

ANSWER KEY WITH EXPLANATIONS

FOR CHAPTER 3

Skill Drill Answers

SD 3.1: Receptor Type Matching

1. **B** — Nicotinic acetylcholine receptor is a ligand-gated ion channel (pentameric cation channel)
 2. **C** — Insulin receptor is a receptor tyrosine kinase
 3. **A** — β 2-adrenergic receptor is a GPCR (couples to Gs)
 4. **D** — Glucocorticoid receptor is an intracellular receptor (cytoplasmic, translocates to nucleus)
 5. **B** — GABAA receptor is a ligand-gated ion channel (pentameric chloride channel)
 6. **A** — Muscarinic acetylcholine receptor is a GPCR (couples to Gq or Gi depending on subtype)
 7. **C** — EGF receptor is a receptor tyrosine kinase
 8. **D** — Estrogen receptor is an intracellular receptor (nuclear)
 9. **A** — Opioid receptors (μ , δ , κ) are GPCRs (couple to Gi)
 10. **B** — NMDA glutamate receptor is a ligand-gated ion channel
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SD 3.2: True/False with Correction

1. **F** — Potency and efficacy are independent. A drug can have high potency (low EC₅₀) but low efficacy (partial agonist).
2. **T** — By definition, partial agonists have intermediate intrinsic activity and cannot achieve maximum response.
3. **F** — Competitive antagonists shift the curve rightward but do NOT reduce E_{max}. The effect can be overcome with sufficient agonist.
4. **T** — Large TI means TD₅₀ is much greater than ED₅₀, indicating separation between therapeutic and toxic doses.
5. **F** — Down-regulation decreases sensitivity (tolerance). Up-regulation increases sensitivity.

6. **F** — Ligand-gated ion channels produce faster responses (milliseconds) than GPCRs (seconds to minutes).
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SD 3.3: Fill in the Blank

1. **affinity**
 2. **intrinsic**
 3. **EC50 (or ED50)**
 4. **inverse agonist**
 5. **therapeutic**
 6. **tolerance (or tachyphylaxis)**
 7. **G (or heterotrimeric G)**
 8. **up-regulation**
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SD 3.4: Agonist-Antagonist Classification

1. **FA** — Full agonists produce maximum response
 2. **PA** — Buprenorphine is a partial μ -opioid agonist
 3. **ANT** — Definition of antagonist
 4. **IA** — Inverse agonists reduce baseline activity
 5. **FA** — Morphine is a full μ -opioid agonist
 6. **PA** — Characteristic of partial agonists
 7. **ANT** — Naloxone is a μ -opioid antagonist
 8. **PA** — Intermediate intrinsic activity defines partial agonists
 9. **PA** — Pindolol has intrinsic sympathomimetic activity (ISA), making it a partial agonist
 10. **ANT** — Propranolol is a β -adrenergic antagonist without ISA
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SD 3.5: Potency vs. Efficacy Sorting

1. **P** — Potency is horizontal position (EC50 location)
2. **E** — Complete vs. incomplete response is efficacy
3. **P** — Dose required for effect compares potency

4. **E** — Maximum height is efficacy (Emax)
 5. **P** — Affinity primarily determines potency
 6. **E** — Partial agonists have lower efficacy than full agonists
 7. **P** — Potency determines dose size/convenience
 8. **E** — Efficacy determines if therapeutic goal is achievable
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SD 3.6: Rapid Recall

1. **GPCR (G protein-coupled receptor)**
 2. **Efficacy (or Emax)**
 3. **Partial agonist**
 4. **Therapeutic Index**
 5. **Gs**
 6. **Gi**
 7. **Competitive**
 8. **Intracellular (or nuclear)**
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SD 3.7: Complete the Sentence

1. **competitive** — Competitive antagonism shifts curve right without reducing Emax
 2. **ligand-gated** — Ion channels directly gate ion flux
 3. **slower** — Gene transcription takes hours to days
 4. **down-regulation** — Chronic agonist reduces receptors
 5. **potency** — EC50 measures potency (lower EC50 = higher potency)
 6. **small** — Small TI drugs require monitoring
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SD 3.8: Signal Pathway Sequencing

Gs Pathway: 2 → 4 → 3 → 1 → 5 (correct order: Agonist binds → GDP/GTP exchange → AC activation → cAMP → PKA → phosphorylation)

Full sequence:

- Agonist binds GPCR: **1**

- G protein α -subunit exchanges GDP for GTP: **2**
- Gs protein activates adenylyl cyclase: **3**
- Adenylyl cyclase converts ATP to cAMP: **4**
- cAMP activates protein kinase A (PKA): **5**
- PKA phosphorylates target proteins: **6**

RTK Pathway:

- Ligand binds receptor, causing dimerization: **1**
- Autophosphorylation of receptor: **2**
- Adaptor proteins bind phosphotyrosines: **3**
- Ras activates MAPK cascade: **4**
- MAPK phosphorylates transcription factors: **5**
- Gene transcription is altered: **6**

SD 3.9: EC50/ED50 Interpretation

1. **Drug A** — Lower EC50 indicates higher potency
2. **TI = 10** — $TI = TD50/ED50 = 50/5 = 10$
3. **Drug D** — Higher Emax (100% vs. 80%) indicates greater efficacy
4. **The antagonist reduced potency without affecting efficacy** — Characteristic of competitive antagonism (rightward shift, Emax preserved)

SD 3.10: Competitive vs. Non-competitive Analysis

1. **C** — Competitive: rightward shift, unchanged Emax
2. **C** — Competitive antagonism is surmountable
3. **NC** — Non-competitive: reduced Emax
4. **NC** — Allosteric binding site = non-competitive
5. **C** — Same binding site = competitive
6. **NC** — Irreversible binding = non-competitive
7. **C** — Surmountable = competitive
8. **NC** — Insurmountable = non-competitive

SD 3.11: Therapeutic Index Calculation

1. **TI = 10** — $TI = 250/25 = 10$
 2. **Drug B is safer** — Higher TI (20 vs. 2) means greater separation between effective and toxic doses
 3. a. **TI = 3** (30/10) b. **CSF = 0.6** (15/25) c. **CSF suggests greater concern** — $CSF < 1$ means the dose toxic to 1% is lower than the dose effective for 99%, indicating some patients will experience toxicity at therapeutic doses
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SD 3.12: Receptor Binding Terminology

1. **B** — B_{max} = maximum binding capacity
2. **F** — Tachyphylaxis = rapid tolerance
3. **A** — K_d = dissociation constant
4. **D** — Spare receptors = receptor reserve
5. **C** — Affinity = binding strength
6. **E** — Desensitization = rapid loss of response via receptor phosphorylation

Case Study Answers

Case 3.1: Beta-Blocker Overdose Management

Question 1. Competitive antagonism can be overcome by increasing agonist concentration. High-dose catecholamines (epinephrine, norepinephrine, isoproterenol) can compete with metoprolol for β -receptor binding. With sufficient agonist concentration, enough receptors will be occupied by agonist to restore cardiac function.

Question 2. Glucagon bypasses the blocked β -receptors entirely. Glucagon receptors (a different GPCR) also couple to G_s proteins and activate adenylyl cyclase $\rightarrow$ cAMP $\rightarrow$ PKA, producing the same downstream effect (increased heart rate and contractility) without requiring β -receptor activation. This demonstrates that different receptors can converge on the same intracellular pathway.

Question 3. No. Phenoxybenzamine binds irreversibly (covalently) to α -receptors. This is non-competitive antagonism—increasing agonist concentration cannot overcome blockade because the bound receptors are permanently inactivated. Recovery requires synthesis of new receptors, which takes days.

Question 4. " β_1 -selective" means metoprolol has higher affinity for β_1 -receptors (heart) than β_2 -receptors (bronchioles, vasculature) at therapeutic doses. However, selectivity is relative, not absolute. At overdose

concentrations, enough drug is present to occupy even lower-affinity β_2 -receptors, causing bronchospasm and vasodilation. Selectivity is lost at supratherapeutic doses.

Case 3.2: Opioid Tolerance and Receptor Changes

Question 1. Chronic μ -opioid receptor activation causes receptor down-regulation through multiple mechanisms: receptor phosphorylation by GRK kinases, β -arrestin binding, receptor internalization via endocytosis, and decreased receptor synthesis. With fewer functional receptors available, higher drug concentrations are needed to achieve the same level of receptor activation and pain relief.

Question 2. Tolerance: Decreased response to drug requiring higher doses (pharmacodynamic adaptation). This patient has tolerance.

Physical dependence: Physiological adaptation resulting in withdrawal symptoms if drug is stopped. Often accompanies tolerance.

Addiction: Compulsive drug use despite harm, characterized by craving and loss of control. Tolerance and dependence can occur without addiction. This patient has tolerance (and likely dependence) from appropriate medical use, not necessarily addiction.

Question 3. Buprenorphine is a partial μ -opioid agonist with a ceiling effect. It may not provide equivalent pain relief compared to full agonist morphine, especially in a patient requiring high opioid doses. Benefits include lower overdose risk and less respiratory depression. However, switching from high-dose full agonist to partial agonist may precipitate withdrawal or inadequate analgesia if done abruptly.

Question 4. During chronic morphine use, receptors down-regulate. If morphine is abruptly discontinued, remaining receptors are suddenly unoccupied and relatively deficient. Additionally, compensatory up-regulation of counter-regulatory systems (e.g., noradrenergic) contributes to withdrawal. Symptoms include anxiety, agitation, muscle aches, sweating, diarrhea, and drug craving—opposite of opioid effects.

Diagram/Table Exercise Answers

DT 3.1: Dose-Response Curve Interpretation

1. **Drug A** — reaches 100% response
 2. **Drug B** — plateaus at 50% (below maximum)
 3. **No** — both curves are at the same horizontal position (same EC_{50})
 4. **50%**
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DT 3.2: Receptor Family Table

Receptor Type	Speed of Response	Example
Ligand-gated ion channel	Milliseconds	GABA-A receptor
GPCR	Seconds to minutes	β -adrenergic receptor
Receptor tyrosine kinase	Minutes to hours	Insulin receptor
Intracellular receptor	Hours to days	Glucocorticoid receptor

DT 3.3: G-Protein Signaling

1. Gs activates: **Adenylyl cyclase**
2. ATP is converted to: **cAMP**
3. This second messenger activates: **PKA (Protein Kinase A)**

DT 3.4: Agonist Classification

Drug Type	Intrinsic Activity	Effect on Response
Full agonist	1 (maximal)	Maximum response
Partial agonist	Between 0 and 1	Submaximal response
Antagonist	0 (zero)	No response
Inverse agonist	Negative	Decreases baseline activity

Multiple-Choice Question Answers

Question 1. Answer: C — Antagonist

An antagonist has affinity (binds receptor) but no intrinsic activity (no response) and blocks agonist access.

Question 2. Answer: B — Emax

Emax (maximum effect) indicates efficacy. EC50 indicates potency.

Question 3. Answer: A — Lower potency, same efficacy

Same Emax (same efficacy); higher EC50 (lower potency—needs more drug).

Question 4. Answer: C — Ligand-gated ion channel

Ion flux through channels occurs in milliseconds—faster than any other receptor type.

Question 5. Answer: C — 10

$TI = TD50/ED50 = 100/10 = 10$

Question 6. Answer: B — Decreased response

Partial agonist competes with full agonist. Receptors occupied by partial agonist produce less response than if occupied by full agonist.

Question 7. Answer: B — Rightward shift with unchanged Emax

Competitive antagonism: surmountable with increased agonist concentration, Emax preserved.

Question 8. Answer: B — Receptor up-regulation

Chronic antagonist exposure causes receptor up-regulation. Sudden removal exposes upregulated receptors to endogenous agonists, causing exaggerated response.

Question 9. Answer: B — Phospholipase C → IP3 and DAG

Gq activates PLC, which cleaves PIP2 into IP3 and DAG.

Question 10. Answer: C — Lower efficacy than morphine

Buprenorphine (partial agonist) has lower maximum effect (ceiling) than morphine (full agonist), indicating lower efficacy. Potency may be higher or lower—that's a separate property.

Question 11. Answer: B — The drug requires careful monitoring because effective and toxic doses are close

TI of 2 means TD50 is only twice ED50—very narrow margin.

Question 12. Answer: D — Inverse agonist

Reducing constitutive (baseline) activity below baseline indicates negative intrinsic activity—definition of inverse agonist.

Question 13. Answer: B — Response will remain reduced because blocked receptors cannot be activated

Irreversible antagonism is insurmountable. Blocked receptors cannot respond regardless of agonist concentration. Recovery requires new receptor synthesis.

Question 14. Answer: C — Receptor down-regulation and desensitization

Chronic agonist exposure causes receptor phosphorylation (desensitization), internalization, and decreased synthesis (down-regulation), reducing response.

Question 15. Answer: A — Drug A is more potent than Drug B and has greater efficacy than Drug C

A vs. B: Same efficacy (100%), A has lower EC₅₀ = more potent A vs. C: Same potency (EC₅₀ = 5 nM), A has higher E_{max} = greater efficacy

Question 16. Answer: B — Has a narrow safety margin with CSF = 0.75

$$\text{CSF} = \text{LD1}/\text{ED99} = 60/80 = 0.75$$

CSF < 1 indicates the dose lethal to 1% of the population is LOWER than the dose effective in 99%. This is extremely dangerous—some patients will die before achieving efficacy.