrotoxicity & ototoxicity**
  5. **Fluoroquinolones: Avoid in pregnancy & children** (cartilage damage)
  6. **Macrolides (azithromycin, clarithromycin, erythromycin): QT prolongation risk**
  7. **Metronidazole: Avoid alcohol (disulfiram-like reaction)**
  8. **Beta-lactam allergy cross-reactivity: Penicillins & cephalosporins (~10%)**
  9. **Fungal infections: Fluconazole for Candida, Amphotericin B for severe infections**
  10. **Tuberculosis treatment: RIPE regimen (Rifampin, Isoniazid, Pyrazinamide, Ethambutol)**
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### **3. Cardiovascular Pharmacology (~10-15%)**

1. Hypertension first-line drugs: ACEIs, ARBs, CCBs, Thiazide diuretics
  2. Beta-blockers contraindicated in: Asthma, heart block, bradycardia
  3. Loop diuretics (furosemide, bumetanide): Hypokalemia, hypocalcemia, ototoxicity
  4. Thiazide diuretics (HCTZ, chlorthalidone): Hypercalcemia, hyperglycemia, hypokalemia
  5. ACE inhibitors (lisinopril, enalapril): Dry cough (bradykinin), angioedema
  6. ARBs (losartan, valsartan): Alternative if ACEI intolerance
  7. Calcium channel blockers (CCBs):
    1. Dihydropyridines (amlodipine): Vasodilation, peripheral edema
    2. Non-dihydropyridines (verapamil, diltiazem): Bradycardia, constipation
  8. Statins: Monitor for myopathy, rhabdomyolysis, hepatotoxicity
  9. Antiplatelet drugs:
    1. Aspirin: Irreversible COX-1/COX-2 inhibitor
    2. Clopidogrel (Plavix): P2Y<sub>12</sub> inhibitor
  10. Warfarin vs DOACs (apixaban, rivaroxaban): Warfarin requires INR monitoring, interacts with Vitamin K
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#### **4. Endocrinology & Diabetes (~10-15%)**

1. **Metformin:** Lactic acidosis risk, avoid in renal impairment
  2. **Sulfonylureas** (glipizide, glyburide): Hypoglycemia, weight gain
  3. **DPP-4 inhibitors** (sitagliptin, linagliptin): Pancreatitis risk
  4. **SGLT2 inhibitors** (empagliflozin, dapagliflozin): UTIs, ketoacidosis risk
  5. **GLP-1 agonists** (liraglutide, semaglutide): Weight loss, nausea
  6. **Insulin types:**
    1. **Rapid-acting** (lispro, aspart) – Meal-time insulin
    2. **Long-acting** (glargine, detemir) – Basal control
  7. **Hypothyroidism** (Levothyroxine): Take on an empty stomach
  8. **Hyperthyroidism** (Methimazole, PTU): PTU preferred in pregnancy
  9. **Cushing's syndrome:** Excess cortisol → Moon face, buffalo hump
  10. **Addison's disease:** Corticosteroid replacement (hydrocortisone, fludrocortisone)
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#### **5. Neurology & Psychiatry (~10%)**

1. **Seizures:** Phenytoin, valproate, levetiracetam (Keppra), lamotrigine
  2. **Parkinson's:** Levodopa + Carbidopa (Sinemet), dopamine agonists (pramipexole)
  3. **Schizophrenia:** Clozapine for refractory cases (agranulocytosis risk)
  4. **Depression:** SSRIs first-line (fluoxetine, sertraline, escitalopram)
  5. **Bipolar disorder:** Lithium, valproate, lamotrigine
  6. **Insomnia:** Benzodiazepines (avoid in elderly), zolpidem (Ambien)
  7. **Alzheimer's:** Donepezil, memantine (NMDA antagonist)
  8. **Migraine prophylaxis:** Propranolol, topiramate, valproate
  9. **Neuropathic pain:** Gabapentin, pregabalin
  10. **Multiple sclerosis (MS):** Interferon-beta, fingolimod
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## **6. Miscellaneous High-Yield (~10%)**

1. Acetaminophen overdose: N-acetylcysteine (NAC)
  2. Opioid overdose: Naloxone (Narcan)
  3. Benzodiazepine overdose: Flumazenil (rarely used, seizure risk)
  4. Iron overdose: Deferoxamine
  5. Lead poisoning: EDTA, succimer
  6. Digoxin toxicity: Digoxin immune Fab (Digibind)
  7. Beta-blocker overdose: Glucagon
  8. Warfarin reversal: Vitamin K, PCC (Prothrombin Complex Concentrate)
  9. Methanol/ethylene glycol poisoning: Fomepizole or ethanol
  10. Serotonin syndrome: Cyproheptadine
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## **Over-the-Counter (OTC) & Miscellaneous (~5%)**

1. NSAIDs: GI ulcers, renal injury, increased BP
  2. Antacids (AlOH, MgOH): Avoid Mg in renal failure
  3. Loperamide: Avoid in bloody diarrhea
  4. Diphenhydramine: Avoid in elderly (anticholinergic effects)
  5. Oral contraceptives: Avoid in smokers >35 (DVT risk)
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## **Highest Yield OPRA Recall Notes**

### **1. Biomedical Sciences (20%)**

#### **Immunology:**

1. Innate immunity includes physical barriers, phagocytes, and complement proteins.
2. Adaptive immunity consists of B-cells (humoral) and T-cells (cell-mediated).
3. Antigen-presenting cells (APCs) include macrophages, dendritic cells, and B-cells.
4. Major histocompatibility complex (MHC) presents antigens to T-cells.
5. CD4+ T-cells activate immune responses, CD8+ T-cells kill infected cells.
6. IgG is the most abundant antibody, crosses the placenta.
7. IgA is found in mucosal surfaces and secretions.
8. IgE mediates allergic reactions via mast cell activation.
9. IgM is the first antibody produced during an infection.
10. Autoimmune diseases result from loss of self-tolerance.
11. Hypersensitivity reactions: Type I (IgE-mediated), Type II (cytotoxic), Type III (immune complex), Type IV (delayed-type).
12. Immunodeficiencies include primary (genetic) and secondary (acquired, e.g., HIV).
13. Vaccines induce active immunity, passive immunity is transferred via antibodies.
14. Cytokines regulate immune responses (e.g., IL-1, IL-6, TNF-alpha).
15. Complement activation (classical, alternative, lectin pathways) leads to pathogen destruction.
16. Toll-like receptors (TLRs) recognize pathogen-associated molecular patterns (PAMPs).
17. Monoclonal antibodies (mAbs) are used in autoimmune diseases and cancer therapy.
18. Graft rejection types: Hyperacute (pre-existing antibodies), Acute (T-cell mediated), Chronic (fibrosis).

19. Immune checkpoints (e.g., PD-1, CTLA-4) regulate T-cell responses.
20. Immunosuppressive drugs (e.g., corticosteroids, cyclosporine) prevent transplant rejection.

### **Disorders of Bodily Fluids:**

1. Hyponatremia causes include SIADH, heart failure, renal disease.
2. Hypernatremia often results from dehydration or diabetes insipidus.
3. Hypokalemia causes: Diuretics, vomiting, diarrhea, insulin overdose.
4. Hyperkalemia causes: Kidney failure, ACE inhibitors, potassium-sparing diuretics.
5. Hypocalcemia causes: Hypoparathyroidism, vitamin D deficiency.
6. Hypercalcemia causes: Hyperparathyroidism, malignancies.
7. Metabolic acidosis: Increased anion gap (e.g., lactic acidosis, DKA) vs normal anion gap (diarrhea, RTA).
8. Metabolic alkalosis causes: Vomiting, diuretic use, hyperaldosteronism.
9. Respiratory acidosis causes: Hypoventilation (COPD, respiratory failure).
10. Respiratory alkalosis causes: Hyperventilation (anxiety, high altitude).
11. Edema occurs due to increased capillary hydrostatic pressure or decreased oncotic pressure.
12. Dehydration types: Isotonic (vomiting, diarrhea), hypertonic (water loss), hypotonic (Na<sup>+</sup> loss).
13. SIADH leads to water retention and dilutional hyponatremia.
14. Diabetes insipidus results in excessive water loss due to ADH deficiency.
15. Osmolar gap helps differentiate causes of metabolic acidosis.
16. Anion gap =  $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$ , normal range: 8-12 mmol/L.
17. Hypoalbuminemia causes: Malnutrition, liver disease, nephrotic syndrome.
18. Hypophosphatemia causes: Refeeding syndrome, DKA, alcohol use.
19. Hyperphosphatemia causes: Chronic kidney disease, tumor lysis syndrome.
20. Corrected calcium formula:  $\text{Ca}^{2+} + (0.8 \times [4 - \text{albumin}])$ .

### **Diagnostic Indicators:**

1. Troponin I and T are specific markers for myocardial infarction.
  2. CK-MB rises in MI but returns to baseline within 48 hours.
  3. BNP and NT-proBNP are markers of heart failure severity.
  4. D-dimer is used to rule out venous thromboembolism (VTE).
  5. CRP and ESR are markers of systemic inflammation.
  6. Liver function tests: ALT (liver-specific), AST (alcoholic liver disease).
  7. ALP is elevated in cholestasis and bone disorders.
  8. GGT is specific for biliary tract disease and alcohol use.
  9. Bilirubin metabolism: Unconjugated (pre-liver), conjugated (post-liver).
  10. Fasting glucose >7.0 mmol/L or HbA1c >6.5% indicates diabetes.
  11. TSH is the initial test for thyroid disorders; T3 and T4 provide further insight.
  12. ACTH stimulation test diagnoses adrenal insufficiency.
  13. Arterial blood gas (ABG) interpretation assesses acid-base balance.
  14. Lactate levels indicate tissue hypoxia (sepsis, shock, ischemia).
  15. INR and aPTT assess coagulation function; warfarin increases INR.
  16. Ferritin is the best indicator of iron stores in the body.
  17. Vitamin B12 and folate deficiency cause macrocytic anemia.
  18. PSA is used for prostate cancer screening.
  19. Urinalysis findings: Proteinuria (kidney disease), ketonuria (diabetes, fasting).
  20. Cerebrospinal fluid (CSF) analysis differentiates bacterial vs viral meningitis.
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## 50 HIGH-YIELD POINTS FOR MEDICINAL CHEMISTRY & BIOPHARMACEUTICS

### Medicinal Chemistry

1. **Lipinski's Rule of Five:** Predicts oral bioavailability ( $MW < 500$ ,  $\log P < 5$ , H-bond donors  $< 5$ , H-bond acceptors  $< 10$ ).
2. **Prodrugs:** Inactive precursors activated via metabolism (e.g., enalapril  $\rightarrow$  enalaprilat).
3. **Bioisosteres:** Structural analogs improving drug efficacy or safety (e.g., fluorine replacing hydrogen).
4. **Stereochemistry:** Enantiomers have different activity (e.g., S-warfarin is more potent than R-warfarin).
5. **Phase I Metabolism:** Oxidation (CYP450), reduction, hydrolysis—introduces functional groups.
6. **Phase II Metabolism:** Conjugation reactions (glucuronidation, sulfation, acetylation) for elimination.
7. **CYP Inducers:** Increase metabolism (e.g., rifampin, carbamazepine, phenytoin).
8. **CYP Inhibitors:** Decrease metabolism (e.g., ketoconazole, grapefruit juice, erythromycin).
9. **Structure-Activity Relationship (SAR):** Modifications affecting potency, selectivity, and stability.
10. **LogP:** Measures lipophilicity; higher values improve membrane permeability but may increase toxicity.
11. **Partition Coefficient (P):** Determines drug solubility in lipid vs. aqueous environments.
12. **pKa and Ionization:** Determines drug solubility and absorption based on pH.
13. **Chirality in Drugs:** One enantiomer may be active while the other causes side effects (e.g., thalidomide).
14. **Hofmann Elimination:** Used to remove alkyl groups in quaternary ammonium salts.
15. **Hydrolysis of Esters:** Produces active/inactive metabolites (e.g., aspirin  $\rightarrow$  salicylic acid).

16. **Nitrosation Reactions:** Can lead to carcinogenic nitrosamines in some drugs.
17. **Tautomerization:** Interconversion of structural isomers, influencing drug stability.
18. **Redox Reactions:** Important in drug metabolism (e.g., oxidation of alcohols to aldehydes).
19. **Halogenated Compounds:** Improve metabolic stability and increase lipophilicity.
20. **Amphiphilic Drugs:** Contain both hydrophilic and lipophilic regions for better absorption.
21. **Biodegradable Polymers:** Used in drug delivery systems for controlled release.
22. **Peptide Drugs:** Prone to enzymatic degradation, requiring special formulation.
23. **Molecular Docking:** Used in drug design to predict binding affinity to targets.
24. **Isoelectric Point (pI):** Determines solubility and charge of peptides and proteins.
25. **Electrophilic/Nucleophilic Reactions:** Key mechanisms in drug metabolism.

## Biopharmaceutics

1. **Bioavailability (F%)**: Fraction of drug reaching systemic circulation (IV = 100%).
2. **First-Pass Metabolism**: Drugs metabolized in liver before systemic circulation (e.g., propranolol).
3. **Routes of Administration**: IV (100% F), oral (first-pass effect), sublingual (bypasses first-pass).
4. **Drug Dissolution Rate**: Influenced by particle size, pH, and excipients.
5. **Noyes-Whitney Equation**: Describes dissolution rate of drugs.
6. **Partition Coefficient & Drug Absorption**: Lipophilic drugs cross membranes better.
7. **Biopharmaceutical Classification System (BCS)**: Classifies drugs by solubility and permeability.
8. **Class I (BCS)**: High solubility, high permeability (best for oral absorption).
9. **Class II (BCS)**: Low solubility, high permeability (e.g., ketoconazole).
10. **Class III (BCS)**: High solubility, low permeability (e.g., metformin).
11. **Class IV (BCS)**: Low solubility, low permeability (poor oral bioavailability).
12. **Controlled Release Formulations**: Slow drug release to maintain therapeutic levels.
13. **Nanoparticles in Drug Delivery**: Improve solubility, permeability, and targeting.
14. **Micelles & Liposomes**: Carrier systems for hydrophobic drugs.
15. **PEGylation**: Increases half-life by reducing renal clearance.
16. **Depot Injections**: Slow-release formulations for long-acting effect (e.g., testosterone enanthate).
17. **Polymorphic Forms**: Different crystal structures affect solubility and stability.
18. **Surfactants in Formulation**: Improve drug solubility and absorption.
19. **pH-Dependent Solubility**: Weak acids absorb better in stomach, weak bases in intestines.

- 20. **Osmotic Pumps:** Use osmotic pressure for controlled drug release.
  - 21. **Complexation in Drug Formulation:** Enhances solubility (e.g., cyclodextrins with hydrophobic drugs).
  - 22. **Hygroscopicity:** Moisture absorption affecting drug stability.
  - 23. **Excipients & Drug Stability:** Buffers, preservatives, and stabilizers extend shelf life.
  - 24. **Parenteral Formulations:** Require strict sterility, isotonicity, and stability.
  - 25. **Biopharmaceutics & Personalized Medicine:** Tailoring drug formulations based on genetic variations.
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## Medicinal Chemistry & Biopharmaceutics - Detailed Keynotes

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### 1. Enalapril Excretion & Activation

- **Prodrug Activation:** Enalapril is a **prodrug** that is **converted in the liver** by esterase enzymes to its **active form**, enalaprilat.
  - **Excretion Pathway:** Since enalapril is excreted **unchanged**, the active metabolite **enalaprilat** undergoes renal excretion.
  - **Clinical Relevance:**
    - **Renal impairment** prolongs enalapril's effect, requiring dose adjustment.
    - **Hepatic impairment does not affect activation**, but renal failure leads to drug accumulation.
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### 2. Water-Soluble Beta-Blockers (Sotalol & Nadolol) & Renal Excretion

- **Physicochemical Properties:**
    - **Sotalol and Nadolol** are **hydrophilic** and do not undergo extensive hepatic metabolism.
    - **Lack of lipophilicity** results in **minimal CNS penetration**, reducing side effects like dizziness or fatigue.
  - **Renal Clearance:**
    - Eliminated **unchanged via urine** → Half-life is prolonged in **renal failure**, requiring dose adjustments.
    - **Not metabolized by the liver**, making them suitable for patients with hepatic dysfunction.
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### 3. CYP3A4 Metabolism & Drug Interactions

- **Major Drug-Metabolizing Enzyme:**
    - CYP3A4 is responsible for metabolizing **statins, calcium channel blockers (CCBs), and immunosuppressants (e.g., cyclosporine, tacrolimus)**.
  - **Inhibition & Induction:**
    - **Inhibitors:** Grapefruit juice, azole antifungals (ketoconazole, itraconazole), macrolides (erythromycin, clarithromycin), protease inhibitors (ritonavir).
      - **Effect:** Increased drug levels → Higher risk of toxicity (e.g., **statin-induced myopathy**).
    - **Inducers:** Rifampin, phenytoin, carbamazepine, St. John's wort.
      - **Effect:** Increased drug metabolism → Reduced therapeutic effect.
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### 4. CYP2D6 Polymorphism & Drug Metabolism Variability

- **Metabolism of Codeine, Beta-Blockers, and Antidepressants:**
    - Codeine requires CYP2D6 **activation to morphine** for its analgesic effect.
    - Beta-blockers (e.g., **metoprolol, carvedilol**) rely on CYP2D6 for metabolism.
    - Antidepressants (e.g., **fluoxetine, nortriptyline, amitriptyline**) have variable metabolism based on CYP2D6 activity.
  - **Genetic Variability & Its Impact:**
    - **Poor Metabolizers (PMs):** Reduced enzyme activity → **Codeine is ineffective** due to lack of conversion.
    - **Ultra-Rapid Metabolizers (URMs):** Increased enzyme activity → **Excessive morphine production**, leading to opioid toxicity.
    - **Clinical Considerations:** Genetic testing may be necessary for safe prescribing in high-risk populations.
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## 5. Phase I Metabolism (Oxidation, Reduction, Hydrolysis) - Functionalization Reactions

- **Purpose:** Introduces or exposes functional groups (–OH, –NH<sub>2</sub>, –COOH) to increase **polarity** for further metabolism or elimination.
  - **Key Reactions:**
    - **Oxidation:** Involves CYP450 enzymes → Converts drugs into more polar metabolites (e.g., paracetamol oxidation).
    - **Reduction:** Converts ketones or nitro groups to alcohols or amines (e.g., warfarin reduction).
    - **Hydrolysis:** Cleaves esters or amides via **esterase enzymes** (e.g., conversion of aspirin to salicylic acid).
  - **Clinical Significance:**
    - Drugs that undergo **extensive Phase I metabolism** (e.g., benzodiazepines, opioids) require careful dose adjustments in elderly patients due to **reduced metabolic function**.
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## 6. Phase II Metabolism (Conjugation Reactions) - Drug Elimination

- **Purpose:** Converts Phase I metabolites into **water-soluble, inactive** forms for **renal or biliary excretion**.
- **Types of Conjugation Reactions:**
  - **Glucuronidation** (most common): Adds glucuronic acid → **Paracetamol, morphine, bilirubin**.
  - **Sulfation:** Adds sulfate → Important for **steroids, acetaminophen**.
  - **Acetylation:** Important for **isoniazid, hydralazine** (slow acetylators at higher risk of toxicity).
  - **Glutathione Conjugation:** Detoxifies reactive metabolites (e.g., **paracetamol overdose detoxification** via glutathione).
- **Clinical Relevance:**
  - **Neonates have immature Phase II enzymes**, leading to jaundice due to inefficient bilirubin conjugation.

- **Isoniazid toxicity** in slow acetylators due to prolonged drug accumulation.
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## 7. First-Pass Metabolism & Bioavailability

- **Definition:** Hepatic metabolism of orally administered drugs before reaching systemic circulation, reducing bioavailability.
  - **Drugs Highly Affected:**
    - **Propranolol:** Extensive first-pass metabolism → Requires **higher oral doses** compared to IV.
    - **Morphine:** Undergoes glucuronidation → **Lower oral bioavailability**.
    - **Nitroglycerin:** Rapid hepatic metabolism → Given **sublingually** to bypass first-pass effect.
  - **Strategies to Overcome First-Pass Metabolism:**
    - **Alternative routes:** Sublingual (nitroglycerin), transdermal (fentanyl), IV (morphine).
    - **Prodrug approach:** Enalapril (inactive form) bypasses metabolism until activated in circulation.
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## 8. Lipophilic Drugs & Volume of Distribution (Vd)

- **Definition:** High Vd means a drug distributes widely into tissues, particularly fat.
  - **Examples of High Vd Drugs:**
    - **Diazepam** (highly lipophilic, accumulates in adipose tissue).
    - **Amitriptyline** (antidepressant with large tissue distribution).
    - **Propofol** (lipophilic anesthetic, rapid redistribution).
  - **Clinical Impact:**
    - Prolonged elimination in obese patients (stored in fat).
    - **Highly lipophilic drugs require hepatic metabolism** rather than renal excretion.
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## 9. Hydrophilic Drugs & Renal Clearance

- **Low Vd Drugs:** Stay within **plasma and extracellular fluid**.
  - **Examples:**
    - **Aminoglycosides (gentamicin, tobramycin):** Stay in extracellular fluid, cleared renally.
    - **Heparin:** Large, hydrophilic, does not enter tissues.
    - **Beta-lactam antibiotics:** Cleared mainly by kidneys.
  - **Clinical Impact:**
    - **Dose adjustment required in renal failure** to prevent accumulation and toxicity.
    - **Hydrophilic drugs have short half-lives**, often requiring frequent dosing.
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## 10. Half-Life ( $t_{1/2}$ ) & Drug Clearance

- **Formula:**
    - $t_{1/2} = (0.693 \times V_d) / CL$
  - **Factors Affecting Half-Life:**
    - $\uparrow V_d = \uparrow t_{1/2}$  (drugs distribute widely, e.g., diazepam).
    - $\downarrow CL = \uparrow t_{1/2}$  (renal/hepatic impairment, e.g., digoxin in kidney failure).
    - $\uparrow \text{Metabolism} = \downarrow t_{1/2}$  (enzyme inducers like rifampin increase drug clearance).
  - **Clinical Implications:**
    - Drugs with **long half-lives (e.g., amiodarone, diazepam)** require **loading doses** for immediate effect.
    - **Renal and liver function tests guide dose adjustments** in chronic disease patients.
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## Pharmacokinetics & Pharmacodynamics - Detailed Keynotes

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### 1. Zero-Order Kinetics Drugs (Phenytoin, Ethanol, Aspirin at High Doses)

- **Definition:**
    - Zero-order kinetics means that a **constant amount** of drug is eliminated per unit time, **regardless of concentration**.
    - Unlike first-order kinetics, elimination **does not** increase proportionally with higher drug levels.
  - **Mechanism:**
    - Drug-metabolizing enzymes or transporters **become saturated**, leading to a **fixed elimination rate**.
    - Once enzymes are at maximum capacity, increasing the drug dose leads to **nonlinear pharmacokinetics** and possible toxicity.
  - **Examples:**
    - **Phenytoin:** At therapeutic doses, it follows first-order kinetics, but at high doses, metabolism becomes saturated, shifting to zero-order kinetics.
    - **Ethanol:** The **alcohol dehydrogenase** enzyme has a fixed capacity, eliminating about **10g/hour** (approximately one drink per hour).
    - **Aspirin (high doses):** Normal doses follow first-order kinetics, but at **toxic levels**, hepatic enzymes become saturated.
  - **Clinical Implications:**
    - **Overdose risk is high** since the body cannot eliminate excess drug efficiently.
    - **Phenytoin dosing requires careful monitoring** to avoid toxicity, as small dose increases can lead to disproportionate plasma level rises.
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## 2. First-Order Kinetics Drugs

- **Definition:**
    - Drug elimination is **proportional to the plasma concentration** (i.e., a **constant fraction** of the drug is removed per unit time).
    - Most drugs follow first-order kinetics under normal dosing conditions.
  - **Mathematical Model:**
    - **Rate of elimination =  $CL \times \text{plasma concentration}$**
    - **Half-life remains constant** regardless of dose.
  - **Examples:**
    - **Most antibiotics (e.g., penicillins, cephalosporins)**
    - **Beta-blockers (e.g., metoprolol, atenolol)**
    - **NSAIDs (except aspirin at high doses)**
  - **Clinical Implications:**
    - Drug elimination is predictable, allowing easy dose adjustments.
    - Unlike zero-order drugs, **doubling the dose will not cause non-linear accumulation.**
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### 3. Loading Dose (LD) Calculation

- **Formula:**

$$LD = \frac{C_p \times V_d}{F}$$

- **C<sub>p</sub>** = Target plasma concentration
  - **V<sub>d</sub>** = Volume of distribution
  - **F** = Bioavailability (for IV drugs, F = 1)
  - **Purpose:**
    - **Achieves therapeutic drug levels rapidly**, especially for drugs with long half-lives.
    - Used in **emergency situations** where waiting for multiple doses to reach steady-state is impractical.
  - **Examples:**
    - **Digoxin** (cardiac glycoside)
    - **Aminoglycosides (e.g., gentamicin)**
    - **Theophylline (for asthma exacerbations)**
  - **Clinical Implications:**
    - **Adjust loading dose for altered V<sub>d</sub>** (e.g., increased V<sub>d</sub> in liver disease, decreased V<sub>d</sub> in dehydration).
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#### 4. Maintenance Dose (MD) Calculation

- **Formula:**

$$MD = \frac{C_p \times CL \times \tau}{F}$$

- **C<sub>p</sub>** = Target plasma concentration
  - **CL** = Clearance
  - **τ** = Dosing interval
  - **F** = Bioavailability
  - **Purpose:**
    - **Keeps drug levels within the therapeutic range** after loading dose administration.
    - Determined by **drug clearance and dosing interval** rather than V<sub>d</sub>.
  - **Examples:**
    - **Warfarin (monitored via INR)**
    - **Antihypertensives (e.g., lisinopril, losartan)**
    - **Antibiotics (e.g., vancomycin, aminoglycosides)**
  - **Clinical Considerations:**
    - Reduced clearance (e.g., **renal failure**) → **Decrease maintenance dose** to avoid toxicity.
    - Increased clearance (e.g., **induced metabolism via CYP3A4**) → **Increase maintenance dose** to maintain efficacy.
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## 5. Therapeutic Index (TI) & Drug Safety

- **Formula:**

$$TI = \frac{TD_{50}}{ED_{50}}$$

- **TD50** = Dose that causes toxicity in 50% of patients.
  - **ED50** = Dose that produces a therapeutic effect in 50% of patients.
  - **Clinical Relevance:**
    - **High TI drugs** → **Safer** (e.g., **penicillins, benzodiazepines**).
    - **Low TI drugs** → Require **close monitoring** (e.g., **warfarin, digoxin, lithium, phenytoin**).
  - **Examples:**
    - **High TI:** Paracetamol, antibiotics, beta-blockers.
    - **Low TI:** Theophylline, chemotherapy drugs, antiarrhythmics.
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## 6. Steady-State Concentration (Css)

- **Definition:**
    - **Css is reached after 4-5 half-lives** of consistent dosing.
    - At steady-state, **drug input = drug elimination**.
  - **Factors Affecting Css:**
    - **Half-life:** Longer half-life → Longer time to reach steady state.
    - **Dose frequency:** More frequent dosing maintains stable levels.
  - **Clinical Example:**
    - **Warfarin** takes ~4-5 days to reach full anticoagulant effect.
    - **SSRIs (e.g., fluoxetine)** take ~2 weeks for steady-state plasma levels.
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## 7. Protein Binding & Drug Displacement

- **Definition:**
    - **Highly protein-bound drugs** (e.g., warfarin, phenytoin) have a **small free drug fraction** (active form).
    - **Drug displacement** occurs when another highly protein-bound drug competes for albumin binding.
  - **Examples:**
    - **Warfarin + NSAIDs** → NSAIDs displace warfarin, increasing free warfarin levels → Increased bleeding risk.
    - **Phenytoin + Valproic acid** → Valproic acid displaces phenytoin, leading to toxicity.
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## 8. Renal Clearance & Drug Elimination

- **Influencing Factors:**
    - **Glomerular Filtration Rate (GFR):** Passive filtration of small, unbound drugs.
    - **Active Secretion:** Transporters excrete drugs (e.g., **penicillin via OAT transporters**).
    - **Tubular Reabsorption:** Lipophilic drugs may be **reabsorbed** rather than excreted.
  - **Clinical Example:**
    - **Metformin** is excreted **unchanged by the kidneys** and requires dose adjustment in renal failure.
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## 9. Urinary pH & Drug Excretion

- **Acidic Drugs (e.g., Aspirin)**
    - Excreted **faster in alkaline urine** (e.g., sodium bicarbonate enhances aspirin elimination in overdose).
  - **Basic Drugs (e.g., Amphetamines)**
    - Excreted **faster in acidic urine** (e.g., ammonium chloride enhances amphetamine clearance).
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## 10. Bioavailability (F%) & First-Pass Metabolism

- **Definition:** Bioavailability (F) is the fraction of administered drug reaching systemic circulation.
  - **Highest F%: IV drugs (100%).**
  - **Lowest F%:** Drugs with high **first-pass metabolism** (e.g., propranolol, nitroglycerin).
  - **Enhancing Oral Bioavailability:**
    - Lipophilic drugs cross membranes better.
    - Prodrugs bypass metabolism until activation in circulation (e.g., enalapril → enalaprilat).
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## Pain Management - High-Yield Notes

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### 1. Types of Pain

- **Nociceptive Pain** → Due to **tissue damage** (e.g., fractures, burns, arthritis).
    - **Somatic Pain** → Localized, sharp, aching (e.g., osteoarthritis).
    - **Visceral Pain** → Diffuse, deep, cramping (e.g., abdominal pain).
  - **Neuropathic Pain** → Due to **nerve damage** (e.g., diabetic neuropathy, post-herpetic neuralgia).
  - **Inflammatory Pain** → Due to **immune activation** (e.g., rheumatoid arthritis, post-surgical pain).
  - **Functional Pain** → No clear structural damage (e.g., fibromyalgia, irritable bowel syndrome).
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### 2. WHO Pain Ladder (Stepwise Approach)

**Mild Pain** → Non-Opioids (NSAIDs, Paracetamol, COX-2 Inhibitors)

**Moderate Pain** → Weak Opioids (Codeine, Tramadol) + Non-Opioids

**Severe Pain** → Strong Opioids (Morphine, Fentanyl, Oxycodone) ± Adjuvants

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### 3. Non-Opioid Analgesics

#### A. Paracetamol (Acetaminophen)

- **Mechanism:**
    - Inhibits **COX-3** in **CNS**, reducing pain & fever **without significant anti-inflammatory effects**.
  - **Uses:**
    - **First-line for mild pain & fever.**
    - **Preferred in pregnancy & children** (no risk of Reye's syndrome).
  - **Side Effects:**
    - **Hepatotoxicity in overdose** (treat with **N-acetylcysteine**).
-

## B. NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)

- **Mechanism:**
  - Inhibits **COX-1 & COX-2**, reducing **prostaglandin synthesis**, which mediates pain, fever, and inflammation.
- **Types:**
  - **Non-Selective NSAIDs** → Ibuprofen, Naproxen, Diclofenac, Ketorolac.
  - **COX-2 Selective Inhibitors** → Celecoxib, Etoricoxib (lower GI risk).
- **Uses:**
  - Musculoskeletal pain (arthritis, gout, sprains, menstrual cramps).
  - Post-operative pain, inflammation, fever.
- **Side Effects:**
  - GI ulcer & bleeding (COX-1 inhibition ↓ protective prostaglandins in stomach).
  - Renal toxicity (↓ renal perfusion → acute kidney injury, fluid retention, hypertension).
  - Cardiovascular risk (especially COX-2 inhibitors, ↑ risk of MI & stroke).

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## C. Aspirin (Acetylsalicylic Acid)

- **Mechanism:**
    - Irreversibly inhibits **COX-1 & COX-2**, reducing thromboxane  $A_2$  ( $TXA_2$ ) & prostaglandin production.
  - **Uses:**
    - **Low dose (75-100 mg/day): Antiplatelet effect** (prevention of MI & stroke).
    - **High dose (300-650 mg/day): Anti-inflammatory & analgesic effect.**
  - **Side Effects:**
    - Gastric ulcers & bleeding.
    - **Reye's syndrome in children** (liver failure + encephalopathy).
    - Tinnitus (salicylate toxicity).
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#### 4. Opioid Analgesics (Narcotics)

Used for **moderate to severe pain**. Work by **binding to opioid receptors ( $\mu$ ,  $\kappa$ ,  $\delta$ ) in the CNS**.

##### A. Weak Opioids

- **Examples:** Codeine, Tramadol
  - **Mechanism:**
    - **Codeine:** Converted to **morphine** (CYP2D6 activation required).
    - **Tramadol:** Weak  $\mu$ -receptor agonist + **serotonin & norepinephrine reuptake inhibition**.
  - **Uses:**
    - **Mild to moderate pain** (post-op, musculoskeletal pain).
  - **Side Effects:**
    - **Constipation, nausea, dizziness.**
    - **Seizure risk (especially with Tramadol in epilepsy patients).**
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##### B. Strong Opioids

- **Examples:** Morphine, Oxycodone, Fentanyl, Hydromorphone, Methadone.
  - **Mechanism:**
    - **$\mu$ -opioid receptor agonists** → Block pain signals in CNS & spinal cord.
  - **Uses:**
    - **Severe acute & chronic pain** (post-op, cancer pain, palliative care).
  - **Side Effects:**
    - **Respiratory depression (dose-dependent, risk of overdose).**
    - **Constipation** (common, requires laxatives like senna or docusate).
    - **Tolerance & dependence (withdrawal symptoms upon discontinuation).**
  - **Fentanyl** is used in transdermal patches for chronic pain (**100x stronger than morphine**).
  - **Methadone** has a long half-life, used in **opioid dependence management**.
  - **Opioid Overdose Treatment** → **Naloxone** (opioid antagonist, rapid reversal of respiratory depression).
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## **5. Adjuvant Analgesics (Neuropathic & Chronic Pain)**

Used **alone or with opioids** for neuropathic pain.

### **A. Antidepressants (TCAs & SNRIs)**

- **Examples:** Amitriptyline, Nortriptyline, Duloxetine, Venlafaxine.
  - **Mechanism:**
    - **Increase serotonin & norepinephrine levels**, modulating pain perception.
  - **Uses:**
    - **Neuropathic pain** (diabetic neuropathy, post-herpetic neuralgia, fibromyalgia).
  - **Side Effects:**
    - **Sedation, dry mouth, dizziness (TCAs).**
    - **Hypertension, nausea (SNRIs).**
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### **B. Anticonvulsants (Calcium Channel Modulators)**

- **Examples:** Gabapentin, Pregabalin.
  - **Mechanism:**
    - **Inhibit calcium channels**, reducing neuronal excitability & pain transmission.
  - **Uses:**
    - **Neuropathic pain, post-herpetic neuralgia, fibromyalgia.**
  - **Side Effects:**
    - **Dizziness, sedation, peripheral edema.**
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### **C. Local Anesthetics**

- **Examples:** Lidocaine (patches), Bupivacaine, Ropivacaine.
  - **Mechanism:**
    - **Block sodium channels**, preventing nerve conduction.
  - **Uses:**
    - **Local pain relief** (nerve blocks, epidurals, post-op analgesia).
  - **Side Effects:**
    - **Numbness, dizziness, cardiac toxicity at high doses (arrhythmias, hypotension).**
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## 6. Special Considerations in Pain Management

Condition	Preferred Pain Management	Avoid
Pregnancy	Paracetamol	NSAIDs (esp. 3rd trimester)
Peptic Ulcer	Paracetamol, Celecoxib	NSAIDs, Aspirin
Renal Failure	Opioids (except morphine)	NSAIDs (reduce GFR)
Liver Disease	NSAIDs	Paracetamol (risk of hepatotoxicity)
Neuropathic Pain	Gabapentin, Amitriptyline	Opioids (less effective)

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### Final Takeaways

- ✓ Use the WHO pain ladder to escalate treatment based on severity.
- ✓ Opioids should be reserved for severe pain & require monitoring for dependence.
- ✓ Adjuvant drugs (antidepressants, anticonvulsants) are first-line for neuropathic pain.
- ✓ NSAIDs should be avoided in GI bleeding, renal failure, and cardiovascular disease.
- ✓ Naloxone should always be available when prescribing high-dose opioids.

# Neurology & Psychiatry - High-Yield Notes

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## 1. Neurology: Key Disorders & Treatments

### A. Seizure Disorders & Epilepsy

#### Types of Seizures:

- **Focal (Partial) Seizures** (one hemisphere, may have aura)
- **Generalized Seizures** (both hemispheres, LOC)
  - **Tonic-Clonic (Grand Mal)** – Loss of consciousness (LOC), muscle rigidity, jerking
  - **Absence (Petit Mal)** – Brief staring episodes, common in children
  - **Myoclonic** – Sudden, brief muscle jerks
  - **Atonic** – Sudden loss of muscle tone (drop attacks)

#### First-Line Antiepileptic Drugs (AEDs):

- **Focal Seizures** → Carbamazepine, Lamotrigine, Levetiracetam
- **Generalized Tonic-Clonic** → Valproate, Levetiracetam, Lamotrigine
- **Absence Seizures** → Ethosuximide (1st-line), Valproate
- **Status Epilepticus** → IV Lorazepam (1st-line), IV Phenytoin (maintenance)

#### Side Effects of AEDs:

- **Valproate** → Hepatotoxicity, neural tube defects, pancreatitis
  - **Carbamazepine** → Aplastic anemia, hyponatremia (SIADH), CYP inducer
  - **Phenytoin** → Gingival hyperplasia, teratogenicity, ataxia, hirsutism
  - **Levetiracetam** → Behavioral changes (agitation, aggression)
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## B. Parkinson's Disease (PD)

### Pathophysiology:

- Loss of **dopaminergic neurons in the substantia nigra** → ↓ Dopamine
- **Classic Symptoms (TRAP):**
  - **Tremor (resting, pill-rolling)**
  - **Rigidity (cogwheel stiffness)**
  - **Akinesia/Bradykinesia (slow movement)**
  - **Postural Instability (falls, shuffling gait)**

### Treatment:

- **Levodopa/Carbidopa** (gold standard) → Increases dopamine in CNS
- **Dopamine Agonists** (Pramipexole, Ropinirole) → Used in younger patients
- **MAO-B Inhibitors** (Selegiline, Rasagiline) → Inhibit dopamine breakdown
- **COMT Inhibitors** (Entacapone, Tolcapone) → Prolongs levodopa effects
- **Anticholinergics (Benztropine, Trihexyphenidyl)** → For tremor in younger patients

### Side Effects:

- **Levodopa** → Dyskinesia (long-term use), N/V, hallucinations
  - **Dopamine Agonists** → Impulse control issues (gambling, hypersexuality)
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### **C. Stroke (Cerebrovascular Accident - CVA)**

#### **Types:**

- **Ischemic Stroke** (85%) – Due to thrombosis, embolism, or hypoperfusion
- **Hemorrhagic Stroke** (15%) – Due to aneurysm rupture, hypertension
- **Transient Ischemic Attack (TIA)** – Temporary symptoms (<24h), warning for stroke

#### **Acute Management:**

- **Ischemic Stroke:**
  - **IV tPA (Alteplase)** if within 4.5h of symptom onset
  - **Aspirin** (if tPA not given), statins, BP control
- **Hemorrhagic Stroke:**
  - **Reverse anticoagulation** (e.g., Vit K for warfarin toxicity)
  - **Blood pressure control** (IV labetalol, nicardipine)
  - **Neurosurgery** for large bleeds

#### **Prevention:**

- **Antiplatelet Therapy** (Aspirin, Clopidogrel)
  - **Anticoagulation for Atrial Fibrillation** (Warfarin, DOACs)
  - **BP & Cholesterol Control** (Statins, ACE inhibitors, lifestyle changes)
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## D. Multiple Sclerosis (MS)

- **Pathophysiology:**
    - Autoimmune demyelination of **CNS white matter**
    - **Relapsing-remitting** is most common type
  - **Symptoms:**
    - **Optic neuritis (vision loss, pain)**
    - **Lhermitte's sign (electric shock sensation down spine)**
    - **Uhthoff's phenomenon (symptoms worsen with heat)**
  - **Diagnosis:**
    - **MRI Brain & Spine** → White matter plaques
    - **CSF** → Oligoclonal bands
  - **Treatment:**
    - **Acute attacks** → High-dose **IV methylprednisolone**
    - **Disease-modifying therapy** → Beta-interferons, Natalizumab, Ocrelizumab
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## 2. Psychiatry: Key Disorders & Treatments

### A. Depression & Bipolar Disorder

#### Major Depressive Disorder (MDD):

- **SIGECAPS** → ↓ **Sleep**, ↓ **Interest**, **Guilt**, ↓ **Energy**, ↓ **Concentration**, **Appetite change**, **Psychomotor changes**, **Suicidal ideation**
- **First-Line Treatment: SSRIs (Fluoxetine, Sertraline, Escitalopram)**
- **Second-Line: SNRIs (Venlafaxine, Duloxetine), TCAs, Mirtazapine**

#### Bipolar Disorder:

- **Type 1** → Manic episodes ± depression
  - **Type 2** → Hypomania + depression
  - **Mood Stabilizers:**
    - **Lithium** (gold standard, narrow therapeutic index, nephrotoxic)
    - **Valproate** (hepatotoxic, teratogenic)
    - **Carbamazepine, Lamotrigine** (for bipolar depression)
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## B. Schizophrenia & Psychotic Disorders

**Positive Symptoms** (delusions, hallucinations, disorganized speech)

**Negative Symptoms** (apathy, social withdrawal, anhedonia)

**Treatment:**

- **First-Generation Antipsychotics (Typical):**
  - **Haloperidol, Chlorpromazine** (block D2 receptors, cause EPS)
- **Second-Generation Antipsychotics (Atypical):**
  - **Risperidone, Olanzapine, Quetiapine, Clozapine** (for treatment-resistant cases)

**Side Effects:**

- **Extrapyramidal Symptoms (EPS)** → Dystonia, akathisia, tardive dyskinesia
  - **Metabolic Syndrome (Atypicals)** → Weight gain, hyperlipidemia, diabetes
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## C. Anxiety Disorders

- **Generalized Anxiety Disorder (GAD):**
    - **Treatment:** SSRIs (first-line), Buspirone, Benzodiazepines (short-term only)
  - **Panic Disorder:**
    - **Treatment:** SSRIs (first-line), Benzodiazepines (short-term)
  - **Obsessive-Compulsive Disorder (OCD):**
    - **Treatment:** SSRIs (Fluoxetine, Fluvoxamine) + CBT (Exposure therapy)
  - **Post-Traumatic Stress Disorder (PTSD):**
    - **Treatment:** SSRIs, Prazosin (for nightmares), CBT
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## D. ADHD (Attention-Deficit Hyperactivity Disorder)

- **Symptoms:**
    - Inattention, hyperactivity, impulsivity
  - **Treatment:**
    - **Stimulants:** Methylphenidate, Amphetamines (first-line)
    - **Non-stimulants:** Atomoxetine (NE reuptake inhibitor), Guanfacine
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### **High-Yield Clinical Pearls**

- ✓ **SSRIs are first-line for depression & anxiety but take 4-6 weeks to work**
  - ✓ **Lithium requires renal function monitoring (risk of toxicity in kidney failure)**
  - ✓ **Benzodiazepines cause dependence & should not be used long-term**
  - ✓ **Clozapine is reserved for treatment-resistant schizophrenia (risk of agranulocytosis)**
  - ✓ **Levodopa should not be given with protein-rich meals (↓ absorption in Parkinson's)**
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