2ND EXAM REVIEWER

Pharmacology Reviewer: Answers & Rationales (1–50)

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1. Primary neurotransmitter released by all preganglionic autonomic fibers

Answer: Acetylcholine

Rationale:
All **preganglionic neurons of both sympathetic and parasympathetic systems release acetylcholine (ACh)**. It acts on **nicotinic (Nn) receptors in autonomic ganglia**.

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2. Propofol + Nitrous oxide during surgery

Answer: It achieves anesthesia with lower doses

Rationale:
Using **multiple anesthetic agents produces additive/synergistic effects**, allowing **lower doses of each drug**, reducing toxicity and adverse effects.

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3. Primary inhibitory neurotransmitter in spinal cord

Answer: Glycine

Rationale:
Glycine is the **major inhibitory neurotransmitter in the spinal cord**, especially in motor control pathways.

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4. Low blood-gas partition coefficient anesthetic (Desflurane)

Answer: It reaches arterial equilibrium faster

Rationale:
Low blood solubility → **faster rise of alveolar concentration → faster brain equilibrium → rapid induction and recovery**.

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5. "Craniosacral" division of ANS

Answer: Parasympathetic nervous system

Rationale:
Parasympathetic outflow originates from **cranial nerves III, VII, IX, X and sacral segments S2–S4**.

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6. ENS function after vagus nerve severed

Answer: It contains complete sensory and motor reflex arcs locally

Rationale:
The **enteric nervous system** has **intrinsic neurons capable of autonomous reflexes**, allowing GI motility even without CNS input.

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7. Significance of cotransmission in ANS

Answer: It modulates the primary transmitter's postsynaptic response

Rationale:
Autonomic nerves may release **multiple transmitters (ATP, neuropeptides)** that **modify the effect of the main transmitter**.

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8. Opioid inhibition of pain transmission

Answer: Closing presynaptic Calcium channels

Rationale:
Opioids **inhibit Ca^{2+} influx**, reducing release of pain neurotransmitters (substance P, glutamate).

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9. Drug causing dissociative anesthesia

Answer: Ketamine

Rationale:
Ketamine produces **dissociative anesthesia** characterized by **analgesia, amnesia, and catalepsy** via **NMDA receptor blockade**.

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10. Cholinergic receptor at neuromuscular junction

Answer: Nm receptor

Rationale:
Skeletal muscle contraction occurs when **acetylcholine activates nicotinic muscle receptors (Nm)**.

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11. Phenylephrine cardiac response

Answer: Decrease in heart rate due to increased vagal nerve firing

Rationale:
Phenylephrine causes **α1 vasoconstriction → increased BP → baroreceptor reflex → vagal stimulation → reflex bradycardia**.

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12. Why Pralidoxime must be given early

Answer: To regenerate the active enzyme at the neuromuscular junction sites

Rationale:
Pralidoxime **reactivates acetylcholinesterase before "aging" occurs** in organophosphate poisoning.

---

13. Tachycardia after vasodilator

Answer: The baroreceptor reflex reduces the vagal inhibitory tone

Rationale:
Vasodilation → **↓BP → baroreceptor reflex → ↓vagal tone + ↑sympathetic activity → tachycardia**.

---

14. Non-selective beta blocker during anaphylaxis

Answer: It prevents the beta-2 mediated reduction in airway resistance

Rationale:
Blocking **β2 receptors prevents bronchodilation**, worsening bronchospasm during anaphylaxis.

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15. NSAID that irreversibly inhibits enzyme

Answer: Aspirin

Rationale:
Aspirin **irreversibly acetylates COX enzymes**, unlike other NSAIDs which inhibit reversibly.

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16. Mechanism of morphine tolerance

Answer: Upregulation of the enzyme Adenylyl cyclase

Rationale:
Chronic opioid use causes **compensatory increase in cAMP signaling**, contributing to tolerance and dependence.

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17. Muscarinic activation in iris

Answer: Miosis

Rationale:
Muscarinic stimulation **contracts circular iris muscle**, causing **pupil constriction**.

---

18. Concept of dominant tone

Answer: The resting activity of one division exceeds the other

Rationale:
Most organs have **baseline activity from one ANS division**, which determines resting function.

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19. Target enzyme of NSAIDs

Answer: Cyclooxygenase

Rationale:
NSAIDs inhibit **COX-1 and COX-2**, reducing **prostaglandin synthesis**.

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20. Effect of selective α1 agonist

Answer: Vasoconstriction

Rationale:
Activation of **α1 receptors on vascular smooth muscle causes vasoconstriction**, increasing BP.

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21. Pilocarpine in glaucoma

Answer: It opens the trabecular meshwork by contracting the ciliary muscle

Rationale:
Muscarinic activation **improves aqueous humor drainage**, lowering intraocular pressure.

---

22. Receptor causing bronchodilation

Answer: Beta-2 receptor

Rationale:
β2 activation **relaxes bronchial smooth muscle**, producing bronchodilation.

---

23. Intrinsic GI nervous system

Answer: Enteric nervous system

Rationale:
The ENS contains **myenteric and submucosal plexuses** controlling digestion.

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24. Beta-1 selective blocker in asthma

Answer: It avoids blocking the receptors that cause bronchodilation

Rationale:
β1-selective drugs avoid **blocking β2 receptors in lungs**, preventing bronchospasm.

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25. Why Bethanechol preferred over ACh

Answer: It is resistant to hydrolysis by Acetylcholinesterase

Rationale:
Bethanechol **lasts longer because AChE cannot easily break it down**.

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26. Edrophonium test for cholinergic crisis

Answer: Worsening of the muscle weakness

Rationale:
In **cholinergic crisis**, excess ACh causes receptor overstimulation → weakness worsens after edrophonium.

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27. Dopamine increase by opioids/cannabinoids

Answer: Disinhibition of the Dopamine-secreting neurons

Rationale:
These drugs **inhibit GABA interneurons**, removing inhibition on dopamine neurons.

---

28. Enzyme terminating ACh action

Answer: AChE

Rationale:
Acetylcholinesterase rapidly hydrolyzes acetylcholine in the synaptic cleft.

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29. Catecholamine released by adrenal medulla

Answer: Epinephrine

Rationale:
Adrenal medulla secretes **~80% epinephrine** during stress.

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30. First-line DMARD for rheumatoid arthritis

Answer: Methotrexate

Rationale:
Methotrexate is the **cornerstone DMARD** due to strong efficacy and long-term disease control.

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31. Receptor increasing HR and contractility

Answer: Beta-1 receptor

Rationale:
β1 receptors in the heart **increase chronotropy and inotropy**.

---

32. Drug reversing opioid overdose

Answer: Naloxone

Rationale:
Naloxone is a **pure opioid antagonist** that rapidly reverses respiratory depression.

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33. Rapid relief asthma drug

Answer: Albuterol

Rationale:
Albuterol is a **short-acting β2 agonist (SABA)** used for acute bronchospasm.

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34. Barrier restricting drug entry to brain

Answer: Blood-brain barrier

Rationale:
Tight junctions in cerebral capillaries **limit entry of polar drugs**.

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35. Side effect of Bethanechol

Answer: Excessive sweating and salivation

Rationale:
Muscarinic stimulation causes **increased secretions, sweating, and GI activity**.

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36. Short-acting AChE inhibitor for MG diagnosis

Answer: Edrophonium

Rationale:
Edrophonium has **very short duration**, making it useful diagnostically.

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37. Methotrexate mechanism in RA

Answer: It increases the release of Adenosine

Rationale:
Low-dose methotrexate **increases anti-inflammatory adenosine signaling**.

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38. Measure comparing potency of inhaled anesthetics

Answer: Minimum Alveolar Concentration (MAC)

Rationale:
MAC is the **concentration preventing movement in 50% of patients**; lower MAC = higher potency.

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39. Opioid receptor causing morphine effects

Answer: Mu (μ) receptor

Rationale:
μ receptors mediate **analgesia, euphoria, respiratory depression, and dependence**.

---

40. High dose epinephrine BP effect

Answer: Alpha receptor activation overcomes beta-2 vasodilation

Rationale:
Low dose → β2 vasodilation
High dose → **α1 vasoconstriction dominates**.

---

41. Fight-or-flight division

Answer: Sympathetic nervous system

Rationale:
Sympathetic activation prepares body for **stress and emergency responses**.

---

42. Effect of AChE inhibition

Answer: Parasympathetic effects dominate

Rationale:
ACh accumulation stimulates **muscarinic receptors in parasympathetic organs**.

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43. Muscarinic agonist for urinary retention

Answer: Bethanechol

Rationale:
Bethanechol **stimulates bladder detrusor contraction**.

---

44. Alpha-2 agonists in hypertension

Answer: They decrease the sympathetic outflow from the brainstem

Rationale:
α2 activation in CNS **reduces sympathetic tone**, lowering BP.

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45. Primary excitatory neurotransmitter in CNS

Answer: Glutamate

Rationale:
Glutamate activates **NMDA and AMPA receptors**, producing excitation.

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46. Why atropine doesn't treat muscle weakness

Answer: It blocks Muscarinic but not Nicotinic receptors

Rationale:
Muscle weakness comes from **nicotinic receptor overstimulation at NMJ**.

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47. Why COX-2 inhibitors reduce GI bleeding

Answer: They spare gastric mucosal protection

Rationale:
COX-1 produces **protective gastric prostaglandins**; COX-2 inhibitors spare this.

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48. Parasympathetic cranial nerves

Answer: CN III, VII, IX, X

Rationale:
Parasympathetic cranial outflow originates from **these four cranial nerves**.

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49. Nicotine addiction mechanism

Answer: It reduces the inhibitory tone on the Dopamine neurons

Rationale:
Nicotine desensitizes **GABA interneurons**, increasing dopamine release.

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50. Most critical epinephrine effect in anaphylactic shock

Answer: Constriction of the resistance vessels via alpha-1 receptors

Rationale:
α1 vasoconstriction **restores blood pressure and reverses shock**.

3rd EXAM REVIEWER (PCOL)

Pharmacology Reviewer (CNS, ANS, and Clinical Applications)

This reviewer summarizes key concepts, drugs, mechanisms, and rationales based on the 50 pharmacology questions discussed.

Antidepressants

- **Bupropion:** Norepinephrine–dopamine reuptake inhibitor; lowers seizure threshold; contraindicated in seizure disorders.
- **SSRIs (Fluoxetine, Paroxetine):** Increase serotonin levels; common adverse effect is sexual dysfunction; strong CYP2D6 inhibitors.
- **Trazodone / Nefazodone:** Antidepressants that block 5-HT2A receptors; often used for depression with insomnia.

Antiseizure Drugs

- **Carbamazepine:** Voltage-gated Na+ channel blocker; metabolized to active epoxide metabolite; strong CYP inducer.
- **Ethosuximide:** Drug of choice for absence seizures; blocks T-type Ca2+ channels in thalamus.
- **Phenytoin:** Na+ channel blocker; chronic adverse effect: gingival hyperplasia.
- **Levetiracetam:** Minimal hepatic metabolism and few drug interactions; useful in patients with multiple medications.

Benzodiazepines and Antagonists

- **Lorazepam:** Preferred IV benzodiazepine for status epilepticus due to longer CNS duration.
- **Flumazenil:** Competitive antagonist at benzodiazepine site on GABA-A receptor; reverses overdose.

Alzheimer's Disease

- **Donepezil:** Reversible acetylcholinesterase inhibitor; increases acetylcholine in brain.
- **Memantine:** Uncompetitive NMDA receptor antagonist; prevents glutamate excitotoxicity.
- **Aducanumab:** Monoclonal antibody that reduces beta-amyloid plaque burden.
- **Risk Factor:** Apolipoprotein E4 allele significantly increases risk of late-onset Alzheimer’s disease.

Antipsychotics

- **Typical antipsychotics:** Strong dopamine D2 blockade; high risk of extrapyramidal symptoms (EPS).
- **Atypical antipsychotics:** Block 5-HT2A receptors and D2 receptors; lower EPS but higher metabolic syndrome risk.

- **Clozapine:** Reserved for treatment-resistant schizophrenia; requires weekly WBC monitoring due to agranulocytosis risk.

Parkinson's Disease

- **Levodopa + Carbidopa:** Carbidopa inhibits peripheral dopa decarboxylase allowing more levodopa to reach the brain.
- **Selegiline / Rasagiline:** MAO-B inhibitors that increase dopamine levels.
- **Entacapone:** COMT inhibitor that prolongs levodopa half-life.
- **Amantadine:** May cause livedo reticularis (mottled skin discoloration).

Sleep Disorders

- **Ramelteon:** Melatonin receptor (MT1/MT2) agonist used for insomnia.
- **Suvorexant / Lemborexant:** Orexin receptor antagonists that promote sleep by reducing wake signaling.
- **Non-pharmacologic therapy:** First-line treatment for insomnia includes sleep hygiene and caffeine reduction.

ANS and Related Drugs

- **Bethanechol:** Muscarinic agonist used for urinary retention.
- **Methacholine:** Muscarinic agonist used in bronchial challenge test for asthma diagnosis.
- **Clonidine / Methyldopa:** Centrally acting alpha-2 agonists that reduce sympathetic outflow.
- **Prazosin:** Alpha-1 blocker used for hypertension and BPH.

Allergy and Emergency Treatment

- **Epinephrine:** Drug of choice for anaphylaxis; causes bronchodilation, vasoconstriction, and increased cardiac output.
- **Diphenhydramine:** First-generation antihistamine used for allergic reactions.
- **Alprostadil:** Prostaglandin E1 analog used in erectile dysfunction.

NSAIDs and GI Drugs

- **Naproxen:** NSAID with relatively lower cardiovascular risk.
- **Famotidine:** Most potent H2 receptor antagonist; reduces gastric acid secretion.

Drug Interactions

- **MAO inhibitors + SSRIs:** Cause serotonin syndrome.
- **MAO inhibitors + tyramine foods:** Cause hypertensive crisis due to norepinephrine release.
- **Carbamazepine:** Strong CYP450 inducer causing reduced levels of many drugs.
- **Fluvoxamine:** Strong CYP inhibitor that greatly increases ramelteon levels.

Rationales

1. Bupropion

Answer: C. Bupropion
Bupropion inhibits dopamine and norepinephrine reuptake but significantly **lowers the seizure threshold**, especially in high doses or overdose. For this reason, it is **contraindicated in patients with seizure disorders or eating disorders**.

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2. Carbamazepine

Answer: Carbamazepine
Carbamazepine blocks **voltage-gated sodium channels**, stabilizing neuronal membranes. It is metabolized in the liver to an **active metabolite (carbamazepine-10,11-epoxide)** which contributes to its antiseizure effects.

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3. Ethosuximide

Answer: Ethosuximide
Ethosuximide selectively blocks **T-type calcium channels in thalamic neurons**, which are responsible for generating absence seizure activity.

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4. Flumazenil

Answer: Flumazenil
Flumazenil is a **competitive antagonist at benzodiazepine binding sites on the GABA-A receptor**, reversing sedation and respiratory depression caused by benzodiazepines.

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5. Lorazepam

Answer: Lorazepam
Lorazepam is preferred in **status epilepticus** because it remains in the CNS longer than diazepam after IV injection, producing more sustained seizure control.

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6. Bradycardia or syncope

Answer: Bradycardia or syncope
Cholinesterase inhibitors increase acetylcholine levels, enhancing **parasympathetic activity**, which can slow heart rate and worsen **bradyarrhythmias or syncope**.

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7. Fluvoxamine

Answer: Fluvoxamine
Fluvoxamine strongly inhibits **CYP1A2**, the enzyme responsible for metabolizing **ramelteon**, causing a dramatic increase in its plasma concentration.

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8. Nigrostriatal pathway

Answer: Nigrostriatal pathway
Dopamine blockade in the **nigrostriatal pathway** interferes with motor control, producing **extrapyramidal symptoms (dystonia, Parkinsonism, akathisia)**.

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9. Oxidation

Answer: Oxidation
Selegiline is metabolized by **oxidative reactions in the liver**, forming metabolites and producing irreversible inhibition of MAO-B.

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10. Apolipoprotein E4 allele

Answer: ApoE4 allele
The **ApoE4 genotype** significantly increases risk for **late-onset Alzheimer's disease**, likely by promoting amyloid deposition in the brain.

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11. Neurofibrillary tau tangles

Answer: Neurofibrillary tau tangles
Tau tangles correlate strongly with **neuronal death and cognitive decline**, making them the best pathological indicator of disease severity.

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12. Orexin

Answer: Orexin
Orexin neurons regulate **wakefulness**. Blocking orexin receptors promotes sleep by reducing arousal signals.

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13. NMDA receptor antagonism

Answer: NMDA receptor antagonism
Memantine blocks **NMDA glutamate receptors**, preventing excitotoxic neuronal damage caused by excessive glutamate.

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14. Ramelteon

Answer: Ramelteon
Ramelteon activates **MT1 and MT2 receptors in the suprachiasmatic nucleus**, regulating circadian rhythm and sleep initiation.

---

15. Sexual dysfunction

Answer: Sexual dysfunction
SSRIs increase serotonin levels which **inhibit dopamine-mediated sexual function**, leading to decreased libido, anorgasmia, and erectile dysfunction.

---

16. Gingival hyperplasia

Answer: Gingival hyperplasia
Phenytoin stimulates fibroblast proliferation in gum tissue, causing **overgrowth of the gums**.

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17. Metabolic syndrome

Answer: Metabolic syndrome
Atypical antipsychotics (e.g., clozapine, olanzapine) increase **weight, glucose, and lipid levels**, leading to metabolic syndrome.

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18. CYP2D6

Answer: CYP2D6
Fluoxetine and paroxetine strongly inhibit **CYP2D6**, affecting metabolism of many drugs including beta blockers and opioids.

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19. 5-HT2A receptor

Answer: 5-HT2A receptor
Trazodone and nefazodone work primarily by **blocking serotonin 5-HT2A receptors**, improving mood and sleep.

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20. Sodium bicarbonate

Answer: Sodium bicarbonate
In TCA overdose, sodium bicarbonate **alkalinizes blood and increases sodium concentration**, reversing cardiac sodium channel blockade.

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21. Metabolism inhibited

Answer: Its metabolism is significantly inhibited
CYP3A4 inhibitors decrease metabolism of eszopiclone, leading to **drug accumulation and excessive sedation**.

---

22. Prolongs levodopa half-life

Answer: It prolongs levodopa plasma half-life
COMT inhibitors prevent peripheral metabolism of levodopa to inactive metabolites.

23. Enzyme induction

Answer: Carbamazepine induces hepatic enzymes
Carbamazepine strongly induces CYP450 enzymes, lowering levels of many medications.

---

24. Reduces amyloid plaques

Answer: It reduces amyloid plaque burden
Aducanumab is a **monoclonal antibody that targets beta-amyloid plaques** in the brain.

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25. 5-HT2A blockade

Answer: They block 5-HT2A receptors causing DA release
Serotonin blockade increases dopamine release in the nigrostriatal pathway, reducing EPS.

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26. Peripheral decarboxylase inhibition

Answer: It inhibits peripheral DOPA decarboxylase
Carbidopa prevents levodopa conversion to dopamine outside the brain, allowing more to reach the CNS.

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27. Stupor and hyperthermia

Answer: It precipitates stupor and hyperthermia
Combining MAO inhibitors with meperidine can produce **severe serotonin toxicity**.

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28. Serotonin syndrome

Answer: It precipitates fatal Serotonin syndrome
Combining MAO inhibitors with SSRIs dramatically increases serotonin levels.

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29. Caffeine reduction

Answer: Counsel on caffeine reduction and sleep hygiene
Lifestyle modification is the **first-line treatment for insomnia**.

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30. Threefold risk

Answer: It increases risk threefold
The ApoE4 allele significantly increases risk but does **not guarantee disease**.

---

31. Reversible cholinesterase inhibition

Answer: Reversible Cholinesterase inhibition
Donepezil increases **acetylcholine availability** in the brain.

---

32. Catecholamine displacement

Answer: Displacement of stored catecholamines
Tyramine displaces norepinephrine, causing **hypertensive crisis**.

---

33. Livedo reticularis

Answer: Livedo reticularis
Amantadine may cause **mottled skin discoloration** due to vascular changes.

---

34. Induced metabolism

Answer: Carbamazepine induces doxycycline metabolism
This reduces doxycycline therapeutic levels.

---

35. Levetiracetam

Answer: Levetiracetam
Minimal CYP metabolism and **few drug interactions**.

---

36. WBC monitoring

Answer: White blood cell counts weekly
Clozapine may cause **agranulocytosis**.

---

37. Centrally acting alpha-2 agonists

Answer: Centrally-acting Alpha-2 adrenoceptor agonists
They reduce sympathetic outflow from the CNS.

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38. Urinary retention

Answer: Urinary retention
Bethanechol stimulates **muscarinic receptors in bladder**, improving urination.

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39. Olodaterol

Answer: Olodaterol
It is a **long-acting beta-2 agonist**, not short acting.

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40. Famotidine

Answer: Famotidine
Famotidine is the **most potent H2 receptor antagonist**.

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41. Methacholine

Answer: Methacholine
Used in **bronchial challenge testing** to diagnose asthma.

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42. Claritin

Answer: Claritin®
Contains **loratadine**, a second-generation antihistamine.

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43. Alprostadil

Answer: Alprostadil
Prostaglandin E1 analog causing **vasodilation in erectile tissue**.

---

44. Tachycardia

Answer: Tachycardia
Antimuscarinic toxicity causes **tachycardia, dry mouth, hyperthermia, and confusion**.

---

45. Prazosin

Answer: Prazosin
Alpha-1 blockade relaxes **prostatic smooth muscle**, improving urine flow.

---

46. Naproxen

Answer: Naproxen
Among NSAIDs, naproxen has **lower cardiovascular risk**.

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47. Pupillary dilation

Answer: Pupillary dilation
Mydriasis occurs via **alpha-1 receptor stimulation**, blocked by prazosin.

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48. Epinephrine

Answer: Epinephrine
Epinephrine reverses **bronchospasm, hypotension, and airway edema**.

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49. Bronchospasm, tachycardia, hypotension, laryngeal edema

Answer: Bronchospasm, tachycardia, hypotension, laryngeal edema
These are classic signs of **systemic anaphylaxis**.

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50. Decreased DAG in salivary glands

Answer: Decreased DAG in the salivary gland tissue
Antimuscarinic drugs block **M3 receptor signaling**, reducing IP3 and DAG pathways and decreasing secretions.

Autonomic Nervous System (ANS) | Physiology of the ANS

I. Parasympathetic Nervous System (Cholinergic Effects)

1. Parasympathetic stimulation of the salivary glands results in:

Answer: Profuse, watery secretion via **M3 receptors**

Rationale:
Parasympathetic stimulation releases **acetylcholine (ACh)** which acts on **M3 muscarinic receptors** in salivary glands. This causes **increased watery salivary secretion** that aids digestion.
In contrast, **sympathetic stimulation produces thick, viscous saliva**.

---

2. The effect of sympathetic stimulation on the pilomotor smooth muscle (hair follicles) is:

Answer: Contraction of smooth muscle walls and relaxation of sphincters via **M3 receptors**

Rationale:
Parasympathetic activity promotes digestion by:

- **Increasing GI motility** (smooth muscle contraction)
- **Relaxing sphincters**
- **Increasing secretions**

This is mainly mediated by **M3 muscarinic receptors**.

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3. In the gastrointestinal tract, parasympathetic activation generally causes:

Answer: Contraction via **M3 receptors**

Rationale:
Parasympathetic stimulation causes:

- **Contraction of detrusor muscle**
- **Relaxation of internal sphincter**

This promotes **urination (micturition)**.

---

4. The effect of parasympathetic stimulation on the ciliary muscle of the eye is:

Answer: Contraction (accommodation for near vision) via **M3 receptors**

Rationale:
Parasympathetic activation contracts the **ciliary muscle**, allowing the lens to become **more convex**, which enables **near vision (accommodation)**.

---

5. The sphincter muscle of the iris (pupillary constrictor) is innervated by the parasympathetic nervous system, causing:

Answer: Contraction (miosis) via **M3 receptors**

Rationale:
Parasympathetic stimulation causes **pupil constriction (miosis)** by contracting the **sphincter pupillae muscle** through **M3 receptors**.

---

6. Which of the following best describes the effect of parasympathetic stimulation on the sinoatrial (SA) node of the heart?

Answer: Decreased heart rate via **M2 receptors**

Rationale:
Parasympathetic stimulation through the **vagus nerve** releases ACh which binds to **M2 receptors** in the **SA node**, resulting in:

- **Decreased heart rate**
- **Decreased conduction velocity**

II. Sympathetic Nervous System (Adrenergic Effects)

7. The effect of sympathetic stimulation on the pilomotor smooth muscle (hair follicles) is:

Answer: Contraction (piloerection) via **Alpha-1 receptors**

Rationale:
Sympathetic stimulation causes **goosebumps** by contracting the **arrector pili muscles** via **α1 receptors**.

8. Which receptor is primarily responsible for the sympathetic stimulation of renin secretion from the kidney?

Answer: Beta-1 receptors

Rationale:
Activation of **β1 receptors** in **juxtaglomerular cells** stimulates **renin release**, which activates the **Renin-Angiotensin-Aldosterone System (RAAS)** and increases blood pressure.

---

9. Sympathetic activation of the blood vessels in skeletal muscle can cause dilation via which receptors?

Answer: Vasodilation via **Beta-2 receptors**

Rationale:
β2 receptor stimulation causes **vasodilation** in skeletal muscle to increase **blood flow during exercise or stress**.

---

10. Activation of the sympathetic nervous system on the radial muscle of the iris causes which of the following effects, and via which receptor?

Answer: Contraction (mydriasis) via **Alpha-1 receptors**

Rationale:
Sympathetic activation contracts the **radial muscle** of the iris, causing **pupil dilation (mydriasis)**.

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11. Sympathetic stimulation of the bronchial smooth muscle results in:

Answer: Relaxation (bronchodilation) via **Beta-2 receptors**

Rationale:
β2 receptor stimulation relaxes bronchial smooth muscle, resulting in **bronchodilation**, which improves airflow.

---

12. Sympathetic activation affects the liver by promoting:

Answer: Glycogenolysis and gluconeogenesis via **Alpha-1 and Beta-2 receptors**

Rationale:
Sympathetic stimulation increases blood glucose by:

- **Breaking down glycogen (glycogenolysis)**
- **Producing glucose (gluconeogenesis)**

---

13. Sympathetic stimulation of the fat cells (adipose tissue) leads to:

Answer: Lipolysis via **Beta-3 receptors**

Rationale:
Activation of **β3 receptors** stimulates **fat breakdown**, releasing **free fatty acids** for energy.

---

14. Sympathetic stimulation of the male sex organs primarily causes:

Answer: Ejaculation via **Alpha-1 receptors**

Rationale:
Sympathetic stimulation causes **contraction of reproductive ducts**, leading to **ejaculation**.

Mnemonic:
Point and Shoot

- **Parasympathetic = Point (Erection)**
- **Sympathetic = Shoot (Ejaculation)**

III. Neurotransmitters and Enzymes

15. Primary Neurotransmitter in Autonomic Ganglia

Answer: Acetylcholine

Rationale:
All **preganglionic neurons** (both sympathetic and parasympathetic) release **acetylcholine**.

16. The primary transmitter released at most sympathetic postganglionic nerve endings is _____.

Answer: Norepinephrine

Rationale:
Most sympathetic postganglionic neurons release **norepinephrine**, except:

- **Sweat glands (ACh)**

---

17. Acetylcholine is synthesized in the cytoplasm from acetyl-CoA and choline through the catalytic action of the enzyme _____.

Answer: Choline Acetyltransferase

Rationale:
ACh is synthesized from:

- **Choline**
- **Acetyl-CoA**

via **choline acetyltransferase**.

CHOLINE ACETYLTRANSFERASE | Responses must match exactly and are case-sensitive

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18. Acetylcholine's action is terminated by metabolism by the enzyme _____.

Answer: Acetylcholinesterase

Rationale:
ACh is rapidly broken down in the synaptic cleft by **acetylcholinesterase**, terminating its effect.

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19. The rate-limiting step in catecholamine transmitter synthesis is the conversion of Tyrosine to dopa by the enzyme _____.

Answer: Tyrosine Hydroxylase

Rationale:
Tyrosine → DOPA is the **slowest and regulatory step** in catecholamine synthesis.

---

20. The vesicular monoamine transporter (VMAT), which transports catecholamines into storage vesicles, can be inhibited by the drug _____.

Answer: Reserpine

Rationale:
Reserpine blocks **VMAT (Vesicular Monoamine Transporter)**, preventing norepinephrine from entering storage vesicles.

---

21. Botulinum Toxin

Answer: Blocks ACh release by cleaving **fusion proteins**

Rationale:
Botulinum toxin destroys **SNARE proteins**, preventing vesicle fusion and **blocking acetylcholine release**.

IV. Autonomic Nervous System Anatomy

22. Sympathetic Division

Answer: Thoracolumbar

Rationale:
Sympathetic preganglionic neurons originate in **T1–L2 spinal cord segments**.

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23. Parasympathetic Division

Answer: Craniosacral

Rationale:
Parasympathetic fibers originate from:

- **Cranial nerves III, VII, IX, X**

- **Sacral spinal cord (S2–S4)**

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24. Enteric Nervous System

Answer: Enteric Nervous System

Rationale:
The ENS is considered the **third division of the ANS** and controls gastrointestinal function.

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25. Myenteric Plexus

Answer: Auerbach's Plexus

Rationale:
Located between GI muscle layers and controls **GI motility**.

V. Important True/False Concepts

26. Tyramine and amphetamines can release stored norepinephrine from nerve endings by a calcium-independent process involving the reversal of the norepinephrine transporter (NET).

Correct Statement: True

Rationale:
They release **stored norepinephrine** by reversing the **norepinephrine transporter (NET)**.

---

27. The enteric nervous system (ENS) can function semi-autonomously, meaning deprivation of input from both the sympathetic and parasympathetic divisions does not abolish its activity.

Answer: True

Rationale:
ENS can function **independently** of sympathetic and parasympathetic input.

---

28. Parasympathetic preganglionic fibers are characteristically short and terminate in ganglia located in paravertebral chains close to the spinal column.

Answer: False

Rationale:
Parasympathetic system has:

- **Long preganglionic fibers**
- **Short postganglionic fibers**

---

29. The adrenal medulla is embryologically analogous to preganglionic sympathetic neurons and releases only norepinephrine into the circulation.

Answer: False

Rationale:
Adrenal medulla releases **both epinephrine and norepinephrine**, not only norepinephrine.

---

30. The enzyme acetylcholinesterase (AChE) is found only in cholinergic synapses and not in other tissues like red blood cells.

Answer: False

Rationale:
AChE is found not only in synapses but also in **red blood cells and other tissues**.

High-Yield Exam Summary (Very Important)

Parasympathetic (M2, M3)

Organ	Effect
Eye sphincter	Miosis
Ciliary muscle	Accommodation
Heart	↓ HR (M2)

Organ	Effect
GI	↑ motility
Bladder	Detrusor contraction

Sympathetic (α, β)

Receptor	Effect
α1	Vasoconstriction, mydriasis
α2	↓ NE release
β1	↑ HR, ↑ renin
β2	Bronchodilation, vasodilation
β3	Lipolysis

ANS Pharmacology | Drugs Affecting the Sympathetic Nervous System

1. Beta-blockers can mask the symptoms of which metabolic condition, making them potentially dangerous for insulin-dependent diabetics?

Answer: Hypoglycemia
Rationale: β-blockers inhibit sympathetic responses such as **tachycardia and tremors**, which are warning signs of **hypoglycemia**. This makes hypoglycemia harder to detect in diabetic patients.

---

2. Which of the following agents is an indirect-acting sympathomimetic that displaces stored catecholamines from the nerve ending?

Answer: Tyramine
Rationale: Tyramine enters adrenergic neurons and **releases stored norepinephrine from vesicles**, increasing sympathetic activity indirectly.

---

3. Timolol is a nonselective beta-blocker widely used in the treatment of:

Answer: Glaucoma
Rationale: Timolol is a **nonselective β-blocker** that decreases **aqueous humor production**, lowering **intraocular pressure**.

---

4. Yohimbine is a selective antagonist for which of the following receptors, sometimes used in research or as a supplement?

Answer: Alpha-2 antagonist
Rationale: Yohimbine blocks **presynaptic α_2 receptors**, increasing **norepinephrine release** and sympathetic activity.

---

5. The use of nonselective beta-blockers like Propranolol SHOULD be avoided or used with caution in patients with asthma because they block:

Answer: Block β_2 receptors in bronchi
Rationale: β_2 receptors cause **bronchodilation**. Blocking them can lead to **bronchoconstriction**, worsening asthma.

---

6. Which of the following sympathomimetic drugs is a prodrug that is converted to Desglymidodrine, an active alpha-1 agonist used for orthostatic hypotension?

Answer: Midodrine
Rationale: Midodrine is metabolized to **desglymidodrine**, an **α_1 agonist** that causes vasoconstriction to treat **orthostatic hypotension**.

---

7. Which of the following beta-blockers has intrinsic sympathomimetic activity (partial agonist activity)?

Answer: Pindolol
Rationale: Pindolol acts as a **partial agonist**, producing mild receptor activation while blocking stronger catecholamine effects.

---

8. Metoprolol is classified as a:

Answer: β_1 selective antagonist
Rationale: Metoprolol primarily blocks **cardiac β_1 receptors**, reducing heart rate and cardiac output.

---

9. The rate-limiting step in the synthesis of catecholamines is the conversion of tyrosine to dopa by which of the following enzymes?

Answer: Tyrosine hydroxylase
Rationale: This enzyme converts **tyrosine → L-DOPA**, the **slowest and regulatory step** in catecholamine synthesis.

---

10. Which of the following beta-blockers also possesses alpha-1 blocking activity, making it useful in the treatment of hypertensive emergencies?

Answer: Labetalol
Rationale: Labetalol blocks **β receptors and α_1 receptors**, reducing heart rate and causing **vasodilation**, useful in **hypertensive emergencies**.

---

11. Which of the following G proteins is coupled to alpha-1 adrenoceptors and leads to the formation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG)?
Answer: Gq
Rationale: Gq activates **phospholipase C**, generating **IP3 and DAG**, which increase intracellular calcium and cause **smooth muscle contraction**.

---

12. Carvedilol is beneficial in the treatment of heart failure because it blocks beta receptors and also:

Answer: Blocks α_1 receptors
Rationale: Carvedilol blocks **β_1, β_2, and α_1 receptors**, reducing cardiac workload and causing vasodilation.

---

13. Prazosin is a selective antagonist for which of the following adrenoceptor subtypes?

Answer: α_1 antagonist
Rationale: Prazosin blocks **vascular α_1 receptors**, causing **vasodilation** and lowering blood pressure.

---

14. Cocaine produces its sympathomimetic effects primarily by:

Answer: Inhibits norepinephrine transporter (NET)
Rationale: Cocaine prevents **reuptake of norepinephrine**, increasing its concentration in synapses.

---

15. Isoproterenol is a potent nonselective agonist that has very low affinity for which of the following receptors?

Answer: Alpha receptors
Rationale: Isoproterenol is a **nonselective β agonist** with minimal or **almost no activity** on **α receptors**.

---

16. Dobutamine is primarily used in the clinical setting to increase cardiac output in heart failure due to its selective action on:

Answer: β_1 receptors
Rationale: β_1 stimulation increases **contractility (positive inotropy)** and cardiac output.

---

17. The cardiovascular effect of low doses of epinephrine is characterized by a decrease in peripheral resistance due to activation of:
Answer: β_2 activation
Rationale: β_2 stimulation causes **vasodilation in skeletal muscle**, decreasing **peripheral resistance**.

---

18. Which of the following catecholamines is the immediate precursor of norepinephrine?

Answer: Dopamine
Rationale: Catecholamine synthesis pathway:
Tyrosine → L-DOPA → Dopamine → Norepinephrine → Epinephrine

---

19. Tamsulosin is an alpha-1 antagonist that shows selectivity for the alpha-1A subtype, making it particularly useful for:

Answer: Benign prostatic hyperplasia
Rationale: Tamsulosin selectively blocks **α_1A receptors in the prostate**, improving urinary flow.

---

20. Apraclonidine is a selective alpha-2 agonist used topically in the eye to:

Answer: Reduce intraocular pressure
Rationale: α_2 agonists decrease **aqueous humor production**.

21. Phenylephrine is a selective agonist for which of the following adrenoceptor subtypes?

Answer: α_1 agonist
Rationale: Causes **vasoconstriction**, used for **nasal decongestion and mydriasis**.

---

22. Which of the following drugs is a selective beta-3 agonist used for the treatment of overactive bladder?

Answer: Mirabegron
Rationale: β_3 stimulation relaxes the **detrusor muscle**, increasing bladder capacity.

---

23. Which of the following effects is primarily mediated by the activation of beta-2 (beta-2) adrenoceptors?

Answer: Relaxation of bronchial smooth muscle
Rationale: β_2 activation causes **bronchodilation**, important in asthma therapy.

---

24. Which of the following adverse effects is MOST likely to be associated with the first dose of Prazosin?

Answer: Orthostatic hypotension
Rationale: Sudden vasodilation can cause **fainting or dizziness when standing**. "***First-dose phenomenon***" causes **precipitous drop in BP upon standing**; common among alpha-1-selective blockers.

---

25. The "cheese reaction" is a hypertensive crisis caused by the ingestion of Tyramine-rich foods in patients taking inhibitors of which enzyme?

Answer: Monoamine oxidase (MAO)
Rationale: MAO normally metabolizes **tyramine**. Inhibition allows tyramine to trigger **massive norepinephrine release**, causing **hypertensive crisis**. **Monoamine oxidase (MAO):** MAO in the gut and liver normally degrades dietary Tyramine. ***MAO inhibitors*** **allow Tyramine to enter circulation** and **release massive amounts of stored catecholamines**.

---

26. Esmolol is a beta-1 selective antagonist characterized by its:

Answer: Very short half-life
Rationale: Esmolol is rapidly metabolized by **red blood cell esterases**, making it useful in **acute cardiac situations**.

---

27. Clonidine primarily exerts its antihypertensive effect by activating which of the following receptors in the central nervous system?

Answer: α_2 receptor activation
Rationale: α_2 stimulation in the CNS **reduces sympathetic outflow**, lowering blood pressure.

---

28. Phenoxybenzamine acts as an irreversible antagonist primarily at which of the following receptors?

Answer: α_1 and α_2 receptors
Rationale: It is an **irreversible nonselective alpha blocker**.

---

29. Which of the following drugs is a beta-1 selective antagonist commonly used for the treatment of hypertension and angina?

Answer: Atenolol
Rationale: Atenolol selectively blocks **β_1 receptors**, reducing heart rate and blood pressure.

---

30. The main clinical use of Phenoxybenzamine is in the preoperative management of:

Answer: Pheochromocytoma
Rationale: Used **preoperatively** to block excessive catecholamine effects from the tumor. Irreversible blockade prevents hypertensive crisis from catecholamine surge during surgery.

ANS Pharmacology Reviewer | DRUGS AFFECTING THE PARASYMPATHETIC NERVOUS SYSTEM

1. Organophosphate poisoning (Parathion)

A 43-year-old farm worker is brought to the emergency department with symptoms of profuse tearing, difficulty breathing, and muscle weakness. Which of the following agents is **MOST** likely responsible for these symptoms by inhibiting the enzyme acetylcholinesterase?

- **Rationale:** Parathion inhibits acetylcholinesterase, causing acetylcholine to accumulate. This overstimulates muscarinic receptors, producing tearing, salivation, bronchoconstriction, and muscle weakness. Classic organophosphate toxidrome.
- "***Parathion*** is not detoxified effectively in vertebrates... distributed to all parts of the body... Acetylcholinesterase is the primary target of these drugs". *Symptoms described* (tearing, difficulty breathing, weakness) are **classic for organophosphate** (cholinesterase inhibitor) **poisoning**.

2. Direct-acting cholinomimetics on the heart (M2 receptor)

Which of the following statements accurately describes the mechanism of action of direct-acting cholinomimetic drugs on the cardiovascular system?

- **Rationale:** M2 receptors in the heart open potassium channels, hyperpolarizing cardiac cells and slowing heart rate (negative chronotropy).
- "Activation of muscarinic receptors also increases potassium flux across cardiac cell membranes... This effect is mediated by the binding of an activated G protein βγ subunit directly to the channel".

3. Glaucoma treatment with muscarinic agonists

A patient with glaucoma is treated with a direct-acting muscarinic agonist. Which of the following effects explains the reduction in intraocular pressure?

- **Rationale:** Contraction of the ciliary muscle opens trabecular meshwork → improves aqueous humor outflow → reduces intraocular pressure.
- "Muscarinic agonists instilled into the conjunctival sac cause contraction... of the ciliary muscle... the trabecular meshwork at the base of the ciliary muscle is opened. This effect facilitates the outflow of aqueous humor".

4. Bethanechol

Which of the following choline esters is highly resistant to hydrolysis by acetylcholinesterase and has significant muscarinic activity but negligible nicotinic activity?

- **Rationale:** Bethanechol is resistant to acetylcholinesterase, acts mostly on muscarinic receptors, and has minimal nicotinic activity, making it ideal for bladder and GI stimulation.
- "Bethanechol chloride [Susceptibility to Cholinesterase]: Negligible... [Nicotinic Action]: None".

5. Neostigmine in Myasthenia Gravis

In the treatment of Myasthenia gravis, which of the following drugs is a quaternary carbamate that does not readily cross the blood-brain barrier?

- **Rationale:** Neostigmine is a quaternary carbamate, does not cross the BBB, and prolongs acetylcholine action at NMJ, improving muscle strength without CNS effects.
- "Neostigmine exemplifies the typical ester composed of carbamic acid... and a phenol bearing a quaternary ammonium group... quaternary cholinesterase inhibitors... do not readily enter the central nervous system".

6. Aging in organophosphate poisoning

Which of the following best describes the "aging" process associated with organophosphate poisoning?
B. Breaking of an oxygen-phosphorus bond strengthening the enzyme-inhibitor bond.

- **Rationale:** “Aging” strengthens the bond between enzyme and organophosphate, making acetylcholinesterase reactivation by pralidoxime more difficult.
- "This process [aging] apparently involves the breaking of one of the oxygen-phosphorus bonds of the inhibitor and further strengthens the phosphorus-enzyme bond".

7. Reversing antimuscarinic toxicity

A patient presents with dry mouth, dilated pupils, and tachycardia. Which of the following drugs would be **MOST** appropriate to reverse these antimuscarinic effects if they are severe?
A. Physostigmine

- **Rationale:** Physostigmine crosses the BBB and reverses central and peripheral antimuscarinic effects (dry mouth, dilated pupils, tachycardia).
- "Physostigmine has been used for this application because it enters the central nervous system and reverses the central as well as the peripheral signs of muscarinic blockade".

8. Nicotinic receptor at NMJ

Which of the following effects is characteristic of nicotinic receptor activation at the neuromuscular junction?

D. Depolarization leading to muscle contraction.

- **Rationale:** Nicotinic receptor activation depolarizes the muscle membrane → triggers contraction.
- "Nicotinic agents cause marked activation of these nicotinic receptors and initiate action potentials... Nicotinic receptors are part of a transmembrane polypeptide whose five subunits form cation-selective ion channels... Na+, K+ depolarizing ion channel".

9. Varenicline for smoking cessation

Varenicline is a partial agonist at which of the following receptors, making it useful for smoking cessation?
C. Nicotinic alpha-4-beta-2 receptors

- **Rationale:** Partial agonist at α4β2 nicotinic receptors → reduces withdrawal symptoms while blocking nicotine's rewarding effects.
- Varenicline is a high-affinity partial agonist specifically at the **nicotinic acetylcholine receptors** in the brain. By partially stimulating these receptors, it reduces withdrawal symptoms and cravings, while its antagonist properties simultaneously block nicotine from binding, reducing the rewarding satisfaction of smoking.

10. Acute nicotine toxicity

Which of the following signs is indicative of acute Nicotine toxicity?
C. Hypertension and cardiac arrhythmias.

- **Rationale:** Nicotine stimulates sympathetic nervous system → hypertension, tachycardia, and arrhythmias.
- "Dramatic hypertension is produced by parenteral injection of nicotine; sympathetic tachycardia may alternate with a bradycardia mediated by vagal discharge".

11. Edrophonium clinical use

Edrophonium is primarily used for which of the following clinical indications due to its short duration of action?
B. Diagnosis of myasthenia gravis.

- **Rationale:** Short-acting cholinesterase inhibitor → ideal for diagnosing myasthenia gravis (Tensilon test).
- "The enzyme-inhibitor complex... is correspondingly short-lived (on the order of 2–10 minutes)... The first group, of which edrophonium is the example". Short duration makes it ideal for diagnosis (Tensilon test).

12. Pilocarpine

Which of the following is a direct-acting cholinomimetic alkaloid that is well absorbed from most sites of administration?

- **Rationale:** Tertiary muscarinic alkaloid → well absorbed → used for glaucoma, xerostomia.
- "The tertiary natural cholinomimetic alkaloids (pilocarpine...) are well absorbed from most sites of administration".

13. Pralidoxime timing

Pralidoxime (2-PAM) is effective in treating organophosphate poisoning only if administered before which process occurs?
D. Aging

- **Rationale:** Reactivates acetylcholinesterase before "aging" occurs; once aging happens, the bond is irreversible.
- "If given before aging has occurred, strong nucleophiles like pralidoxime (PAM) are able to break the phosphorus-enzyme bond... Once aging has occurred, the enzyme-inhibitor complex is even more... stable".

14. Adverse effects of systemic muscarinic agonists

Which of the following adverse effects is most likely to occur with the use of systemic muscarinic agonists?
D. Bronchoconstriction

- **Rationale:** Muscarinic stimulation contracts bronchial smooth muscle → bronchoconstriction.
- "Muscarinic stimulants contract the smooth muscle of the bronchial tree... This combination of effects can occasionally cause symptoms, especially in individuals with asthma".

15. M3 receptors in vascular endothelium

Activation of M3 receptors in the vascular endothelium results in vasodilation primarily through the release of:
C. Nitric oxide

- **Rationale:** M3 receptor activation releases nitric oxide → vasodilation.
- "Arteries, veins... Dilation (via EDRF)". EDRF is Endothelium-Derived Relaxing Factor, known as Nitric Oxide.

16. Scopolamine

Which of the following drugs is a tertiary amine antimuscarinic agent often used for its effects on the CNS, one of which is the relief of motion sickness?
C. Scopolamine

- **Rationale:** Tertiary amine → crosses BBB → used to prevent motion sickness via CNS action.

- "Scopolamine (Hyoscine) occurs in *Hyoscyamus niger*... Scopolamine is rapidly and fully distributed into the CNS, where it has greater effects than most other antimuscarinic drugs".

17. Atropine mechanism

Atropine causes reversible blockade of cholinomimetic actions at muscarinic receptors. This type of blockade is best described as:
A. Competitive antagonism

- **Rationale:** Atropine is a competitive antagonist at muscarinic receptors; its effect can be overcome by high acetylcholine levels.
- "Atropine causes reversible (surmountable) blockade... of cholinomimetic actions at muscarinic receptors; that is, blockade by a small dose of atropine can be overcome by a larger concentration of acetylcholine".

18. Ocular effects of Atropine

Which of the following ocular effects is produced by the administration of Atropine?
C. Mydriasis and cycloplegia.

- **Rationale:** Blocks muscarinic receptors → mydriasis (pupil dilation) and cycloplegia (paralysis of accommodation).
- Antimuscarinics cause the **opposite of agonists:** ***dilation*/*mydriasis*** and paralysis of accommodation/**cycloplegia**.

19. Ipratropium

Which of the following antimuscarinic agents is a quaternary ammonium derivative used via inhalation for the treatment of asthma and COPD?

- **Rationale:** Quaternary ammonium → inhaled → acts locally in lungs → minimal CNS effects → treats asthma and COPD.
- "Quaternary amines for gastrointestinal and pulmonary applications (peptic disease, COPD): ... **Ipratropium**".

20. Antimuscarinics in BPH

A patient with benign prostatic hyperplasia **SHOULD** avoid antimuscarinic drugs primarily because they can precipitate:
B. Urinary retention

- **Rationale:** Reduce detrusor contraction → can worsen urinary retention in men with enlarged prostates.
- "In elderly men, antimuscarinic drugs should always be used with caution and should be avoided in those with a history of prostatic hyperplasia". (Due to risk of urinary retention).

21. Mecamylamine

Which of the following drugs is a ganglion-blocking agent that competitively blocks nicotinic receptors at autonomic ganglia?

- **Rationale:** Ganglion blocker → competitively blocks nicotinic receptors at autonomic ganglia → affects both sympathetic and parasympathetic tone.
- "Mecamylamine, a secondary amine... Mecamylamine, unlike the quaternary amine agents... crosses the blood-brain barrier" and is listed under ganglion-blocking drugs.

22. Scopolamine clinical use

Scopolamine is most effective clinically for which of the following conditions?
C. Motion sickness prevention.

- **Rationale:** Crosses CNS → blocks vestibular input → prevents motion sickness.
- "Scopolamine has more marked central effects... producing drowsiness... and amnesia... Transdermal scopolamine is used for the prevention of motion sickness".

23. Contraindication of antimuscarinics

Which of the following is a contraindication for the use of Atropine and other antimuscarinic drugs?
B. Angle-closure glaucoma

- **Rationale:** Can precipitate angle-closure glaucoma by dilating the pupil, raising intraocular pressure.
- "Antimuscarinic drugs are contraindicated in patients with glaucoma, especially angle-closure glaucoma. **Even systemic use... may precipitate angle closure**".

24. Oxybutynin

- **Rationale:** Reduces bladder spasms → treats overactive bladder by blocking detrusor muscarinic receptors.
- "Receptors for acetylcholine on the urothelium... provide a broad basis for the action of antimuscarinic drugs in the treatment of overactive bladder. Oxybutynin... is used to relieve bladder spasm".

25. Atropine overdose

- **Rationale:** Causes “hot, dry, red, blind, mad” symptoms: hyperthermia, dry skin, mydriasis, CNS agitation.
- "Atropine intoxication... may cause prolonged severe behavioral disturbances... Symptomatic treatment may require temperature control with cooling blankets". (Classic "hot as a hare, dry as a bone").

- ***Recall the "**Alice in Wonderland**" toxidrome mentioned during the discussion.

26. Atropine flush

The "Atropine flush" observed in toxic doses is primarily due to:
C. Cutaneous vasodilation.

- **Rationale:** Vasodilation in skin occurs as a compensatory response to blocked sweating.
- "Atropine flush" is a known sign. While the reference mentions "Symptomatic treatment may require temperature control", the flush mechanism is a standard physiological response to block of sweating (hyperthermia compensation).

27. Pralidoxime

Which of the following drugs is used to regenerate acetylcholinesterase in cases of organophosphate poisoning?

- **Rationale:** Strong nucleophile → regenerates acetylcholinesterase before aging.
- "Strong nucleophiles like ***Pralidoxime (PAM)*** are able to **break the phosphorus-enzyme bond**".

28. Glycopyrrolate

Glycopyrrolate is often preferred over Atropine for reversing neuromuscular blockade because it:
B. Lacks significant central nervous system effects.

- **Rationale:** Does not cross BBB → avoids CNS effects → preferred over atropine for reversing NM blockade.
- Glycopyrrolate is often preferred over Atropine for reversing neuromuscular blockade (typically with neostigmine) because its **onset and duration of action more closely match those of neostigmine**, leading to better hemodynamic stability. It produces less initial tachycardia, fewer cardiac arrhythmias, and has a longer duration of action (2–4 hours). Additionally, it **does not cross the blood-brain barrier,** reducing central nervous system effects.

29. Antimuscarinic effects on gastric acid

Antimuscarinic drugs reduce gastric acid secretion less effectively than they reduce salivary secretion because:
Correct: C. Acid secretion is least sensitive to Atropine blockade.

- **Rationale:** Gastric parietal cells less sensitive to atropine than salivary glands → acid secretion minimally affected.
- "Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands. *Secretion of acid* by the gastric parietal cells is **the least sensitive**".

30. Ganglionic blockade

Which of the following effects is NOT typically seen with ganglionic blockade?
E. Muscle fasciculations

- **Rationale:** Affects autonomic ganglia → causes orthostatic hypotension, constipation, urinary retention; does NOT cause muscle fasciculations.
- Muscle fasciculations are characteristic of ***depolarizing* neuromuscular blockade** (like Succinylcholine) or ***organophosphate poisoning***, **NOT *ganglionic blockade***. Ganglion blockers cause "marked orthostatic hypotension", "sexual dysfunction", "constipation", "urinary retention".

31. Nicotinic receptor action

Activation of nicotinic cholinoceptors directly opens ligand-gated ion channels, resulting in cellular depolarization and potential generation of an action potential.

- **Rationale:** Nicotinic receptors open cation channels → depolarization → action potential.
- "Nicotinic agents cause marked activation of these nicotinic receptors and initiate action potentials in postganglionic neurons". "*Nicotinic receptors* are part of a transmembrane polypeptide whose five subunits form **cation-selective ion channels**".

32. Bethanechol hydrolysis

- **Rationale:** Resistant to acetylcholinesterase → longer duration than acetylcholine.
- "**Bethanechol**... are still ***more resistant to hydrolysis by cholinesterase*** and have correspondingly longer durations of action". "Bethanechol chloride [Susceptibility to Cholinesterase]: **Negligible**".

33. Acetylcholine-induced vasodilation

- **Rationale:** Acts on endothelial muscarinic receptors → releases nitric oxide → vasodilation, not direct on smooth muscle.
- "Arteries, veins... Dilation (via EDRF)". The reference notes that muscarinic receptors are located on "endothelial cells of blood vessels" which are ***not*** innervated by parasympathetic nerves.

34. Muscarinic agonists in glaucoma

- **Rationale:** Contraction of ciliary muscle opens trabecular meshwork → outflow into canal of Schlemm → reduces IOP.
- "Muscarinic agonists instilled into the conjunctival sac cause contraction... of the ciliary muscle... As a result, the iris is pulled away from the angle of the anterior chamber, and the trabecular meshwork at the base of the ciliary muscle is opened. This effect facilitates the outflow of aqueous humor into the canal of Schlemm, which drains the anterior chamber".

35. Neostigmine CNS effects

- **Rationale:** Quaternary ammonium → negligible CNS penetration → lacks central effects, unlike physostigmine.
- "Physostigmine... distributed into the central nervous system". In contrast, "Neostigmine... exemplifies the typical ester composed of carbamic acid... and a phenol bearing a quaternary ammonium group" and "Distribution into the central nervous system is negligible".

36. Edrophonium duration

- **Rationale:** Short-acting, non-covalent binding → ideal for diagnosis, not chronic therapy.
- The enzyme-inhibitor complex does not involve a covalent bond and is correspondingly ***short-lived*** (on the order of 2–10 minutes)". "The first group, of which ***Edrophonium*** is the example, consists of quaternary alcohols".

37. Pralidoxime in organophosphate poisoning

- **Rationale:** Only works if aging has NOT occurred; cannot reactivate aged enzyme.
- Therapy often also includes treatment with ***Pralidoxime***... which, by prior binding to the enzyme, impedes binding of organophosphate agents... After the **initial binding-hydrolysis step**, the **phosphorylated enzyme complex** may *undergo* a process called ***aging***".

38. Postganglionic autonomic receptors

- **Rationale:** Nicotinic receptors (Nn) are on postganglionic neurons; muscarinic receptors are on effector organs.
- "The **Nn** [***Neuronal type***, ganglion receptor]... [Location]: CNS, postganglionic cell body, dendrites". "Nicotinic receptors are located in plasma membranes of postganglionic cells in all autonomic ganglia".

39. Atropine reversible blockade

- **Rationale:** Competitive blockade → effect can be surmounted with high acetylcholine.
- "Atropine causes ***reversible (surmountable) blockade***... of **cholinomimetic actions** at **muscarinic receptors;** that is, blockade by a small dose of Atropine can be overcome by a larger concentration of Acetylcholine".

40. Atropine eye drops

- **Rationale:** Cause mydriasis and cycloplegia, opposite of agonist effects (not miosis).
- "Effects on the iris and ciliary muscle persist for ≥72 hours". (Note: Antimuscarinics cause ***mydriasis*** and ***cycloplegia***, the opposite of the agonist effects listed in **Table 7-3**).

41. Ipratropium CNS effects

- **Rationale:** Quaternary amine → inhaled → limited systemic absorption → minimal CNS effects.
- "Quaternary amine antimuscarinic agents... have been developed to produce more peripheral effects and reduced CNS effects". "Quaternary amines for gastrointestinal and pulmonary applications (peptic disease, COPD): ... **Ipratropium**"

42. Antimuscarinics in BPH

- **Rationale:** Can worsen urinary retention in men with enlarged prostate → caution in elderly males.
- "In elderly men, **antimuscarinic drugs should always be used with caution** and should be ***avoided*** in those with a **history of prostatic hyperplasia**"

43. Oxybutynin in urinary disorders

- **Rationale:** Reduces detrusor muscle spasms → alleviates overactive bladder and urge incontinence.
- "Oxybutynin... is used to **relieve bladder spasm**... It is also valuable in reducing involuntary voiding... Receptors for acetylcholine... on the detrusor muscle provide a broad basis for the action of antimuscarinic drugs".

44. Ganglion-blocking drugs

- **Rationale:** Block nicotinic receptors at autonomic ganglia → reduce sympathetic and parasympathetic activity, not muscarinic directly.
- "Ganglion-blocking agents competitively block the action of acetylcholine and similar agonists at **neuronal nicotinic receptors** of both parasympathetic and sympathetic autonomic ganglia".

45. Atropine and heart rate

- **Rationale:** Atropine blocks parasympathetic vagal input → prevents vagal slowing → increases heart rate (tachycardia).
- "Sinoatrial node... Decrease in rate (negative chronotropy)" is the agonist effect. Atropine "causes reversible... blockade... of cholinomimetic actions". Therefore, blocking the vagal (parasympathetic) slowing causes tachycardia.

Autonomic Pharmacology & Cholinergic/Anticholinergic Drugs

Cholinesterase Inhibitors & Organophosphate Poisoning

1. **Parathion (Organophosphate poisoning)**

A 43-year-old farm worker is brought to the emergency department with symptoms of profuse tearing, difficulty breathing, and muscle weakness. Which of the following agents is **MOST** likely responsible for these symptoms by inhibiting the enzyme acetylcholinesterase?

- **Mechanism:** Inhibits acetylcholinesterase → accumulation of acetylcholine at synapses.
- **Symptoms:** Profuse tearing, salivation, bronchospasm, muscle weakness. Classic "cholinergic toxidrome."
- **Key Point:** Organophosphates are not detoxified efficiently in humans; treatment may include atropine and pralidoxime.

2. **Aging of organophosphate-inhibited AChE**
   - **Mechanism:** Breaking of oxygen-phosphorus bond strengthens enzyme-inhibitor complex → resistant to reactivation.
   - **Clinical relevance:** Pralidoxime must be given **before aging** to regenerate acetylcholinesterase.
3. **Pralidoxime (2-PAM)**

- **Mechanism:** Strong nucleophile that cleaves phosphorus-enzyme bond before aging occurs.
- **Use:** Treatment of organophosphate poisoning.

27. **Pralidoxime & enzyme regeneration**

- **True:** Only effective if given **before aging** of the phosphorylated AChE.

Direct-Acting Cholinomimetics (Muscarinic Agonists)

2. **M2 receptor activation in heart**
   - **Mechanism:** G-protein βγ subunit opens K^+ channels → hyperpolarization → slows SA node.
   - **Effect:** Decreased heart rate; direct M2 stimulation reduces excitability.
3. **Muscarinic agonists in glaucoma**
   - **Effect:** Contraction of ciliary muscle → opens trabecular meshwork → facilitates aqueous humor outflow → lowers intraocular pressure.
4. **Bethanechol**
   - **Features:** Resistant to acetylcholinesterase hydrolysis → long duration, muscarinic selective, minimal nicotinic activity.
   - **Use:** Stimulates bladder and GI smooth muscle.
5. **Pilocarpine**

- **Type:** Tertiary natural alkaloid → well absorbed systemically.
- **Use:** Glaucoma, xerostomia.

14. **Adverse effect of systemic muscarinic agonists**

- **Bronchoconstriction**: smooth muscle contraction in airways → can worsen asthma.

15. **M3 receptor in endothelium**

- **Effect:** Activation releases **nitric oxide** → vasodilation.
- **Clinical note:** Endothelium-dependent relaxation.

Cholinesterase Inhibitors (Indirect-Acting)

5. **Neostigmine in Myasthenia Gravis**
    - **Type:** Quaternary carbamate → does **not** cross BBB → no CNS effects.
    - **Use:** Improves skeletal muscle strength.
6. **Edrophonium**

- **Short-acting** AChE inhibitor → useful for **diagnosis** (Tensilon test), not long-term therapy.

32. **Bethanechol hydrolysis**

- **Fact:** Resistant to cholinesterase → longer duration than acetylcholine.

36. **Edrophonium**

- **False:** It is short-acting, not long-acting; used for diagnosis.

35. **Neostigmine vs Physostigmine**

- **Neostigmine:** Quaternary, minimal CNS penetration.
- **Physostigmine:** Tertiary, crosses BBB → CNS effects.

37. **Pralidoxime**

- **True/False:** Only effective if given before **aging**, works by regenerating AChE.

Antimuscarinic Drugs

7. **Physostigmine for antimuscarinic toxicity**
    - **Mechanism:** Crosses BBB → reverses central & peripheral muscarinic blockade.
    - **Indication:** Severe atropine or scopolamine overdose.
8. **Scopolamine**

- **Type:** Tertiary amine → CNS penetration.
- **Use:** Motion sickness, central anticholinergic effects.

17. **Atropine antagonism**

- **Type:** Competitive/ reversible → blockade overcome by high agonist concentration.

18. **Atropine ocular effect**

- **Effect:** Mydriasis + cycloplegia (paralysis of accommodation).
- **Opposite of muscarinic agonists.**

19. **Ipratropium**

- **Quaternary ammonium derivative of atropine** → inhaled for asthma/COPD → minimal CNS effects.

20. **BPH & antimuscarinics**

- **Caution:** Risk of **urinary retention**.

24. **Oxybutynin**

- **Use:** Overactive bladder; reduces detrusor spasms.

25. **Atropine overdose**

- **Signs:** Hot, dry skin, hyperthermia, mydriasis, CNS excitation → classic anticholinergic toxidrome ("hot as a hare, dry as a bone, blind as a bat, mad as a hatter").

26. **Atropine flush**

- **Mechanism:** Cutaneous vasodilation due to blocked sweat glands → compensatory response.

28. **Glycopyrrolate**

- **Advantage:** Does not cross BBB → fewer CNS effects → preferred with neostigmine for NM blockade reversal.

29. **Gastric vs salivary sensitivity to atropine**

- **Observation:** Gastric acid secretion less sensitive; salivary glands highly sensitive to muscarinic blockade.

Nicotinic Agents

8. **Nicotinic receptor at NMJ**
    - **Mechanism:** Ligand-gated ion channels → depolarization → muscle contraction.
9. **Varenicline**
    - **Partial agonist:** Nicotinic α4β2 receptors → reduces cravings and blocks nicotine reward.
10. **Acute nicotine toxicity**

- **Signs:** Hypertension, arrhythmias, tachycardia/bradycardia alternation.

21. **Mecamylamine**

- **Ganglion blocker:** Competitively blocks nicotinic receptors in autonomic ganglia.

30. **Ganglionic blockade effect NOT seen**

- **Muscle fasciculations:** Seen in depolarizing NM blockade (succinylcholine, organophosphates), **not ganglion blockers**.

38. **Primary receptor in postganglionic neurons**

- **Fact:** Nicotinic, not muscarinic.

31. **Nicotinic cholinoceptor activation**

- **True:** Opens ligand-gated ion channel → depolarization, AP generation.

44. **Ganglionic blockers**

- **False:** Block **nicotinic**, not muscarinic receptors at autonomic ganglia.

True/False Recap

33. **Acetylcholine-induced vasodilation** → **Endothelium**, not smooth muscle.
34. **Muscarinic agonists in glaucoma** → True, contraction of ciliary muscle → outflow via trabecular meshwork.
35. **Atropine eye drops** → False, cause **mydriasis and cycloplegia**, not miosis.
36. **Ipratropium inhalation** → False, reduces systemic effects due to quaternary structure.

37. **Antimuscarinics in BPH** → True, risk of urinary retention.
38. **Oxybutynin use** → True, reduces detrusor smooth muscle tone/spasms.
39. **Atropine effect on heart rate** → True, blocks vagal tone → tachycardia.

☑ Key Takeaways

- **Muscarinic agonists:** Increase parasympathetic tone; effects: ↓HR (M2), ↑glandular secretion, bronchoconstriction, miosis, ↑GI/bladder motility.
- **Muscarinic antagonists:** Block parasympathetic tone; effects: ↑HR, mydriasis, dry mouth, urinary retention, CNS effects if tertiary amine.
- **Nicotinic agents:** Depolarize NMJ → muscle contraction; ganglionic blockers → inhibit both sympathetic & parasympathetic outflow.
- **Cholinesterase inhibitors:** Increase acetylcholine at synapses; organophosphates → irreversible if aged; treatment includes atropine + pralidoxime.