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

1. Classify the drug-drug interactions resulting in additive, synergistic, or antagonistic effects.
2. Describe the receptor-mediated and non-receptor-mediated pharmacodynamic mechanisms of drug-drug interactions and their effects.
3. Explain the pharmacokinetic mechanisms of drug-drug interactions related to absorption, metabolism, distribution, and excretion and their effects.
4. List the common inducers and inhibitors of CYP3A4 and P-glycoprotein, and the effect of smoking use on the CYP1A family.
5. Give examples of positive and negative drug-drug interactions.
6. Explain how drug interactions contribute to adverse effects at the cellular, tissue, and organ system level and the impact of overlapping or combined toxicities.

Mechanisms Mechanisms Mechanisms – and Effects

Key points

- Drug interactions can result from pharmacokinetic alterations (eg, changes in absorption, distribution, and elimination), pharmacodynamic changes (additive, synergistic, or antagonistic effects), or a combination of both.
- Coadministration of drugs that interact can:
  1- Increase drug effect, causing toxicity, or
  2- Decrease drug effect leading to subtherapeutic levels.
- Patient-specific factors and drug-specific factors influence the likelihood that a drug-disease, drug-drug, drug-botanical, or drug-food interaction occurs.
- Mechanisms of drug interactions related to pharmacodynamics – therapeutic and toxic: additive effects, synergistic effects/potentiation, antagonistic effects.
- Mechanisms of drug interactions related to pharmacokinetics: absorption, distribution/transport, metabolism, and excretion.

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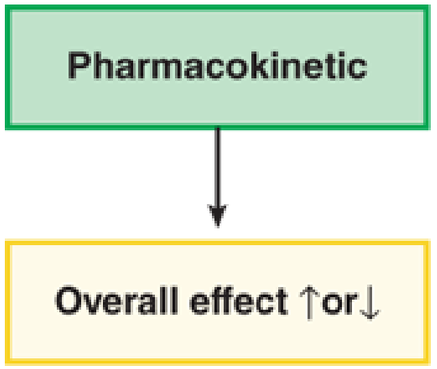
Key points

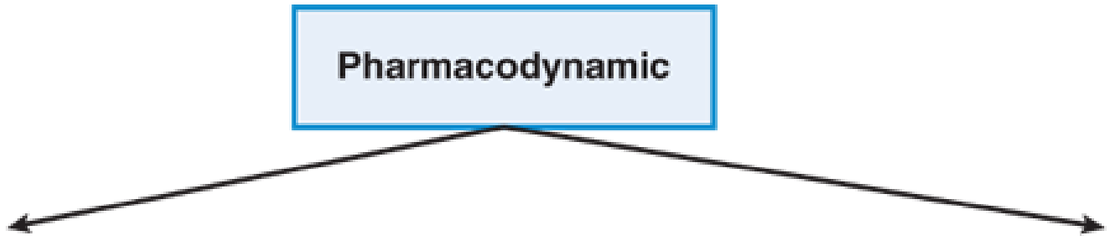
- Mechanisms of drug-disease interactions: Drugs can exacerbate diseases.
- ***Knowledge of drug-drug, drug-food, drug-herbals (botanicals), and drug-disease interactions, careful selection of therapeutic alternatives, and continuous monitoring to identify adverse effects could reduce the risks of adverse drug events.***
- Be able to explain the mechanisms and potential adverse effects of drug interactions when given examples.

NYITCOM's Medical Library includes access to

UpToDate / Lexidrugs Drug Interaction Tool

https://www.uptodate.com/drug-interactions/?source=responsive_home#di-druglist





↑Overall effect	
Additive	Combined effect of two drugs equals the sum of the effect of each agent given alone
Synergistic	Combined effect exceeds the sum of the effect of each drug given
Potentiation	Accentuation of the effect of one drug due to the presence of another drug that alone has no effect

Antagonism – ↓Overall effect	
Physiological	Two xenobiotics produce opposite effects on the same physiological function
Chemical	Reaction between two chemicals neutralizes their effects
Receptor	Blockade of the effect of one drug by another drug that competes at a common binding site or acts at an allosteric site

The terms synergy and potentiation are commonly used interchangeably.

Mechanisms and classification of drug interactions.

Drugs can interact by a single mechanism or multiple mechanisms.

Slide adapted by LG

Students please note:

The following examples name specific drugs and their mechanisms of drug interactions.

You should be able to explain the **mechanisms and effects**.

You do not need to remember drug names *at this time*. You will learn the names and what they do later.

Items related to drug interactions on quizzes and exams will provide enough information to be able to identify mechanisms and effects. A crucial test-taking skill is to be able to select to specific clues needed to identify the correct answer.

Examples of Pharmacodynamic Drug-Drug Interactions (DDIs)

The effect of the interaction may be **therapeutic** or **toxic**.

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Additive: Sum of the effect of each agent given alone

diphenhydramine + tricyclic antidepressants → additive anticholinergic side effects

- dry mouth, blurry vision, drowsiness, memory problems, constipation, difficulty urinating

nitroglycerin (for angina) + sildenafil (Viagra for erectile dysfunction) → ↑cGMP vasodilation + ↓cGMP degradation (Some resources designate this interaction as synergistic.)

- profound and potentially catastrophic hypotension - Dangerous

Synergy / Potentiation: Enhanced effect exceeds the sum of the effects of each agent given alone

codeine + acetaminophen → enhanced analgesic effect

- Beneficial: lower doses of each may be adequate for pain relief

sulfonamide (antibiotic) + trimethoprim (antibiotic) → different mechanisms enhance antibacterial action

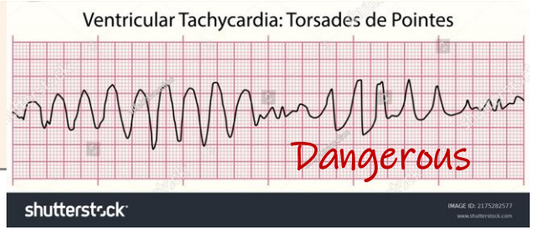
- Beneficial: each drug alone has a bacteriostatic effect; together they are bactericidal

amoxicillin (antibacterial) + clavulanic acid ("bodyguard") → enhanced antibacterial activity

- Beneficial: clavulanate inactivates bacterial enzymes that would hydrolyze the drug

methadone (opioid for OUD) + itraconazole (antifungal) → ventricular arrhythmia

- Both drugs cause QT interval prolongation on the ECG → torsades de pointes



OUD: opioid use disorder. Methadone is a mu opioid receptor full agonist.

Examples of PD DDIs by Antagonistic Mechanisms

Competitive antagonism: One drug competes with another drug for the active site

morphine (MOR agonist) + naloxone (MOR antagonist) → treatment of opioid overdose

- Both drugs bind the active site of mu opioid receptor (MOR). Naloxone blocks the receptor and prevents the opioid from activating the receptor → may cause abrupt withdrawal symptoms

nerve agent (poison) + atropine (anticholinergic) → treatment of cholinergic poisoning

- The nerve agent increases levels of acetylcholine neurotransmitter. Atropine blocks muscarinic receptors, which prevents the toxic effects of the overabundant acetylcholine.

Noncompetitive antagonism: Interference by drug binding at allosteric site

ketamine (NMDA receptor antagonist) + glutamate (NMDA receptor agonist) → anesthesia / dissociation
(therapeutic effect / adverse effect)

- Ketamine binds to the ion channel without competing for the glutamate binding site → biologic response is blocked.

Physiologic antagonism: Opposite physiologic effects (opposite functions) / Unrelated mechanisms

- Insulin (↓ blood sugar) + prednisone (steroid, ↑ blood glucose) → hyperglycemia (adverse effect)
- Insulin (↓ blood sugar) + glucagon (↑ blood glucose by hepatic synthesis) → reversal of hypoglycemia

Chemical antagonism: Compound directly binds and sequesters a drug, preventing distribution to the target

- Protamine combines with heparin in plasma, inactivating heparin → beneficial reversal agent
- Antacid chelates tetracycline (antibiotic) in the gut → reduces antibiotic efficacy

Pharmacokinetic Drug Interactions

Modification of ADME properties may affect levels of one or both interacting drugs

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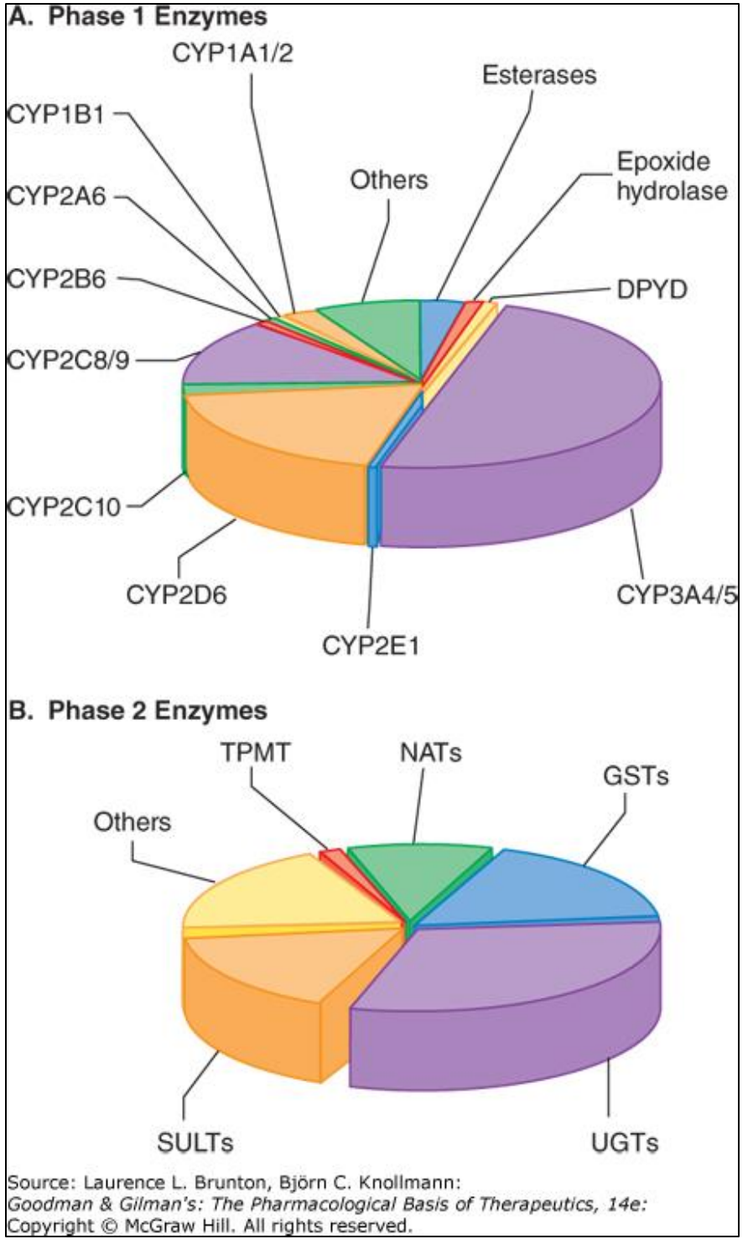
Alterations	Mechanism	Possible Effect
Absorption	Sequestration of drug in gut or increased gastric pH reduces systemic levels	Reduces therapeutic effect
Distribution	Changes in volume of distribution ↑or↓ fluid or tissue mass may ↑or↓ the plasma concentration of free drug	Increase risk of adverse effects or reduce therapeutic effect, respectively
	Inhibiting efflux transporters (eg, P-gp) may increase systemic drug levels	Increases risk of adverse effects
Metabolism	Inhibiting or inducing drug metabolizing enzymes may ↓ or ↑ clearance, respectively	Increase risk of adverse effects or reduce therapeutic effect, respectively
Excretion	Inhibiting secretion of drug into nephron (eg, OATs, OCTs) may decrease clearance	Increase risk of adverse effects

The fraction of clinically used drugs metabolized by the major phase 1 and phase 2 enzymes, based on the literature

The relative size of each pie section represents the estimated percentage of drugs metabolized by:

- Panel A: The major phase 1 drug metabolizing enzymes
- Panel B: The major phase 2 drug metabolizing enzymes

In some cases, more than a single enzyme is responsible for metabolism of a single drug.



Source: Laurence L. Brunton, Björn C. Knollmann: *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e:*

Citation: Chapter 5 Drug Metabolism, Brunton LL, Knollmann BC. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 14e;* 2023, Figure 5-3. Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3191&sectionid=266700137 Accessed: August 09, 2023

McGraw Hill slide rearranged by LG

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Test your knowledge: Explain the PK or PD mechanism of each.

1. Drug A is taken orally to increase gastric pH. The absorption of Drug B requires an acid stomach for optimal absorption. What is the potential effect on blood levels when the two drugs are administered concomitantly?

2. A drug that is a positive allosteric modulator enhances the inhibitory effects of a chloride ion channel in the CNS. Alcohol is also a positive allosteric modulatory at the same target acting at a different site. What is the likely adverse drug effect when the two chemicals are used simultaneously?

3. A patient is taking an antiplatelet drug following a heart attack and an anticoagulant due to recent knee replacement surgery. What is the potential adverse drug event that could result from this drug-drug interaction?

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Test your knowledge: Explain the PK or PD mechanism of each.

4. A patient with several comorbidities treated with various drugs is evaluated for an oral antiviral drug that contains a potent CYP3A4 inhibitor for the treatment of COVID-19. What effects may be anticipated when the antiviral is taken together with the patient's chronic medications?

5. What can the prescriber do to mitigate the potential adverse effects of this DDI?

6. An 87-year-old patient with compensated congestive heart failure takes a medication that is a P-glycoprotein substrate, has a narrow therapeutic window and potential for serious toxicity. She is evaluated for antibiotic therapy for a bacterial lung infection. The preferred drug is a P-glycoprotein inhibitor. What is the potential effect of this drug-drug interaction?

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Test your knowledge: Explain the PK or PD mechanism of each.

7. A 57-year-old patient with long-standing type 2 diabetes mellitus takes an ACE inhibitor for its “renoprotective” effects by reducing glomerular filtration pressure, which reduces mechanical stress on the glomerular capillaries. Patient education (in easy-to-understand language) includes the caution that he should not take any over-the-counter pain medications (NSAIDs) that also decrease glomerular filtration pressure. What is the potential effect of this drug-drug interaction?

8. A patient with hypercholesterolemia who has not achieved goal lipid levels with statin therapy agrees to the addition of a bile acid sequestrant, which is a resin that forms a complex with bile acids (synthesized from cholesterol) in the gut. The drug-bile acids complex is excreted in the feces. The patient is advised to take the statin several hours after the resin. Why separate the administration of the two drugs by several hours?

- Drug interactions occur when one drug modifies the actions of another drug in the body.
- Drug interactions can result from pharmacokinetic alterations, pharmacodynamic changes, or a combination of both.
- The pharmacodynamic characteristics of different drugs administered concomitantly may lead to additive, synergistic, or antagonistic effects.
- Pharmacokinetic interactions related to absorption, distribution, metabolism and excretion may increase or decrease blood levels, resulting in potential toxicities or reduced efficacy, respectively.
- Strong inducers of CYP3A4 and P-glycoprotein include carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's wort.
- CYP1A2 isoenzymes are induced by tobacco/marajuna smoking.
- Clinically relevant CYP3A4 and P-glycoprotein inhibitors include cimetidine, macrolide antibioitcs (erythromycin and clarithromycin), azole antifungal agents, ritonavir, grapefruit juice, and many more
- Exaggerated drug effects and other toxicities, as well as reduced efficacy can all lead to adverse drug events.

Test your knowledge: Explain the PK or PD mechanism of each.

1. Drug A is taken orally to increase gastric pH. The absorption of Drug B requires an acid stomach for optimal absorption. What is the potential effect on blood levels when the two drugs are administered concomitantly?

- PK absorption: Systemic levels of Drug B are decreased, which could reduce its therapeutic efficacy of the antifungal agent (Drug B).

2. A drug that is a positive allosteric modulator enhances the inhibitory effects of a chloride ion channel in the CNS. Alcohol is also a positive allosteric modulatory at the same target acting at a different site. What is the likely adverse drug effect when the two chemicals are used simultaneously?

- PD: Synergistic CNS depressant effects may lead to death, especially when combined with a mu opioid agonist and/or a benzodiazepine.

3. A patient is taking an antiplatelet drug following a heart attack and an anticoagulant due to recent knee replacement surgery. What is the potential adverse drug event that could result from this drug-drug interaction?

- PD: Additive or synergistic effects can lead to potentially serious bleeding, including hemorrhagic stroke.

Test your knowledge: Explain the PK or PD mechanism of each.

4. A patient with several comorbidities treated with various drugs is evaluated for an oral antiviral drug that contains a potent CYP3A4 inhibitor for the treatment of COVID-19. What effects may be anticipated when the antiviral is taken together with the patient's chronic medications?

- PK metabolism: Inhibiting the metabolism of the concurrent drugs that are CYP3A4 substrates can lead to elevated blood levels of the substrate drugs and increase the risk of adverse effects.

5. What can the prescriber do to mitigate the potential adverse effects of this DDI?

- Concomitant use of many other medications with this particular oral COVID-19 antiviral drug should be avoided. Prescribers should refer to published Drug Interaction information for prescribing guidance.

6. An 87-year-old patient with compensated congestive heart failure takes a medication that is a P-glycoprotein substrate, has a narrow therapeutic window and potential for serious toxicity. She is evaluated for antibiotic therapy for a bacterial lung infection. The preferred drug is a P-glycoprotein inhibitor. What is the potential effect of this drug-drug interaction?

- PK distribution / excretion: P-gp inhibition decreases P-gp drug efflux by intestinal epithelial cells and decreases drug secretion into the proximal tubule, resulting in elevated blood levels of the heart drug. This interaction could lead to serious toxicity by the heart drug.

Test your knowledge: Explain the PK or PD mechanism of each.

7. A 57-year-old patient with long-standing type 2 diabetes mellitus takes an ACE inhibitor for its "renoprotective" effects by reducing glomerular filtration pressure, which reduces mechanical stress on the glomerular capillaries. Patient education (in easy-to-understand language) includes the caution that he should not take any over-the-counter pain medications (NSAIDs) that also decrease glomerular filtration pressure. What is the potential effect of this drug-drug interaction?

- Drug-disease interaction: NSAID use on its own increases the risk of kidney injury in patients with conditions like diabetic nephropathy.
- PD interaction: NSAID in combination with an ACE inhibitor has synergistic negative effects that result in decreased glomerular filtration rate, which could lead to acute kidney injury in the vulnerable (at risk) patient.

8. A patient with hypercholesterolemia who has not achieved goal lipid levels with statin therapy agrees to the addition of a bile acid sequestrant, which is a resin that forms a complex with bile acids (synthesized from cholesterol) in the gut and excretes the drug-bile acids complex in the feces. The patient is advised to take the statin several hours after the resin. Why separate the administration of the two drugs by several hours?

- PK absorption: When taken at the same time, or near the same time, the resin (cholestyramine) sequesters *many* drugs in the GI tract – not only bile acids – preventing absorption and resulting in reduced blood levels and reduced efficacy of the orally absorbed drugs, such as statins.