Learning objectives – Pharmacology – Basics of pathology – Prologue 2

Student should be able to:

Chapter 1

- Define receptors
- Know what agonists and antagonists do when they bind the receptors
- Differentiate receptor and inert binding sites from each other
- Know which part of the receptor competitive inhibitors, allosteric activators and allosteric inhibitors bind and what is the result of binding
- Know the meaning of permeation
- Understand the concepts of aqueous diffusion, lipid diffusion, transport by special carriers and endocytosis/exocytosis
- Understand the Fick's law of diffusion _ be able to identify which values increase and which one's decrease the rate of drug absorption;
- Differentiate charged and uncharged molecules in terms of aqueous and lipid solubility;
- Understand the Henderson-Hasselbach equation: what it can be used for and how;
- Know how protonation/deprotonation affects ionization of weak acids and bases;
- Clinically correlate ionization of weak acids and basis with renal excretion of drugs;
- Know which factors influence the absorption of drugs;
- Understand the concept of bioavailability;
- Know the common routes of administration;
- Recall which route of administration has the optimal bioavailability;
- Recall which route of administration is associated with first pass metabolism;
- Understand the concept of first-pass metabolism;
- Know the determinants of drug distribution;
- Understand the concept of volume of distribution;
- Calculate the volume of distribution;
- Know the percentages of total body water, intracellular water and extracellular water;
- Understand the concept of metabolism;
- Know the difference between excretion and elimination;
- Understand what are the effects that metabolism can have on different drugs;
- Differentiate first-order kinetics from zero order kinetics: understand what is the difference between their rates of elimination and half-lives;
- Identify the graphs of zero-order vs. first order kinetics;
- Recall the drugs that have zero-order kinetics;
- Distinguish distribution and elimination phases;
- Know which drugs need acute toxicity testing;
- Know types of animal tests;
- Know the categories of drug safety in pregnancy _ be able to identify how safe the drug is based on its category;
- Understand the terms: mutagenic, carcinogenic, teratogenic;
- Understand the terms: single-blind study, double blind study;

- Know what Ames test is and what it is used for;
- Know what dominant lethal test is;
- Know all four phases of clinical trials: purpose of each phase, approximate amounts of participants, target groups.
- Understand the concept of adaptive clinical trials.
- Know the meaning of orphan drugs.

Chapter 2

- Understand the dose-response relationships; be able to identify EC50 and Emax on curves;
- Understand the concepts of efficacy and potency; be sure to know the pattern of their association with EC50 and Emax values;
- Know the effect of competitive antagonist in presence of full agonist; Be able to recall the shift on a dose-response curve; be able to recall the effect of a noncompetitive antagonist on EC50 and/or Emax and therefore on potency and/or efficacy;
- Know the effect of noncompetitive antagonist in presence of full agonist; Be able to recall the shift on a dose-response curve; be able to recall the effect of a noncompetitive antagonist on EC50 and/or Emax and therefore on potency and/or efficacy;
- Know the concepts of inverse agonist, full agonist, partial agonist, neutral antagonist and there Log Dose activity curves;
- Understand the concepts of biased agonist, competitive antagonist, irreversible antagonist, physiologic antagonist, chemical antagonist;
- Know the meaning of constitutive activity;
- Understand the concepts of median effective, median toxic and median lethal doses.
- Read the quantal dose-response plots and bell-shaped curves and identify ED50 and LD50 on it.
- Know what is a therapeutic window and what it means clinically to have a wide or narrow therapeutic window;
- Know what is therapeutic index and what it means to have a high or low therapeutic index;
- Know 5 types of signaling mechanisms; Be able to identify which type of receptor is used by steroids, vitamin D, nitric oxide, insulin, EGF.
- Know the concepts of tachyphylaxis and receptor upregulation and downregulation; Be able to identify which ones of them are long-term/short-term.

Chapter 3

- Know the meaning of an effective drug concentration;
- Understand volume of distribution; be able to recall formula and calculate accordingly;
- Understand how the Vd changes in case of liver disease and kidney disease.
- Know the effect of plasma protein binding or tissue protein binding on Vd.
- Understand the concept of clearance; be able to recall the formula and calculate accordingly;
- Understand the concept of half-life; be-able to recall the formula and calculate accordingly; be able to calculate the dose patient took or current plasma concentration of the drug using the understanding of half-life;

- Understand the concept of steady state; be able to name the amount of half-lives needed tor each a steady state;
- Understand the concept of bioavailability;
- Know which route of administration has the optimal bioavailability;
- Know the factors that influence bioavailability;
- Understand the concept of area under the curve;
- Understand the concept of extraction ratio;
- Recall loading dose formula and calculate accordingly;
- Recall maintenance dose formula and calculate accordingly;
- Understand the concept of therapeutic window; Know how its width correlates with drug safety;
- Know the formula of corrected dosage in patients with altered clearance in case of renal impairment;

Chapter 4

- Understand different effects of biotransformation on drugs;
- Name Phase I reactions; Know what are the characteristics of metabolites made by these reactions;
- Name phase II reactions; Know what are the characteristics of metabolites made by these reactions;
- Know what are important sites of drug metabolism;
- Name the determinants of biotransformation rate;
- define suicide inhibitors;
- Know what are MDR-1 proteins and where they are commonly seen;
- Know high yield CYP correlations **(Please see the annex);** Be able to identify which drugs are CYP inhibitors or CYP inducers and which ones are metabolized by CYP enzymes (hint _ use First Aid for an organized list of most important CYP inducers and inhibitors. FA 2019 page 251 "cytochrome P450 interactions); Understand how inducers and inhibitors may change the drug metabolism;
- Understand the concept of toxic metabolism using an example of acetaminophen;

Chapter 5

- Understand the concept of personalized medicine;
- Understand how gene polymorphisms may effect the drug metabolism;
- Recall the information given on table 5-1, columns 1 and 3;
- Understand the importance of HLA polymorphisms;
- Know the importance of P-glycoprotein;
- Name the drugs that are contraindicated in enhanced metabolizers of the HLA-B*57:01 type.

Chapter 6

1. Recall anatomic divisions (Parasympathetic, sympathetic, enteric), location of ganglia and characteristics of Autonomic nervous system (difference in terms of length of pre and postganglionic nerves)
2. Name the cranial nerves that are part of parasympathetic nervous system

3. Recall which receptors respond to autonomic transmitters and drugs but receive no innervation
4. Name primary neurotransmitters of parasympathetic and sympathetic nervous system and recall exceptions (thermoregulatory sweat glands)
5. List steps of Acetylcholine synthesis, storage and release with corresponding drugs that block these steps.
6. Understand process of docking and recall proteins that mediate it
7. Understand process of termination of action of acetylcholine and know the name of enzyme that cleaves it.
8. List steps of Norepinephrine synthesis, storage and release with corresponding drugs that block these steps.
9. Differentiate between process of termination of action of Acetylcholine and Norepinephrine
10. Name cotransmitters released together with primary neurotransmitters
11. Recall types of cholinoreceptors, Adrenoreceptors and Dopaminergic receptors, their location, secondary messenger systems that they use for signal transmission and effects of their activation/inhibition
    a. Predict effects of these inhibitors on the function of major organ systems (cardiovascular, respiratory, GI, GU, reproductive, exocrine, endocrine, CNS, skeletal muscle)
12. Have general understanding of what nonadrenergic, noncholinergic transmission means
13. Recall substances that inhibit transmitter release, transmitter uptake after release
    a. Describe the action of several toxins that affect nerve function: tetrodotoxin, saxitoxin, botulinum toxin and Iatrotoxin
14. Describe the control of blood pressure
    a. Baroreceptor neural reflex
    b. Renin-Aldosterone-Angiotensin hormonal response
15. Describe baroreceptor response for the following conditions
    a. Blood loss
    b. Administration of vasodilator
    c. A vasoconstrictor
    d. A cardiac stimulant
    e. Cardiac depressant
16. Recall effects of Ganglion blockade
17. Name different receptors and response to their activation/inhibition in parts of an eye
    a. Accommodation, pupil size changes

Chapter 7

1. Differentiate between actions of direct and indirect cholinomimetic agonists
1. Know which cholinomimetic agents have shortest/longest duration of action
2. Name Direct-acting cholinomimetic agents and
    a. Their spectrum of action (muscarinic,nicotinic or activation of both receptors)
    b. Their clinical use
    c. Key pharmacokinetic functions (short./long acting, can cross Blood-Brain Barrier or not, degraded by cholinesterase or not)
    d. Mechanism of action

3. Name Indirect acting cholinomimetic agents and
    a. Their spectrum of action (muscarinic, nicotinic or activation of both receptors)
    b. Their clinical use
    c. Key pharmacokinetic functions (short/long acting, can cross Blood-Brain Barrier or not)
    d. Mechanism of action
4. List cholinergic receptors
    a. Their second messenger systems
5. Understand why and how the tissue and organ level effects of nicotinic ganglionic stimulation depend on the autonomic innervation of the organ
6. Understand mechanism of vasodilation and sweat gland activation
7. Describe all symptoms of cholinergic toxicity
    a. Differentiate between muscarinic and nicotinic toxicity
    b. Name drug used to reverse muscarinic toxicity and drug that reverses nicotinic effects
8. Describe mechanism of action of Pralidoxime and meaning of enzyme "Aging"
9. Recall drug used for diagnosis of Myasthenia
    a. Used for differentiating Myasthenic and Cholinergic crises
10. Describe Difference between Malathion and Parathion, clinical use of malathion

Chapter 8

1. Name antimuscarinic drugs
    a. Their relative selectivity to specific receptors
    b. Which organ systems do they affect
    c. Clinical use
2. Name antinicotinic agents
    a. Whether they block ganglion or neuromuscular junction signal transmittion
    b. Clinical use
3. Name cholinesterase regenerator, its mechanism of action and clinical use
4. Describe effects of muscarinic blocking drugs on CNS, Eye, Bronchi, GI and GU tracts, Heart, Blood vessels, Glands and skeletal muscle and which receptors are blocked
5. Student must know all predictable and other toxicities associated with Atropine (anticholinergic) toxicity
6. Recall treatment of atropine toxicity
7. Name contraindications to the use of antimuscarinic agents
8. Name ganglion blocking drugs and their effect on major organ systems.

Chapter 27

<u>Neuromuscular blocking drugs</u>

1. Know the difference between mechanism of action of Depolirizing and Nondepolirizing neuromuscular blockers from the standpoint of tetanic and post-tetanic twitch strength.

1. Recall prototype drug for depolirizing NM blockers
    a. Its pharmacokinetic properties
    b. Mechanism of action
    c. Describe phase 1 and phase 2 of blockade
    d. Name which of this phases can be overcome by increased acetylcholine levels and which can become worse
    e. Its effects on cardiac muscarinic receptors, autonomic ganglia and histamine release
    f. Specific effects of succinylcholine in specific groups of patients (burn victims, peripheral nerve dysfunction, muscular dystrophy, spinal cord injury)
    g. Possible aspiration of gastric contents
    h. Interaction of succinylcholine with other medications
2. List nondepolarizind agents
    a. Describe what phase of blockade does it have
    b. Whether blockade can be reversed by increasing acetylcholine level or not
    c. Mechanism of action
    d. Name which of these agent affects cardiac muscarinic receptors and how
    e. Name which of them is not used anymore because of toxic metabolite

3. Effects of aging and disease on nondepolarizing and depolarizing NM blocker action

<u>Spasmolytic drugs</u>

1. Name drugs used for chronic spasms
    a. Their mechanism of action
    b. Specific clinical application
    c. side effects
2. Describe which electrolyte abnormality characterizes malignant hyperthermia
    a. Agent used to treat malignant hyperthermia
    b. Its mechanism of action

Annex

<u>Important CYP correlations:</u>

- 1A2 _ Important inducers: Benzopyrene (hydrocarbons from tobacco smoke), omeprazole, cruciferous vegetables. Metabolizes theophylline/acetaminophen. Inhibited by quinolones and macrolides.
- 2E1 _ inducers: ethanol, isoniazid. Metabolizes ethanol, acetaminophen.
- 3A4 _ metabolizes statins (excluding pravastatin) and macrolides. Metabolizes most drugs together with 3A5
- 2D6 metabolizes opioids, cardiovascular and CNS drugs. Inhibited by haloperidol and quinidine.
- 2C19 metabolizes clopidogrel, Omeprazole

- CYP-2C9 _ warfarin/phenytoin; metabolism also affected by VKORC1(Vitamin K epoxide reductase complex) polymorphisms.
- P-450c17 – has both 17a-hydroxylase and 17,20 lyase activities, and is a key enzyme in the steroidogenic pathway that produces progestins, mineralocorticoids, glucocorticoids, androgens and estrogens; inhibited by ketoconazole.
- CYP enzyme inducers increase metabolism of vitamin D thus increasing risk of Osteoporosis.(fractures)
- CYP enzymes metabolize procarcinogens into carcinogens
- Ethanol has higher first-pass metabolism in men compared to women

Chapter 9

Student should be able to:

- Name the types of adrenoreceptors; Know their mechanism of action; Know which tissues they are in (Table 9-1)
- Know the difference between concepts of direct and indirect acting sympathomimetics;
- Name examples of indirect acting sympathomimetics and explain their mechanism of action;
- Know how catecholamines are metabolized;
- Know which route of administration is optimal for direct adrenoreceptor agonists;
- Know which route of administration is optimal for amphetamines;
- Explain how tyramine interacts with MAO inhibitors;
- Associate each type of adrenoreceptor with appropriate second messenger system;
- Associate each type of dopamine receptor with appropriate second messenger system;
- Know CNS effects of sympathomimetic drugs;
- Understand effects of sympathomimetic drugs on eyes;
- Understand effects of sympathomimetic drugs on bronchi;
- Understand effects of sympathomimetic drugs on GI tract;
- Understand effects of sympathomimetic drugs on GU tract;
- Location of different sympathetic receptors in vascular beds;
- Understand effects of sympathomimetic drugs on heart;
- Understand net cardiovascular actions of sympathomimetic drugs;
- Understand Figure 9-1; be able to identify a drug based on a figure;
- Metabolic and hormonal effects of sympathomimetic drugs;
- Know the treatment of anaphylaxis;
- Know the CNS indications of sympathomimetic drugs;
- Know the eye related indications of sympathomimetic drugs;
- Name short-acting and long-acting symptahomimetics used for asthma treatment;
- Know cardiovascular indications of sympathomimetic drugs;
- Know indications and side effects of beta2 agonists in pregnant women;
- Know GU indications of sympathomimetic drugs;
- Understand toxicity of sympathomimetic drugs

Chapter 10

- Name primary subgroups of Adrenoreceptor antagonists
- Name nonselective alpha receptor blockers
    - Compare reversible and irreversible alpha blockers
    - Clinical use
- List selective alpha 1 receptor blockers
    - Most common clinical application
- Describe Toxicity of selective and nonselective alpha receptor blockers
- Explain most common cardiovascular effects of nonselective alpha blockers
- Explain "Epinephrine reversal" in a patient who has received an alpha blocker
    - Compare to phenylephrine effect
- Name beta 1 receptor blockers
    - mechanism of action
    - clinical application
- Name nonselective beta receptor blockers
    - mechanism of action
    - clinical application
- Name beta blockers who have inverse agonist action
- Recall which beta blockers are short acting and which are long acting
- List drugs that have both, alpha and beta receptor blocking effect
- Recall toxicity of beta blockers
- Name drugs used in glaucoma
    - Mechanism of action
    - Method of administration