

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.

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

Examples of Pharmacodynamic Drug-Drug Interactions (DDIs)

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

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

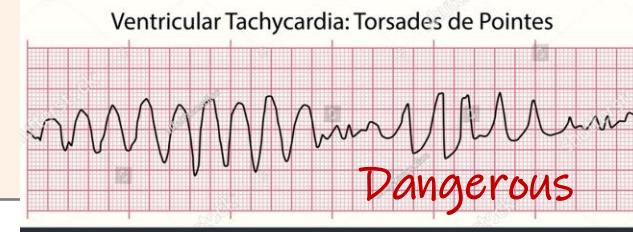
- **Beneficial:** each drug alone has a bacteriostatic effect; together they are bactericidal

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



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

therapeutic effect adverse effect

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

- 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 (\downarrow blood sugar) + prednisone (steroid, \uparrow blood glucose) → hyperglycemia (adverse effect)
- Insulin (\downarrow blood sugar) + glucagon (\uparrow 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

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

Drug-Disease Interactions

Some drug therapies can exacerbate (worsen) existing medical conditions.

- Hypertension
 - Liver disease
 - Renal disease
 - Heart disease
 - Peripheral vascular disease
 - Diabetes
-
- Peptic ulcer disease
 - Gout
 - Asthma
 - Hypo- or Hyperthyroidism
 - **Special problems of the elderly**

Older individuals are twice as likely as younger adults to have an adverse drug reaction and are seven times more likely to be hospitalized as the result of an adverse drug event.

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?

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?

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 antibiotics (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.

Enzyme Inhibition

Competition of co-administered drugs
for the same enzyme

↓ rate of metabolism of the drug that is
blocked from accessing the active site

↑ circulating levels of that drug

*Increases the potential for
adverse drug effects*

Enzyme Induction

Activate gene transcription →
expression of metabolic enzymes

↑ rate of drug metabolism

↓ levels of drug in circulation

*may reduce the efficacy of the
affected drugs*

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.