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I am available to groups and individuals for pharmacology help and discussions by appointment.

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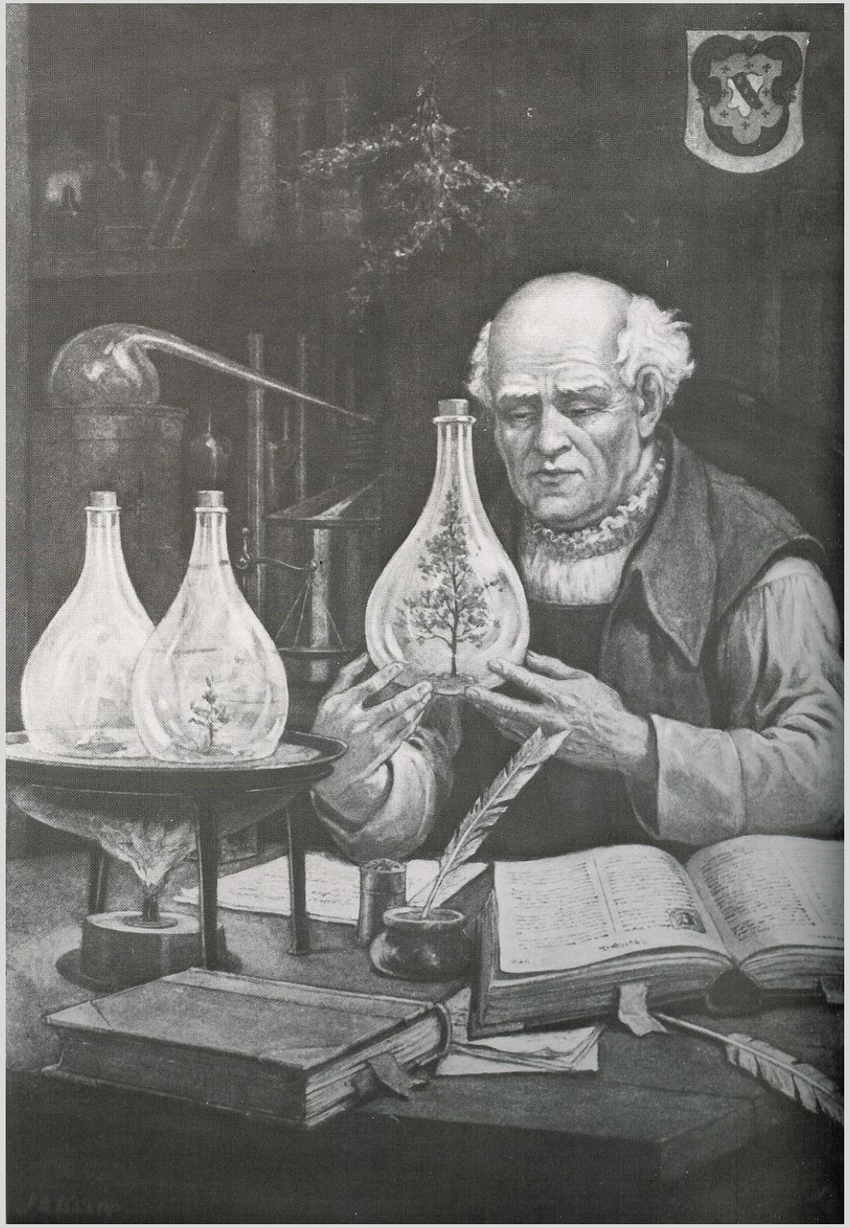
Do.
Make.
Heal.
Innovate.
Reinvent the Future.



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"All things are poison, for there is nothing without poisonous qualities; only the dose permits something not to be poisonous."

Paracelsus 1493-1541

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After completing the preparation materials, students should be able to:

1. Define adverse drug reactions.
2. Give examples of the personal and economic impact of adverse drug events.
3. Describe the mechanisms of drug toxicities on the cells, tissues, and organ systems.
4. Link maternal drug use during the three trimesters of pregnancy to the potential toxic effects on the fetus and neonate.
5. Apply the FDA Pregnancy and Lactation Labeling Rule to the clinical care of pregnant women, nursing infants, and females and males of reproductive potential.
6. Explain how pharmacogenomic variants in drug-metabolizing enzymes, transporters, genetic variants of metabolic disorders, and HLA variant alleles may contribute to individual variation in drug response and give examples of specific harmful consequences.

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Preparation Materials (links are on the next slide)

Required

- ScholarRx Bricks | Practice Questions

Highly relevant optional materials:

- Dr. Goldstein's Word handout | Video Lectures | Guided reading questions (GRQs)

SUGGESTIONS:

- ***Use the resources that work best for you.***
- ***You do not need to study all of them. (ScholarRx Bricks & Practice Questions are required.)***
- ***Work through the GUIDED READING QUESTIONS with pen/pencil and paper.***

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- ***Practice questions (not graded) will help you assess your own learning and understanding. The practice questions consist of case vignettes to help you start integrating and applying concepts in the context of clinical scenarios.***

Links

Scholar Rx Bricks: (Required)
General Pharmacology > Principles of Pharmacology > Pharmacokinetics and Pharmacodynamics
Pharmacokinetics: Drug Administration, Metabolism, and Excretion
The following sections:

- Phases of Hepatic Drug Transformation
- What Can Affect Drug Metabolism?
- Pharmacologic Modification
- Genetic Modification
- Physiologic Modification

https://exchange.scholarrx.com/brick/drug-administration-metabolism-and-excretion

Optional resources by McGraw-Hill
Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14e, 2023; and Chapter 7: Pharmacogenetics & Pharmacogenomics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3191&sectionid=268215725

Goodman & Gilman's Chapter 9: Principles of Clinical Toxicology
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3191&sectionid=268044850

Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 5: Pharmacogenomics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382&sectionid=281747341

Katzung's Pharmacology: Examination and Board Review, 14e, 2024; Chapter 5: Pharmacogenomics
https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461&sectionid=285589482

This lecture provides many examples to help students visualize the concepts and put them into a clinical context – caring for patients.

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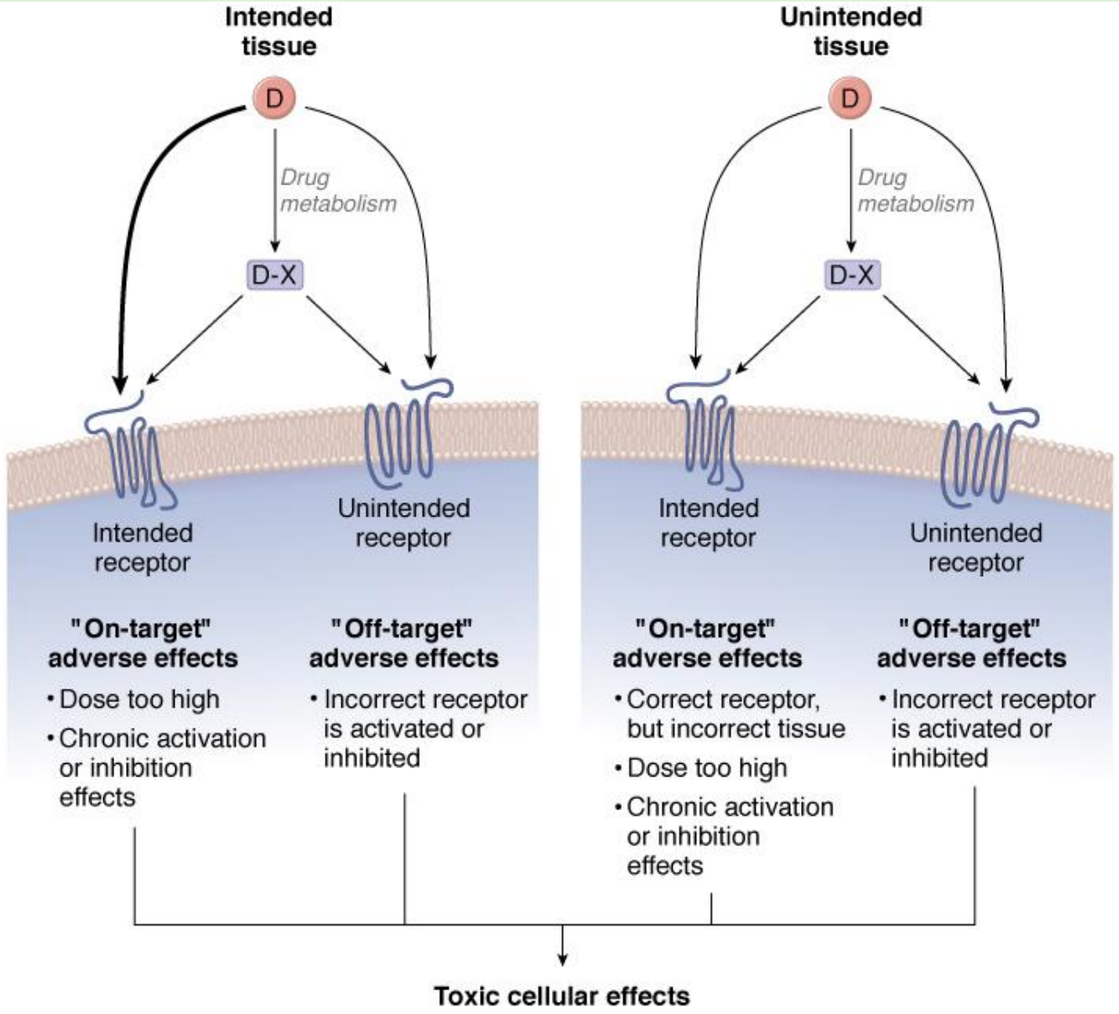
In addition to learning the terminology, be able to recognize, explain in your own words to a friend or relative, and apply the following:

- Types of adverse drug reactions (ADRs)
- Risk factors / causes of adverse drug reactions / adverse drug events
- Mechanisms, mechanisms, mechanisms of drug toxicity
- Toxic effects: acute, delayed, cumulative, local, systemic, reversability
- Harmful effects on cells and organs
- Therapeutic drug use in pregnancy and the main ideas of the Pregnancy and Lactation Labeling Rule, three subsections (no need to memorize the wording)
- Harmful effects of maternal drug use on the fetus and neonate
- Mechanisms and causes of immunological adverse drug events
- Pharmacogenomics principles
- Specific starred (✳) genetic variants that increase patients' risk for ADRs.

From: **6 Drug Toxicity**
Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy Fourth Edition, 4e, 2017



On-target and off-target adverse drug effects.

ADRs are typically,

- **Predictable:** Based on knowledge of the mechanisms of action and adverse effects, distribution to tissues, and dose-response relationship
- **Dose-dependent:** Related to the concentration of drug in the body and to the duration of the exposure

ON-TARGET effect results from the drug interacting with its therapeutic target in intended or unintended tissue.

Anticoagulants increase the time to form clots → high dose can cause hemorrhage.

Nifedipine lowers blood pressure by relaxing vascular smooth muscle (intended tissue) but hypotension at high doses by acting on cardiac tissue (unintended tissue).

OFF-TARGET effect results from the drug interacting with a target or targets other than the intended target in intended or unintended tissue.

Tricyclic antidepressant → sedation, dry mouth, hypotension (blockade of histaminic, muscarinic, and adrenergic receptors)

Slide adapted by LG

Toxic effects may be acute, delayed, or cumulative

Adverse effects may cause …

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Local reactions

Systemic reactions

Immunogenic reactions

- Hypersensitivity reactions
- Mechanism-related immune system upregulation

  Example: anticancer immune checkpoint inhibitors

Photosensitivity

Fetal toxicity

Cellular toxicity

- Apoptosis
- Necrosis

DNA damage

- Mutagenesis:

  Gene mutations give rise to altered proteins.
- Carcinogenesis

  Mutations in genes that regulate cell growth may lead to induction of cancer.

Organ toxicity

- Liver
  - Hepatitis / necrosis
  - Cirrhosis
- Kidney
  - Glomerular nephropathy
  - Tubular necrosis
  - Interstitial nephritis
- Nerves
  - Neuropathy
  - Seizures
  - Coma
- Bone marrow toxicity
  - Neutropenia
  - Anemia
  - Thrombocytopenia

Effects may be reversible or irreversible.
Effects may range from minor discomfort to significant morbidity and mortality.

Pregnancy and Lactation (Drug) Labeling Rule

Labeling to facilitate prescriber counseling for patients of reproductive potential.

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Three subsections:

1. **Pregnancy including labor and delivery:**
   - **Pregnancy registry** collects data and notes any potential risk of medication use on the developing fetus and the mother.
   - **Risk summary** provides information on potential adverse effects on developing fetus throughout pregnancy and PK parameters altered during pregnancy.
   - **Clinical considerations** are provided about initiation, continuation, and withdrawal of treatment during pregnancy and the data are listed in the drug monographs.
2. **Lactation:**
   - **Risk summary** of information about the timing of breastfeeding, excretion of drugs in breast milk, and risks to the infant are provided. **Clinical considerations** and **data** supporting the recommendations are listed in the drug monographs.
3. **Reproductive considerations for females and males**
   - **Pregnancy testing recommendations** prior to beginning drug therapy
   - **Contraception advice** for female of reproductive potential about the use of contraception during and after therapy with specific drugs
   - **Information for males** who wish to father a child about infertility as it relates to specific drugs and Manufacturers may provide recommendations for contraception with partners who may become pregnant during and after therapy.

Question

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- What information is provided in the Pregnancy and Lactation Labeling Rule that can be helpful to clinicians in educating pregnant patients and individuals with reproductive potential about drug use during pregnancy?

Drug-Immune System Interactions → Hypersensitivity Reactions

- The drug may act as an antigen and elicit a hypersensitivity response.
- The drug may interact with immune receptors and lead to activation of specific immune cells.
- **Adverse drug events: Drugs can induce all types of immune-mediated hypersensitivity – allergic – reactions that can cause significant morbidity and lead to death.**

Mechanisms of drug-immune system reactions

Haptens	Small chemicals (drugs or their metabolites) that are not reactive in their original state become immunogenic by covalent binding to host proteins on cells or in plasma forming hapten-carrier complexes. Hapten-peptide fragments are presented by antigen presenting cells to T cells, ultimately eliciting allergic reactions.
Biologic drugs	Protein drugs, such as monoclonal antibodies, recombinant proteins, solubilized receptors, cytokines, enzymes, antisera, and vaccines can preferentially stimulate antibody responses and some T cell responses.
Drug-induced autoimmunity	An autoimmune phenomenon where the patient develops symptoms similar to the autoimmune disease. The pathogenesis is not understood. Examples: lupus-like disorder, pemphigus-like disorder, IgA bullous dermatosis

Most drugs are small molecular weight compounds with simple chemical structures, which are not easily recognized by the immune cells and too small to interact with immune receptors with enough strength to activate T and B cells.

Examples of genetic polymorphisms influencing drug response

Stars ✳ on examples on the following list mean students should learn the Mechanisms of these specific examples and be able to apply them in a clinical context.

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Gene product	Drugs	Responses affected
✳*NAT2* N-acetyl transferase Poor metabolizer	• hydralazine • isoniazid • procainamide	• Lupus-like syndrome • Hepatotoxicity • QTc interval prolongation (arrhythmia)
✳*CYP2D6*	• codeine • antipsychotics • antidepressants • beta-blockers	• Codeine ultrarapid metabolizers: Increased risk of respiratory depression Codeine $^{CYP2D6\ UM}\rightarrow$ ↑ morphine concentration for a given dose → respiratory depression risk
✳*UGT1A1* UDP-glucuronosyl tranferase	• Bilirubin • Lipophilic molecules	Deficient UGT1A1 • → unconjugated bilirubin can accumulate blood → jaundice in neonate and adult • → increased toxicity of a certain cancer chemotherapeutic that is detoxified by UGT1A1

Know mechanisms and effects not drug names

- Adverse drug reactions and adverse drug events from overdose, dose reductions, abrupt withdrawal of a drug, resistance to therapy, paradoxical effects, and drug-disease, drug-drug-, drug-supplement, and drug-food interactions. Effects may range from relatively benign to serious, causing significant morbidity or death. They may be acute, delayed, and chronic.
- ADRs/ADEs can result from overdose, dose reductions, abrupt withdrawal of a drug, resistance to therapy, paradoxical effects, and drug interactions.
- Drug-induced deleterious effects to cells and organs can be caused by the parent drug, toxic metabolites, or reactive oxygen species. Small chemicals may form hapten-protein complexes that activate the immune system against the complex. Some drugs can directly activate a hypersensitivity reaction (allergy) in sensitive individuals.
- Mechanisms include “on-target” (desired target in intended and unintended tissue) and “off-target” (unintended target in intended and unintended tissue) drug actions.
- Drugs taken by a pregnant person can cause teratogenicity or other fetotoxicity. Neonates can manifest abstinence syndrome resulting from maternal use of addictive drugs. Other effects on neonate include premature birth and low birth weight. The Pregnancy and Lactation Labeling Rule helps prescribers communicate the risks of pharmacologic treatment to pregnant and breastfeeding patients and preconception advice to females of reproductive potential and males who wish to father a child.

- Polymorphisms in metabolic enzymes, are thought to underlie individual differences in the rate at which drugs are metabolized. The categories are poor, intermediate, extensive, and ultra-rapid metabolizers. Genetic variants in transporters, drug targets, and variant HLA alleles may also relate to an individual's response to drug therapy.
- Pharmacogenomics research is the systematic examination of genes, gene products, and variation in gene expression and function, using tools for surveying the entire genome. Pharmacogenomics researchers evaluate multigenic determinants of that may predict drug response – efficacy and safety or drug toxicity – in an individual or across a population.
- An aim of pharmacogenomics research is to guide decisions on prevention, diagnosis, and disease management strategies using an individual's clinical and genetic information. This information may be included in the labeling of specific drugs, which may help clinicians select the drugs and doses best suited for the individual patient based on their individual genes.
- Precision medicine is an approach to tailoring disease prevention and treatment that accounts for differences in patients' genes, lifestyles, and environment.

Right drug | Right patient | Right dose | Right route | Right time