

Neuropharmacology revision

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BENZODIAZEPINES & BARBITURATES

SEDATIVES & ANXIOLYTICS

PANIC DISORDER



ANXIETY DISORDERS

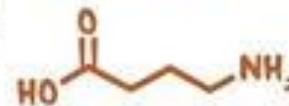


INSOMNIA

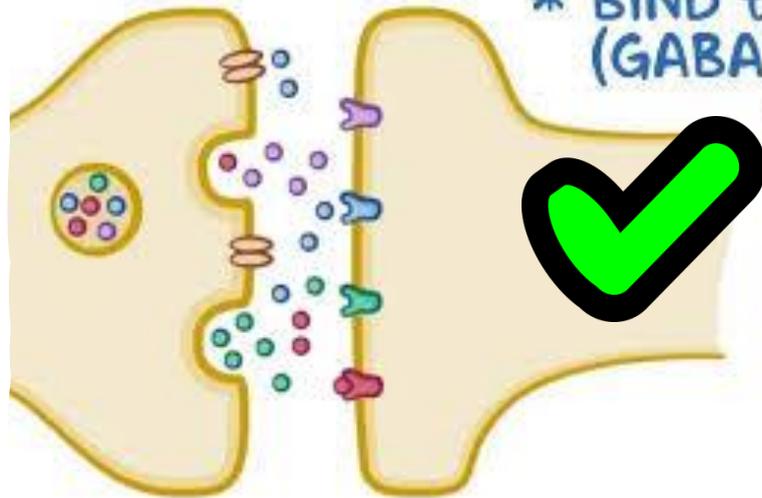


* BIND to GAMMA-AMINOBUTYRIC ACID (GABA) RECEPTORS

↳ ↑ AFFINITY of RECEPTOR to BIND to GABA



↳ 1^o INHIBITORY NEUROTRANSMITTER





COMMON USES OF BENZODIAZEPINES



01

Anxiety disorders



02

Insomnia

03

Seizure disorders

04

Muscle spasms

05

Medical procedures

Question

A 42-year-old man recently diagnosed with generalized anxiety disorder had started a treatment with sertraline, but the drug caused some sexual dysfunction, and the psychiatrist decided to switch to a short course of alprazolam. Which of the following **molecular actions on neuronal membranes** most likely mediated the therapeutic effect of **alprazolam** in the patient's disorder?

- A. Decreased outward Na^+ current
- B. Increased inward Cl^- current
- C. Decreased outward K^+ current
- D. Increased inward Ca^{2+} current
- E. Increased inward H^+ current

Question

A 58-year-old man was admitted to the hospital for a laparoscopic surgery. Anesthesia was induced by IV diazepam, and the patient lost consciousness in about 1 minute. He regained consciousness about 35 minutes later. Knowing that the half-life of diazepam is about 40 hours, which of the following items best explains the short action of the drug?

- A. Rapid metabolism of the drug within the central nervous system
- B. Rapid excretion of the drug by the kidneys
- C. Redistribution of the drug from central nervous system to other tissues
- D. Biotransformation of the drug into inactive metabolites
- E. Development of a rapid tolerance to drug effects

Question

A 26-year-old woman, suffering from cerebral palsy secondary to head injury, was seen in a clinic for a scheduled visit. She was **spastic** and unable to walk. Which of the following drugs would be appropriate to improve her muscle spasms?

- A. Buspirone
- B. Lithium
- C. Fluoxetine
- D. Haloperidol
- E. Diazepam

BARBITURATES

~ DECREASE EXCITATORY SIGNALS

AMOBARBITAL

BUTABARBITAL

METHOHEXITAL

PENTobarbital

PRIMIDONE

PHENobarbital

THIOPENTAL



EXTENDED HOURS TONIGHT!

LOWER DOSES:

~ ↑ DURATION of Cl^- CHANNELS OPENING

BENZODIAZEPINES

~ ↑ FREQUENCY of Cl^- CHANNELS OPENING

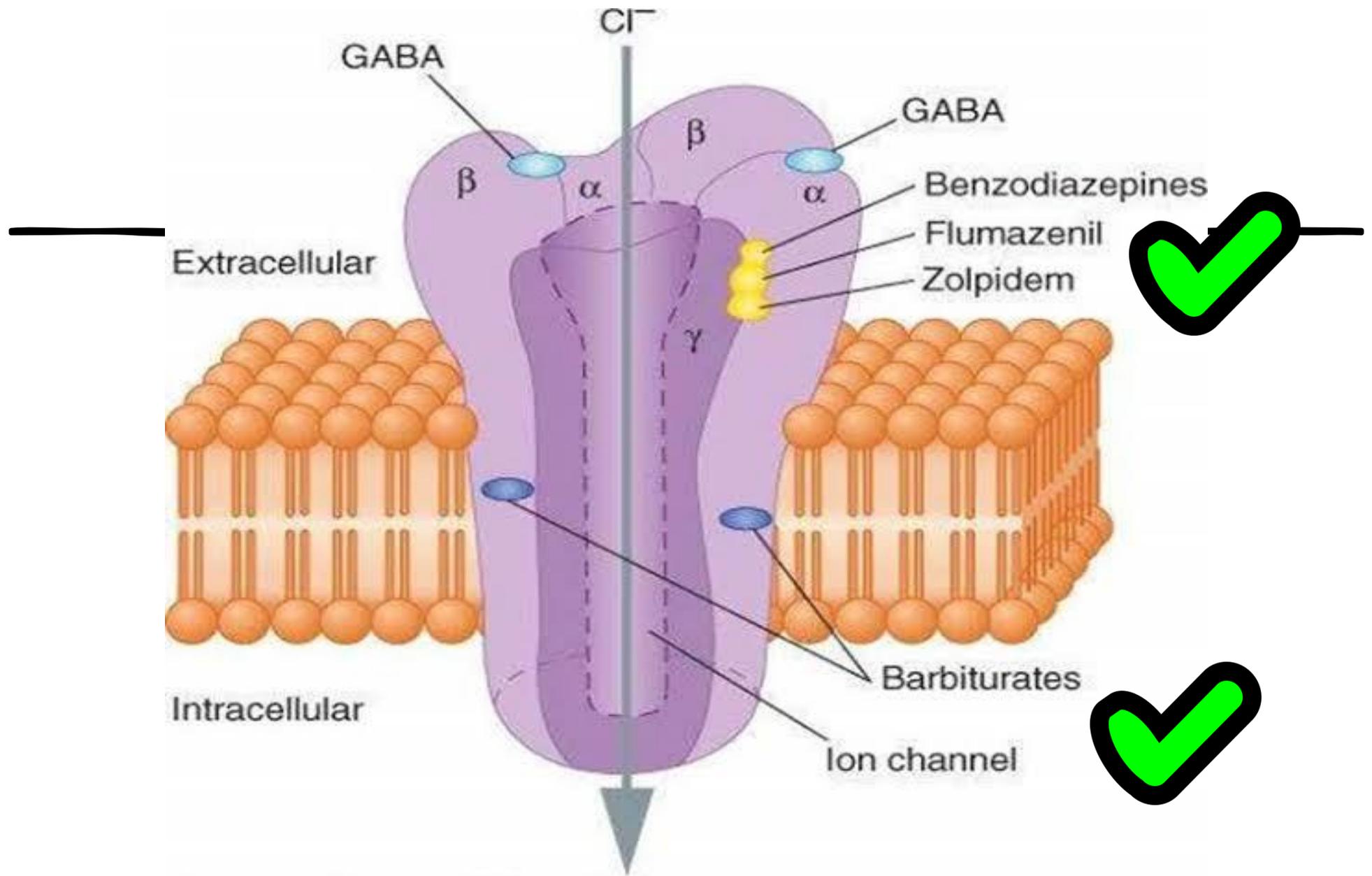
HIGHER DOSES:

~ TRIGGER OPENING of CHANNELS without GABA



Approved Medication for Insomnia Treatment

Categories of Medication:	Receptors:
Benzodiazepines	GABA-A 
Non-benzodiazepine hypnotics	GABA-A alpha-1 subunit 
DORAs	Orexin-1 and orexin-2 
Melatonin agonists	Melatonin-1 and melatonin-2 
H1 antagonists	H1 



Question

A	Q
A. Alprazolam	1. A partial agonist at 5-HT _{1A} receptors <u>buspirone</u>
B. Buspirone	2. A competitive antagonist at benzodiazepine receptors
C. Clonazepam	<u>flumazenil</u>
D. Flumazenil	3. A hypnotic drug with negligible effects on sleep
E. Lorazepam	architecture and stages <u>Zolpidem</u>
F. Midazolam	4. The barbiturate most frequently used to induce
G. Phenobarbital	general anesthesia
H. Thiopental	5. A benzodiazepine with a very short half-life (about 2
I. Zolpidem	hours) <u>midazolam</u>
	6. An anxiolytic drug with negligible abuse liability <u>buspirone</u>

Question

A 63-year-old woman complained to her physician of difficulty in falling asleep. She denied nocturnal insomnia or early awaking. The doctor prescribed **ramelteon**, one tablet at bedtime. Which of the following **molecular actions** most likely mediated the therapeutic effect of the drug?

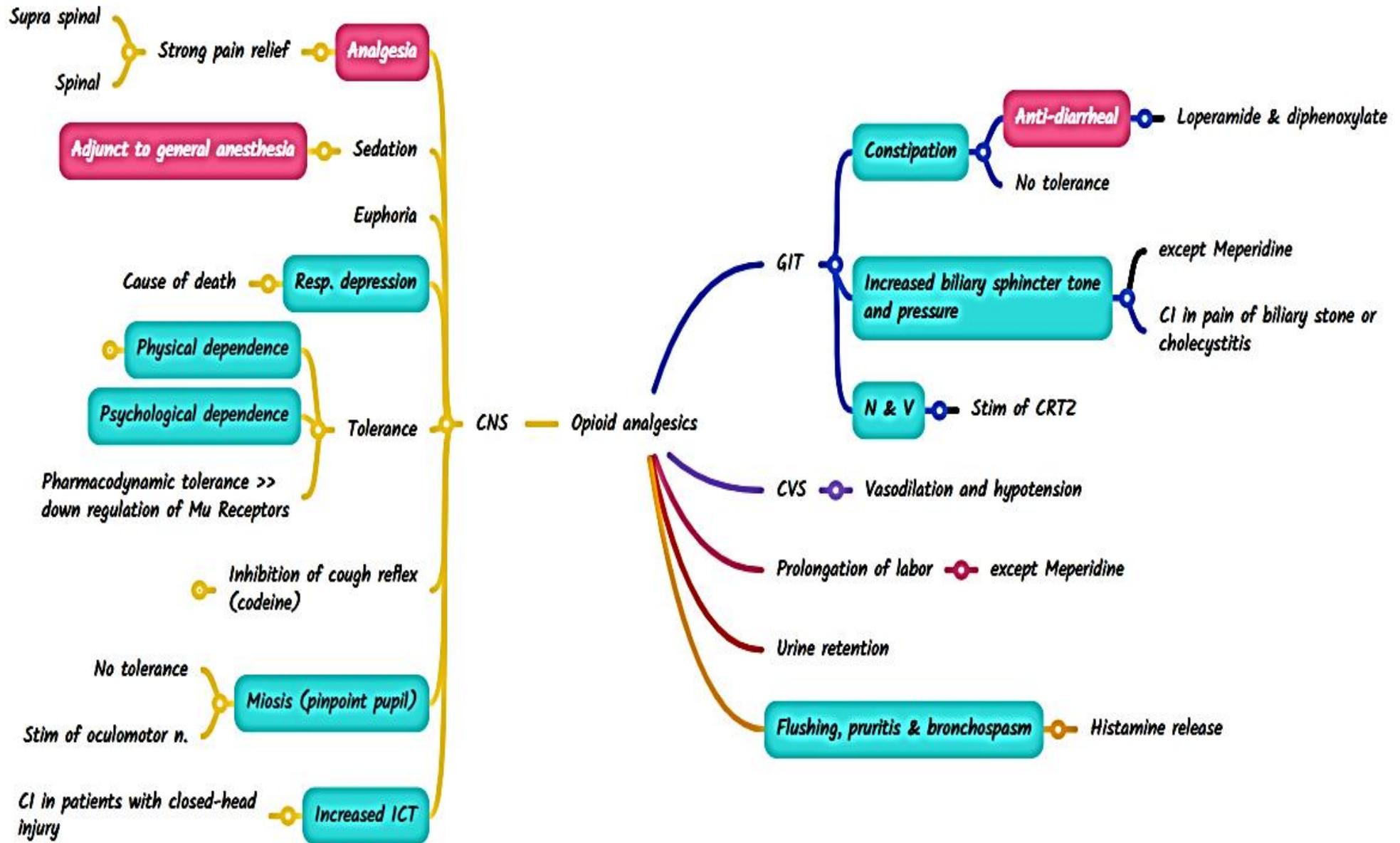
- A. Activation of GABAB receptors
- B. Blockade of $\alpha 1$ receptors
- C. Activation of melatonin receptors
- D. Blockade of glutamate receptors
- E. Activation of serotonin 5-HT₃ receptors

Question

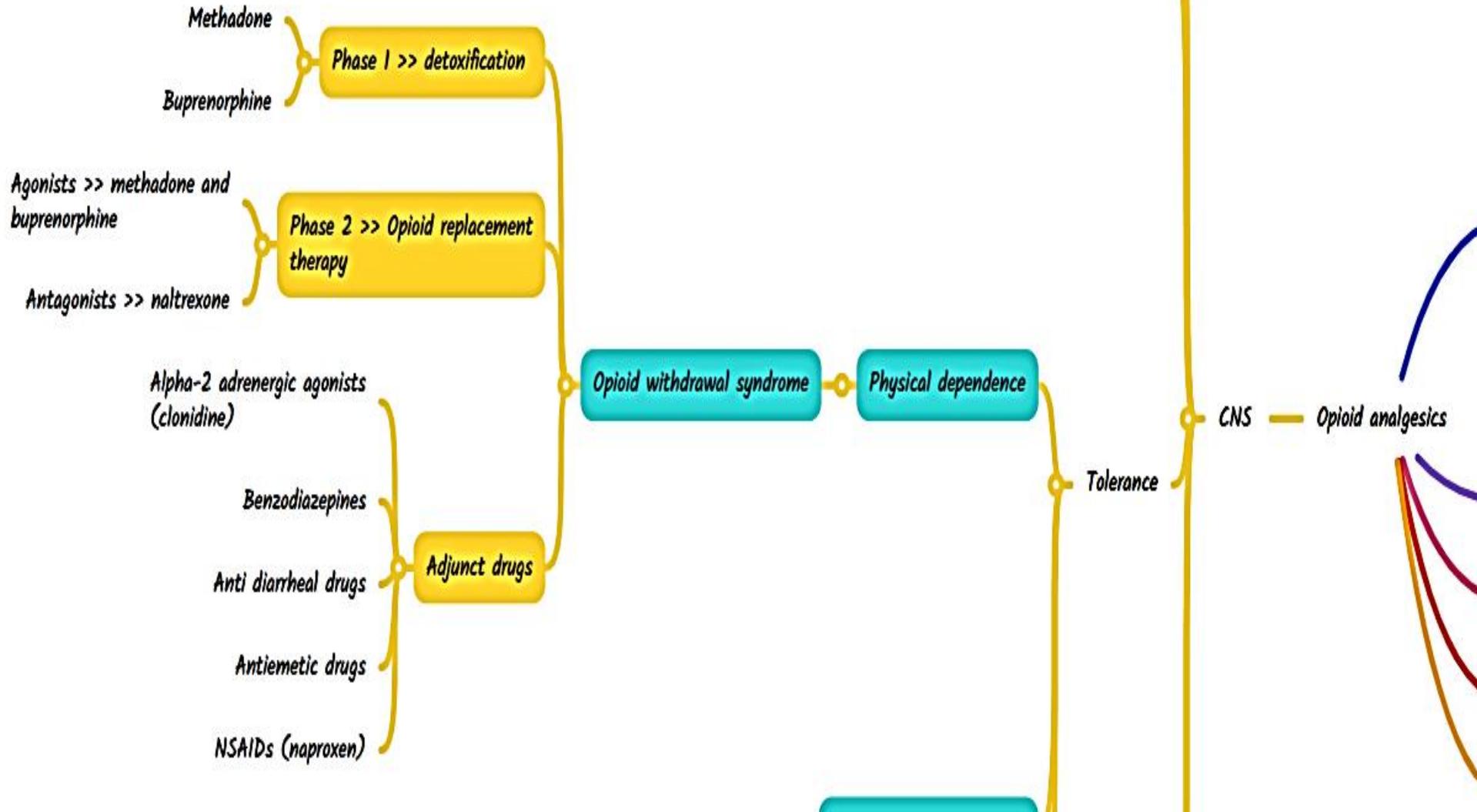
A 36-year-old man was referred to a psychiatrist because of **irritability, worrying thoughts, palpitations, dry mouth, and insomnia** of 1-month duration. The man had **a history of alcohol abuse**, but he was able to quit 1 year ago after psychological counseling and drug therapy. Recently, he suffered from **erectile dysfunction**, treated with sildenafil. A provisional diagnosis of generalized anxiety disorder was made, and cognitive behavioral therapy with a drug treatment was prescribed. Which of the following drugs would be most appropriate for this patient?

- A. Diazepam
- B. Fluoxetine
- C. Lorazepam
- D. Haloperidol
- E. Lithium
- F. Buspirone

Opioid analgesics



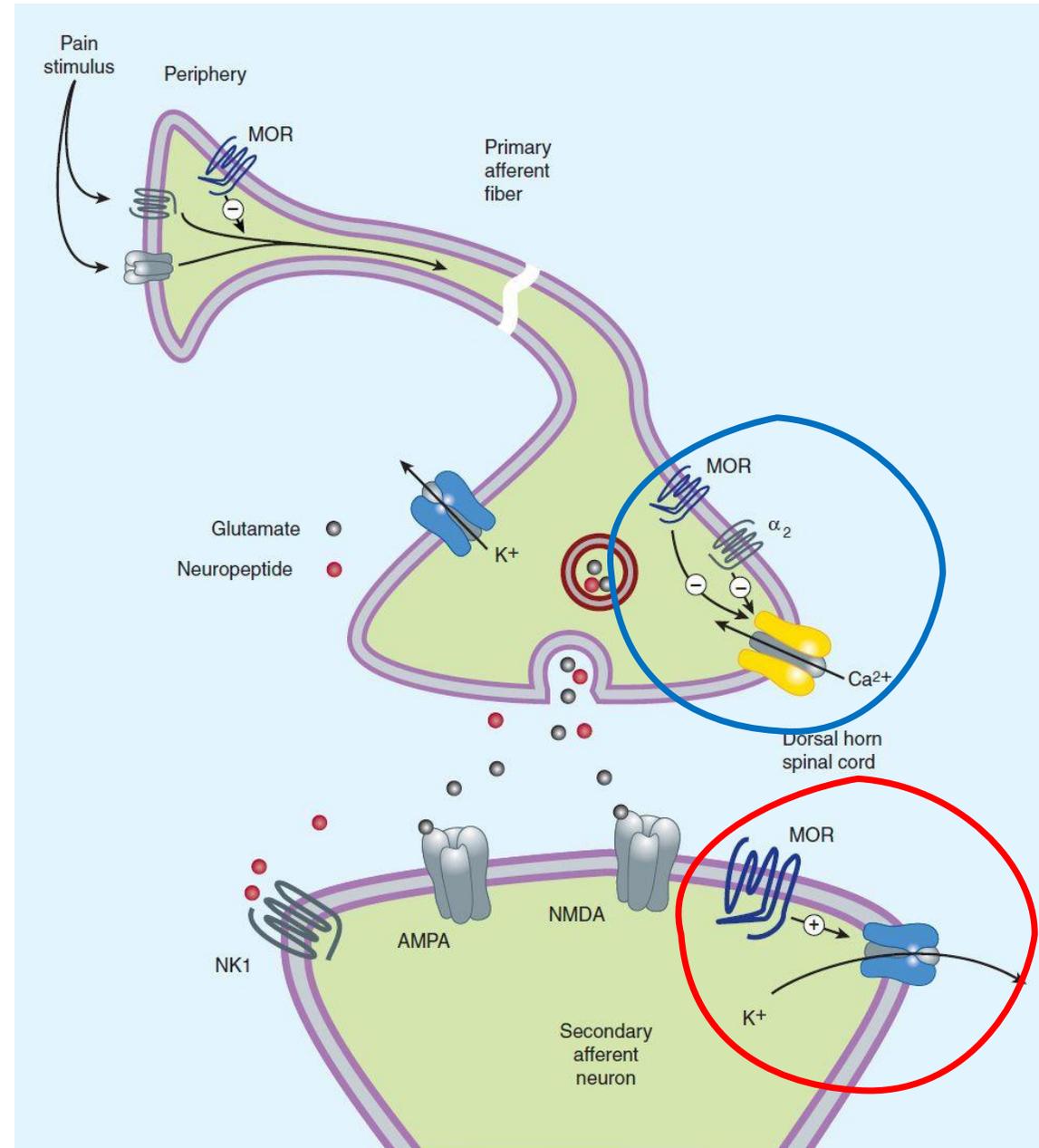
Opioid analgesics



Opioid receptors

- Opioid receptors localized at **presynaptic** neurons
↓ **release of pain neurotransmitters** (substance P & glutamate) mainly through ↓ in Ca^{++} influx
- Opioid receptors localized at **postsynaptic** neurons **decrease firing** through increase in K^+ efflux → hyperpolarization

The net effect of μ receptor activation is to inhibit neuronal activity → so pain transmission is either blocked or diminished



Pharmacological effects of Morphine

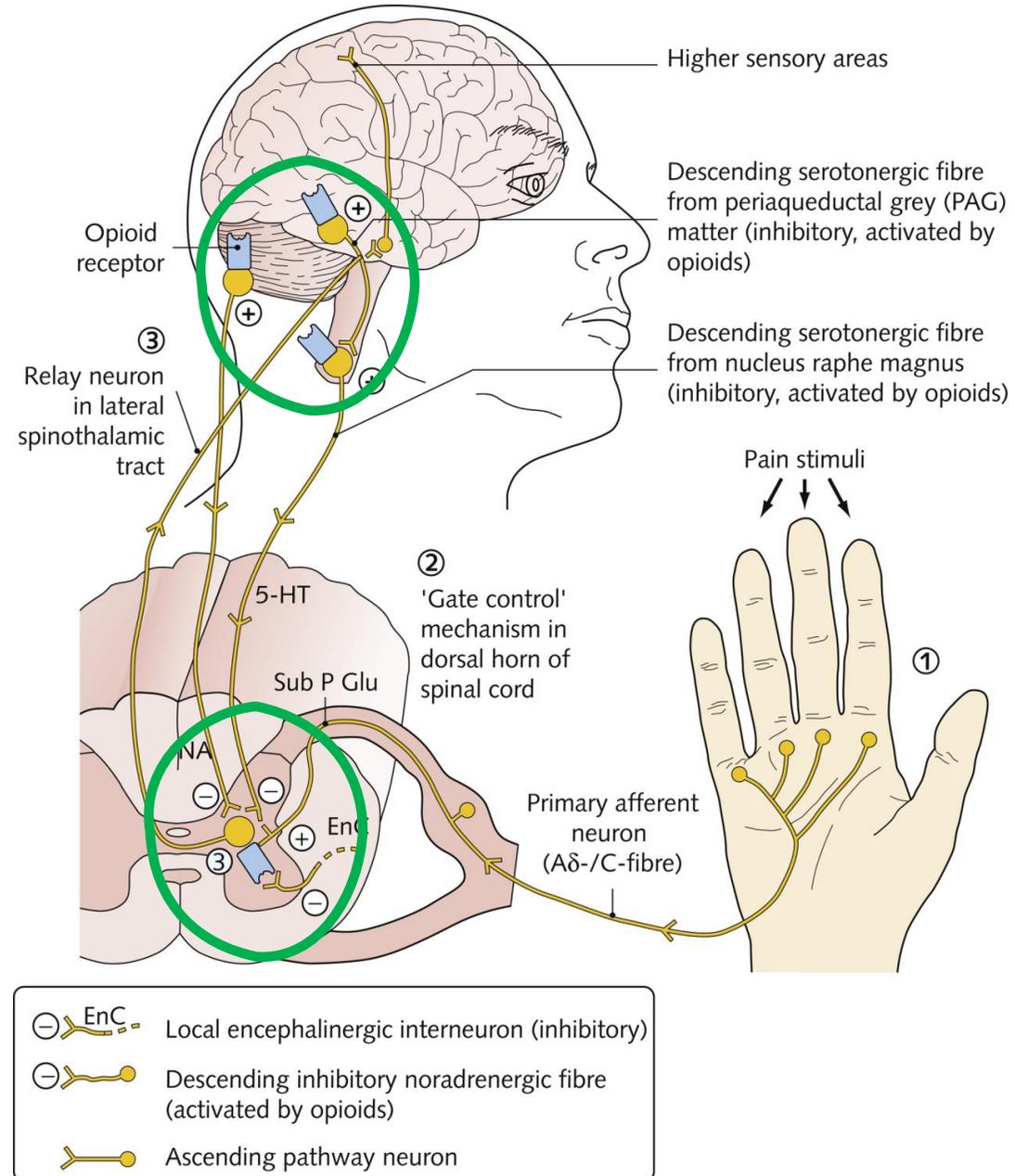
Analgesia

Supra spinal

- Activation of the descending inhibitory tracts

Spinal

- Decrease substance P & glutamate release from presynaptic neuron
- Hyperpolarization of the post synaptic neuron



Question

A 34-year-old woman was admitted to the emergency department because of multiple fractures sustained in a car accident. The patient complained of severe pain, and an **intramuscular injection of morphine** was given. Which of the following molecular actions most likely **mediated the analgesic effect of the drug** in this patient?

- A. Opening of Ca^{2+} channels on presynaptic nerve terminals
- B. Closing of chloride channels on postsynaptic neurons
- C. Stimulation of substance P release from nociceptive nerve terminals
- D. Opening of K^{+} channels on postsynaptic neurons
- E. Closing of Na^{+} channels on presynaptic nerve terminals
- F. Stimulation of glutamate release from nociceptive nerve terminals

Question

A 61-year-old woman complained of severe pain a few hours after surgery for renal cancer. An intramuscular injection of **morphine** was given. Which of the following actions most likely contributed to the **analgesic effect** of morphine?

- A. Activation of brain stem neurons that modulate pain transmission
- B. Stimulation of substance P release from nerve terminals in the spinal cord
- C. Induction of dissociative feeling and dysphoria
- D. Inhibition of adrenergic pathways from the locus ceruleus
- E. Inhibition of serotonergic pathways from the raphe nuclei

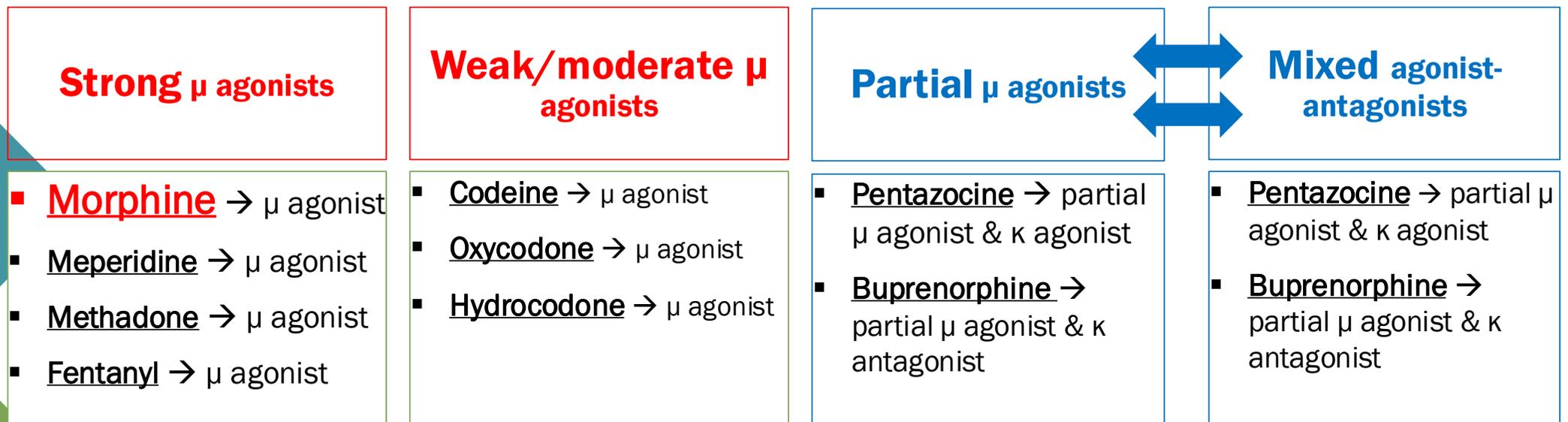
Question

A	Q
<p>A. Buprenorphine</p> <p>B. Codeine</p> <p>C. Fentanyl</p> <p>D. Heroin</p> <p>E. Loperamide</p> <p>F. Methadone</p> <p>G. Morphine</p> <p>H. Naloxone</p> <p>I. Pentazocine</p> <p>J. Propoxyphene</p> <p>K. Tramadol</p>	<ol style="list-style-type: none">1. A partial agonist at μ (mu) opioid receptors and antagonist at κ (kappa) opioid receptors <u>Buprenorphine</u>2. A full opioid agonist with the highest oral bioavailability <u>methadone</u>3. A drug with very weak opioid activity used in the treatment of diarrhea <u>loperamide</u>4. A partial agonist at μ (mu) opioid receptors and full agonist at κ (kappa) opioid receptors <u>pentazosine</u>5. A drug with high affinity but no intrinsic activity at opioid receptors <u>naloxone</u>

Classification of opioid analgesics

- Opioid analgesics can be classified as **full μ agonists**, **partial μ agonists/mixed agonist-antagonists**.
- Based on their analgesic potency, full μ agonists can be further subdivided into **strong** or **moderate** agonists.

N.B. Pure opioid antagonists have no analgesic effects. They are used to counteract the adverse effects of opioid analgesics taken in overdose and for the treatment of opioid dependence.



Question

Morphine, all are true **EXCEPT**:

- A. Acts as an agonist at opioid receptors (especially μ) in the brain and spinal cord
- B. Causes pupillary constriction by stimulation of the Edinger-Westphal nucleus in the mid-brain
- C. Acts as an antihistamine
- D. Is subject to presystemic metabolism
- E. Stimulates the chemoreceptor trigger zone

Question

A 36-year-old man complained of severe abdominal pain after surgery to remove a kidney stone. An **analgesic drug was administered** intramuscularly. Shortly after the administration, an **itchy weal** developed at the injection site, along with **generalized pruritus**. Which of the following drugs was most likely given to the patient?

- A. Morphine
- B. Acetaminophen
- C. Indomethacin
- D. Clonidine
- E. Ibuprofen

Question

A 34-year-old woman complained to her physician of annoying **constipation**. One week earlier, she had developed a sore throat and **a dry, nonproductive cough** and was diagnosed with acute bronchitis. A drug treatment was started, and **the cough gradually disappeared**. Which of the following drugs most likely caused the constipation reported by the patient?

- A. Buprenorphine
- B. Fentanyl
- C. Albuterol
- D. Codeine
- E. Theophylline
- F. Morphine

Question

A young man is brought to the emergency department in an **anxious** and **agitated** state. He informs the attending physician that he uses “street drugs” and that he gave himself an intravenous “fix” approximately 12 h ago. He now has **chills** and **muscle aches** and has also been **vomiting**. The attending physician notes that his **pupil size is larger than normal**. What is the most likely cause of these signs and symptoms?

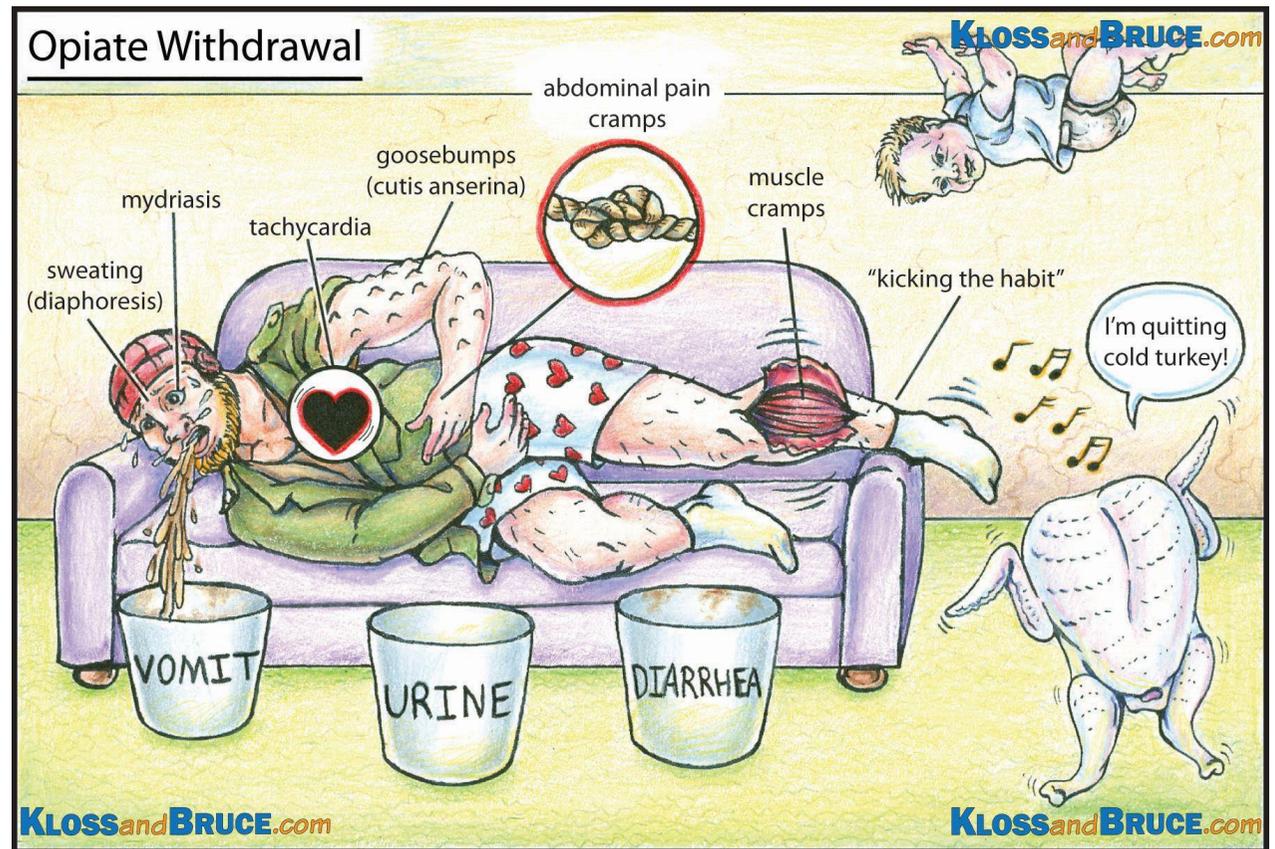
- (A) The patient had injected amphetamine
- (B) The patient has hepatitis B
- (C) The patient has overdosed with an opioid
- (D) The signs and symptoms are those of the opioid withdrawal syndrome
- (E) These are early signs of toxicity due to contaminants in “street heroin”

Opioid withdrawal syndrome

A state of irritable and sometimes aggressive behavior, plus:

- Fever and sweating
- Tachycardia.
- Nausea and vomiting.
- Pupillary dilation is an important sign of opioid withdrawal (X opioid intoxication causes pinpoint pupils).
- Piloerection.
- Abdominal cramps and diarrhea.

Opioid withdrawal is not life-threatening.



Question

Which drug will be most effective in **alleviating the symptoms** experienced by the patient in the previous case?

- (A) Naloxone
- (B) Codeine
- (C) Methadone
- (D) Naltrexone
- (E) Tramadol

Antiepileptic drugs

Antiepileptic drugs

Drugs that inhibit Voltage-gated Na^+ channels >> use-dependent

Phenytoin

Carbamazepine

Valproic acid

Lamotrigine

Drugs that inhibit T-type Ca^{++} channels

Ethosuximide

Drugs that potentiate GABA activity

Stimulate GABA/ Cl^- receptor complex

Block GABA reuptake >> Tiagabine

GABA-mimetics >> Gabapentin & Pregabalin

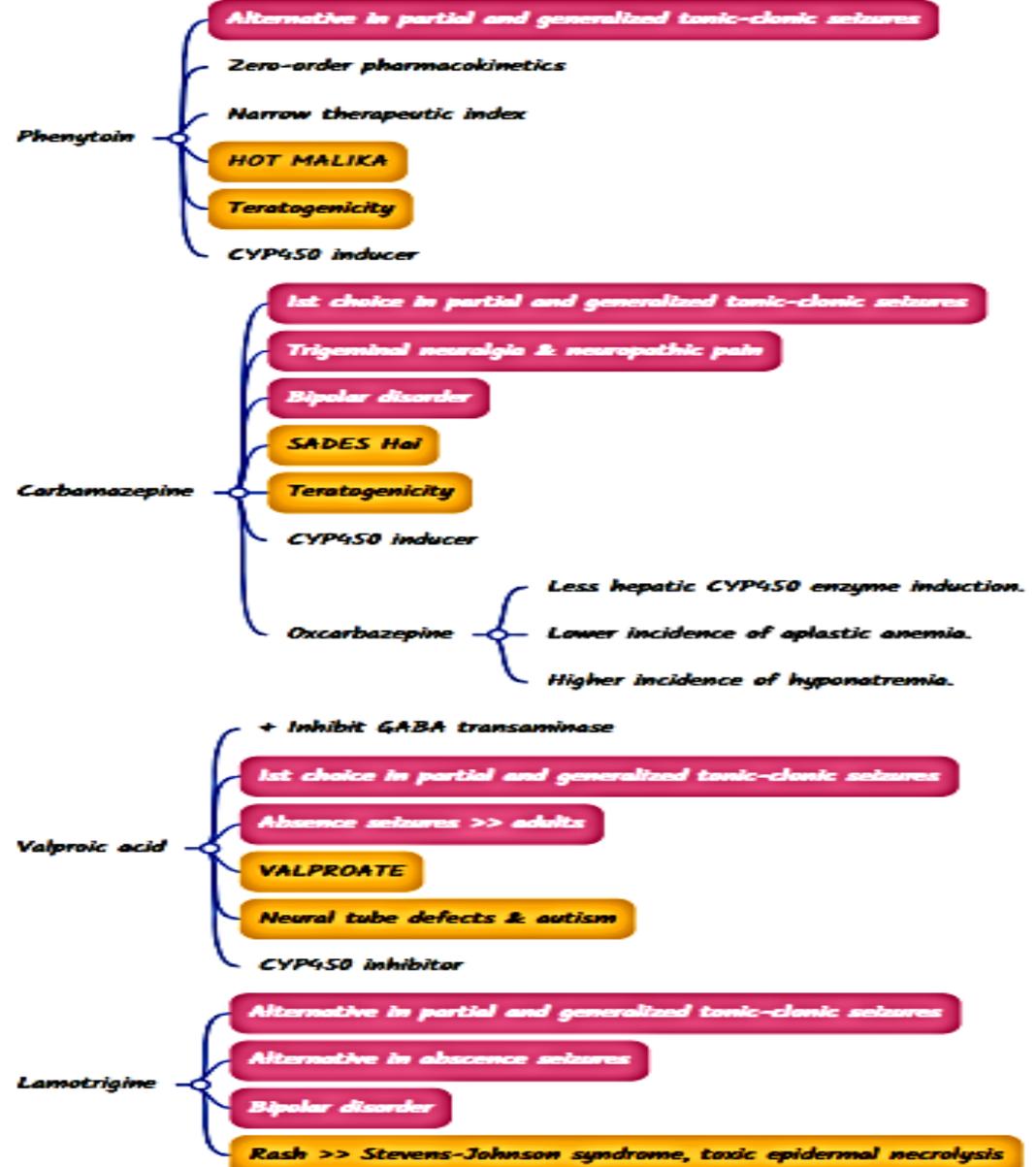
Decrease GABA degradation >> Vigabatrin

Antiepileptic drugs

Upgrade Now

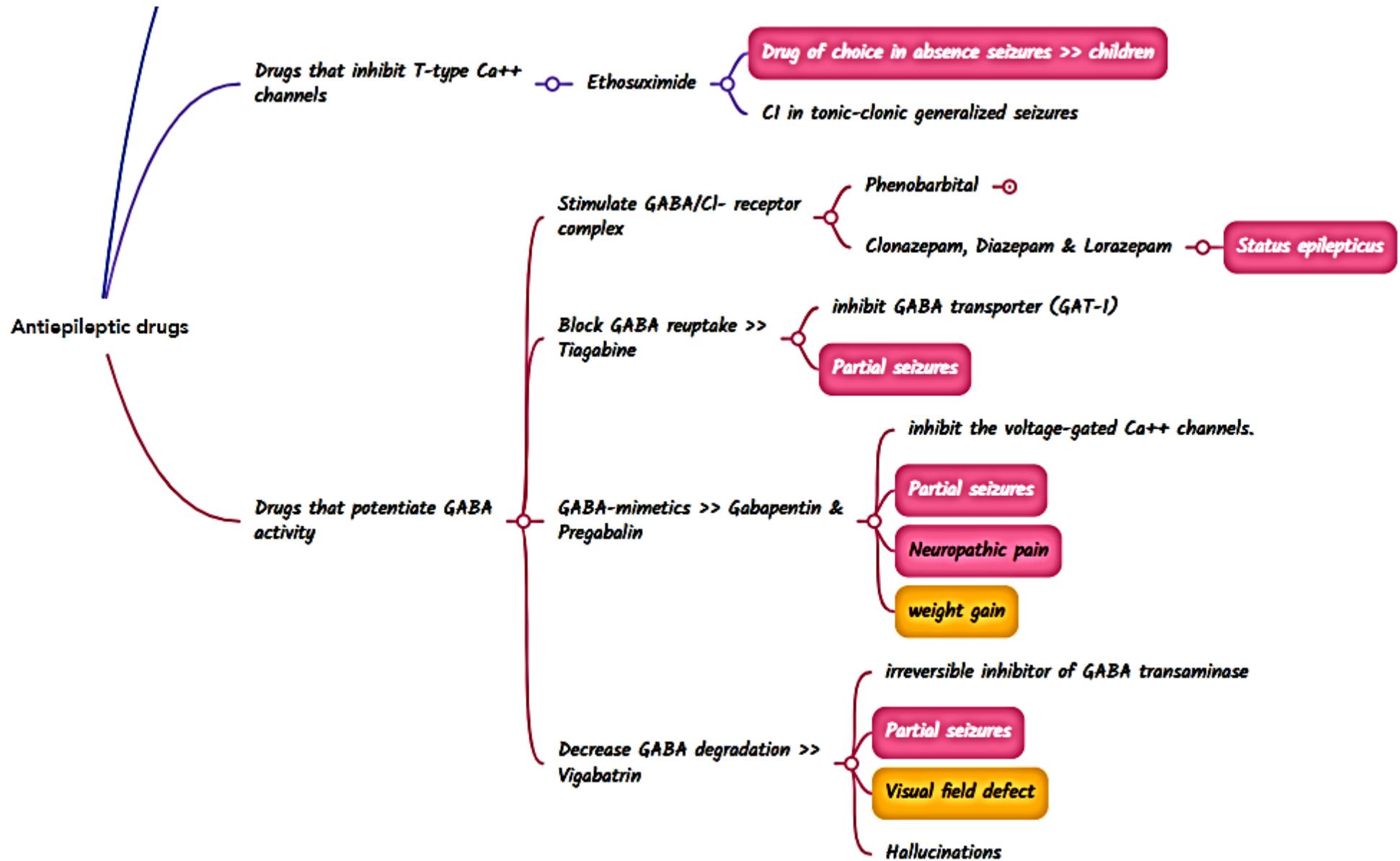
Antiepileptic drugs

Drugs that inhibit Voltage-gated Na⁺ channels >> use-dependent



Drugs that inhibit T-type Ca²⁺

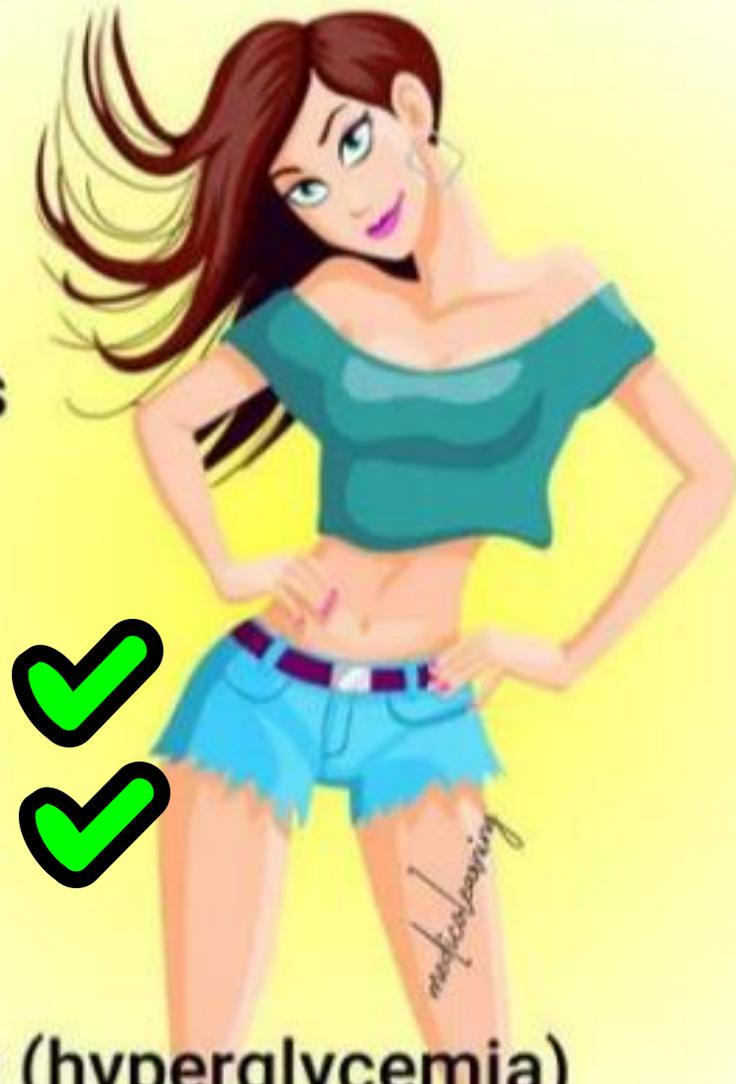
Antiepileptic drugs



Adverse Effect Of Phenytoin

mnemonic : **HOT MALIKA**

- **H**irsutism ✓
 - **H**ypertrophy of gums
- **O**steomalacia ✓
- **T**eratogenicity ✓
- **M**egaloblastic anemia ✓
- **A**taxia and nystagmus ✓
- **L**ymphadenopathy
- **I**nhibits insulin release (hyperglycemia) ✓



Carbamazepine side effects

SADES Hai

S ✓ Steven-Johnson syndrome / Rashes

A ✓ Aplastic Anemia (Agranulocytosis)

D ✓ Diplopia, Ataxia (Neurotoxic)

E Eosinophilia

S ✓ SIADA (Dilutional hyponatremia)

Hai Hepatotoxic

MNEMONIC

Valproate Side Effects (VALPROATE)

Vomiting

Alopecia

Liver toxicity

Pancreatitis/pantcytopenia

Retention of fat (weight gain)

Oedema (edema)

Appetite increase

Tremor/thrombocytopenia

Enzyme inhibitor (liver)



Question

A 37-year-old woman was at a routine neurology clinic visit. The woman had a long history of refractory grand mal epilepsy. She was being treated with several drugs, but with poor results. The neurologist decided to prescribe **phenytoin**. Blockade of which of the following types of **ion channels is most likely to mediate the therapeutic efficacy** of the drug in the patient's disease?

- A. Na⁺ channels in the resting state
- B. Na⁺ channels that open and close at high frequency
- C. Na⁺ channels that open and close at low frequency
- D. K⁺ channels in a resting state
- E. K⁺ channels that open and close at high frequency
- F. K⁺ channels that open and close at low frequency

Question

The mechanism of antiseizure activity of **carbamazepine** is:

- (A) Block of sodium ion channels
- (B) Block of calcium ion channels
- (C) Facilitation of GABA actions on chloride ion channels
- (D) Glutamate receptor antagonism
- (E) Inhibition of GABA transaminase

Question

Which statement concerning the proposed **mechanisms of action of anticonvulsant drugs** is most accurate?

- (A) Benzodiazepines facilitate glutamate-mediated inhibitory actions
- (B) Ethosuximide selectively blocks potassium ion (K^+) channels in thalamic neurons
- (C) Phenobarbital produces a selective blockade of calcium ion (Ca^{2+}) channels
- (D) Phenytoin prolongs the inactivated state of the Na^+ channel
- (E) Zonisamide blocks voltage-gated K^+ channels

Question

A 37-year-old man recently diagnosed with generalized seizures started treatment with valproic acid, but 1 month later the frequency of seizures was not significantly reduced. His neurologist decided to add a second-generation antiepileptic drug that blocks voltage-gated Na⁺ channels and may inhibit the synaptic release of glutamate. Which of the following drugs was most likely prescribed?

- A. Gabapentin**
- B. Lamotrigine**
- C. Phenobarbital**
- D. Diazepam**
- E. Ethosuximide**
- F. Felbamate**

Question

Which statement about **phenytoin** is accurate?

- (A) Displaces sulfonamides from plasma proteins
- (B) Drug of choice in myoclonic seizures
- (C) Half-life is increased if used with phenobarbital
- (D) Isoniazid (INH) decreases steady-state blood levels of phenytoin
- (E) Toxic effects may occur with only small increments in the dose

Question

A 32-year-old woman complained to her physician that two breakthrough seizures occurred last week. One month earlier the woman was diagnosed with simple partial seizure and started treatment with an antiepileptic drug. The physician increased the dose of the drug, thinking that the decreased effect was most likely because the drug is **a potent enzyme inducer and can induce its own metabolism**. Which of the following drugs did the patient most likely take?

- A. Valproic acid
- B. Carbamazepine
- C. Lamotrigine
- D. Ethosuximide
- E. Clonazepam

Question

A 26-year-old woman discovered she was **unexpectedly pregnant**. She had been regularly **taking an oral contraceptive medication** for several years. Two months earlier, she was **diagnosed with complex partial seizures** and started the prescribed therapy. Which of the following drugs was she most likely taking?

- A. Lamotrigine
- B. Valproic acid
- C. Clonazepam
- D. Gabapentin
- E. Levetiracetam
- F. Carbamazepine

Question

A 50-year-old man complained of occasional episodes of excruciating **unilateral facial pain that arose near the mouth, diffused toward the nostrils and eyes**, and seemed to be triggered by eating or talking. The pain lasted about 1 minute. He was referred to a neurologist, who made a presumptive diagnosis and ordered an appropriate treatment . Which of the following drugs would be appropriate for this patient?

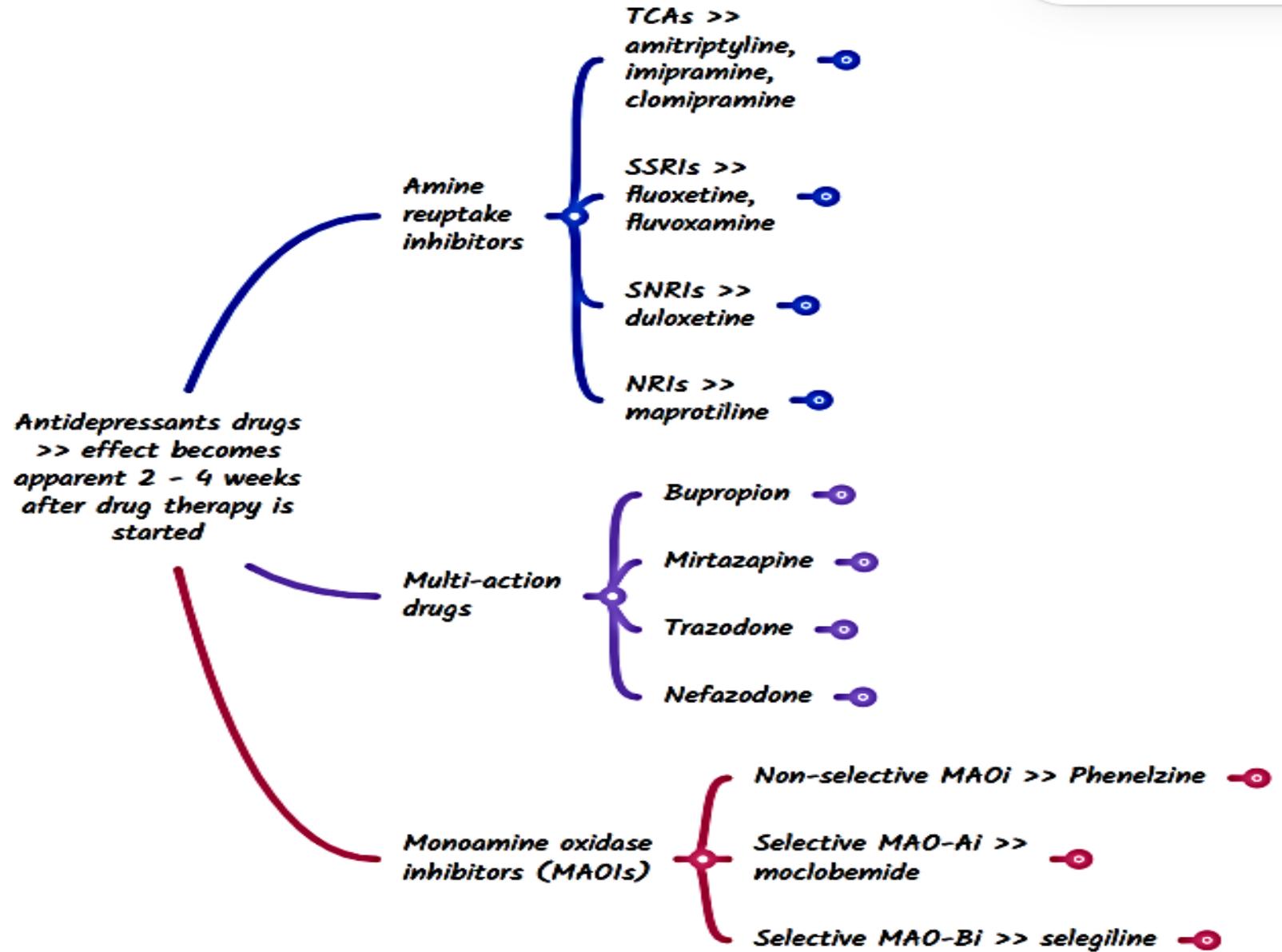
- A. Phenobarbital
- B. Clonazepam
- C. Codeine
- D. Diclofenac
- E. Carbamazepine

Question

A 36-year-old woman recently diagnosed with simple partial seizures started a therapy with **lamotrigine**. Which of the following adverse effects is most likely to occur during the therapy?

- A. Macrocytic anemia
- B. Hallucinations
- C. Liver cirrhosis
- D. Pancreatitis
- E. Lupoid syndrome
- F. Erythematous skin rash

Antidepressants



Antidepressants

Amine reuptake inhibitors

TCA's >>
amitriptyline,
imipramine,
clomipramine

↓ neuronal reuptake of NE and SHT

Block muscarinic receptors → Dry mouth, blurred vision & urine retention

Block α_1 -adrenergic receptor → Orthostatic hypotension

Block of H1 receptors → Sedation

Weight gain

Cardiac arrhythmias >> ttt w NaHCO₃

SSRIs should not be used with MAOIs → Serotonin syndrome

SSRIs >>
fluoxetine,
fluvoxamine

Selectively block the neuronal reuptake of SHT → Sexual dysfunction

SSRIs should not be used with MAOIs → Serotonin syndrome

SNRIs >>
duloxetine

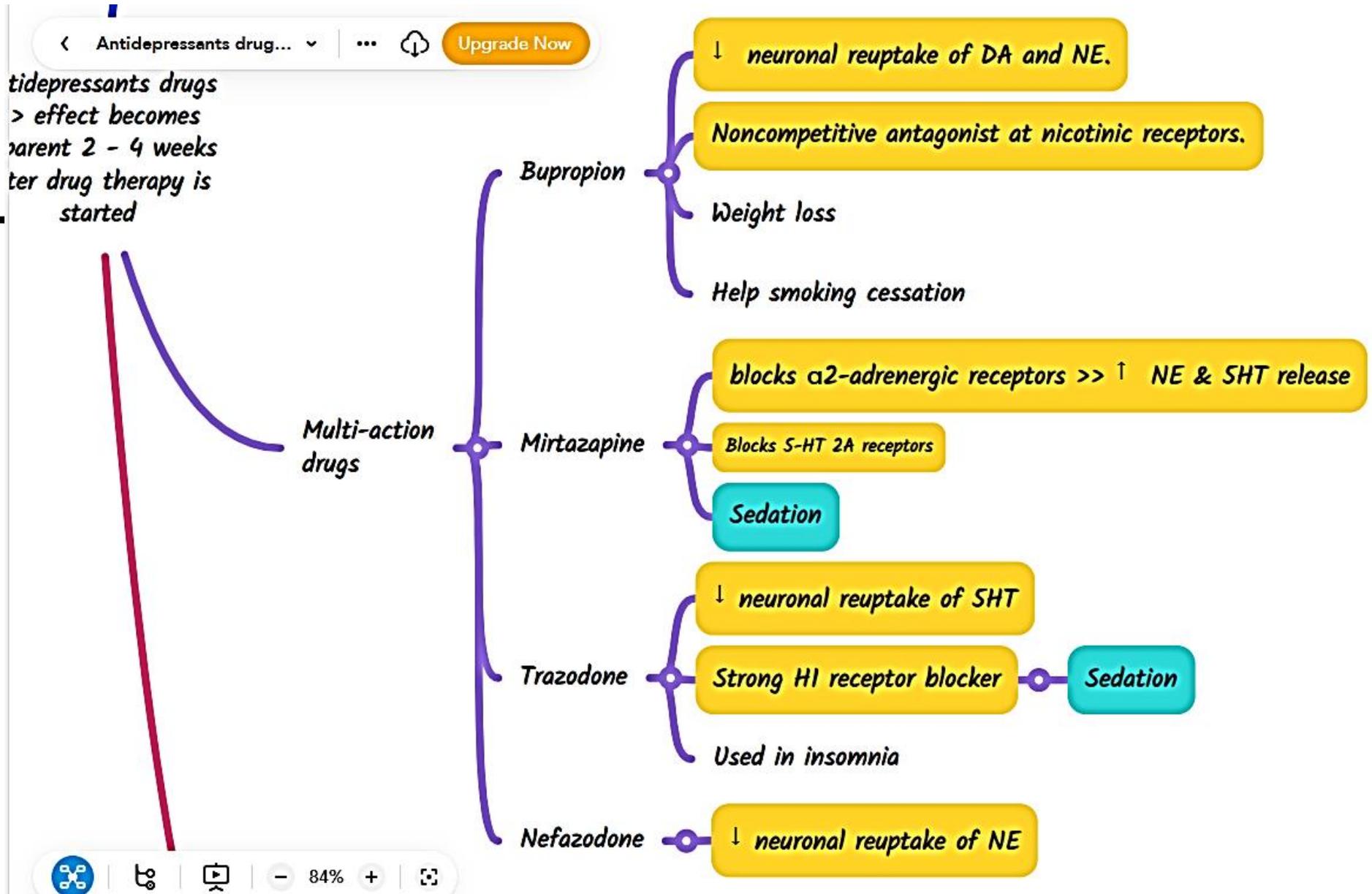
↓ neuronal reuptake of NE and SHT

SSRIs should not be used with MAOIs → Serotonin syndrome

NRIs >>
maprotiline

↓ neuronal reuptake of NE

Antidepressants



Antidepressants

Monoamine oxidase inhibitors (MAOIs)

Non-selective MAOI >> Phenelzine — Irreversible

Selective MAO-Ai >> moclobemide — Reversible — metabolizes 5HT

Selective MAO-Bi >> selegiline — metabolizes DA >> Used in Parkinson disease

interact with SSRIs & TCAs — Serotonin syndrome

Cheese reaction

Question

A patient under treatment for a major depression is brought to the emergency department after ingesting **30 tablets of imipramine**. Which of the following would be **LEAST** useful?

- (A) Administer bicarbonate to correct acidosis.
- (B) Administer lidocaine to control cardiac arrhythmias.
- (C) Initiate hemodialysis to hasten drug elimination.
- (D) Maintain heart rhythm by electrical pacing
- (E) Use intravenous diazepam to control seizures

Question

A 36-year-old woman presents with symptoms of major depression. Drug treatment is to be initiated with **sertraline**. In your information to the patient, you would tell her that:

- (A) Sertraline may take 2 wk or more to become effective
- (B) It is preferable that she take the drug in the morning
- (C) Insomnia is likely to decrease with continued use
- (D) She should notify you if she anticipates using other prescription drugs
- (E) All of the above

Question

Which drug is **an antagonist at 5-HT₂ receptors** and can be used for the management of **insomnia**?

- (A) Estazolam
- (B) Flurazepam
- (C) Trazodone
- (D) Triazolam
- (E) Zolpidem

Question

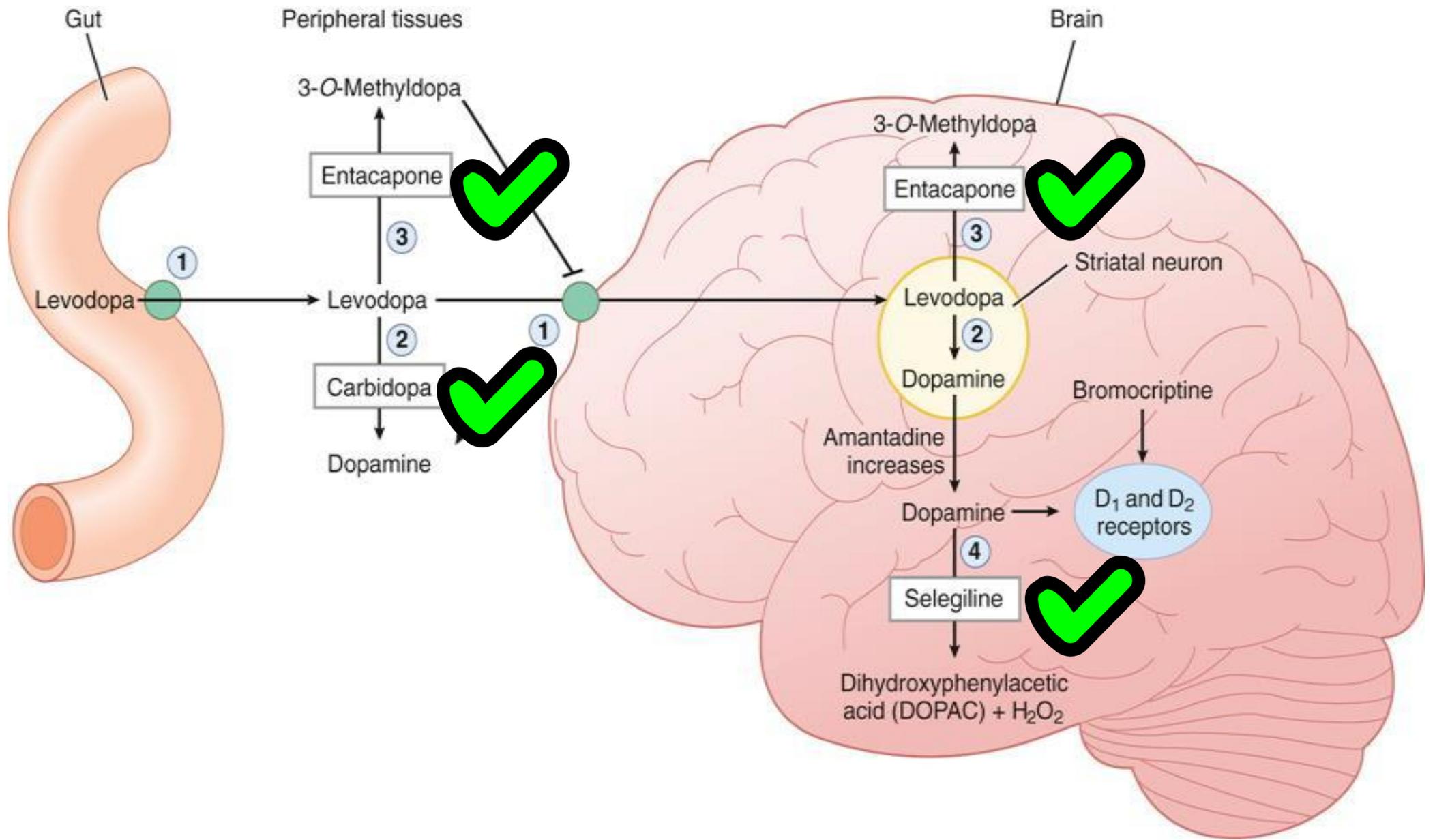
17-year-old girl was admitted to **an eating disorder** clinic with a 3-month history of binge eating and vomiting and purging episodes occurring from twice per week to four times a day. After physical examination and lab tests, psychotherapy and a drug treatment were prescribed. Which of the following drugs would be appropriate for this patient?

- A. Fluoxetine
- B. Diazepam
- C. Phenobarbital
- D. Haloperidol
- E. Clozapine
- F. Lithium

Question

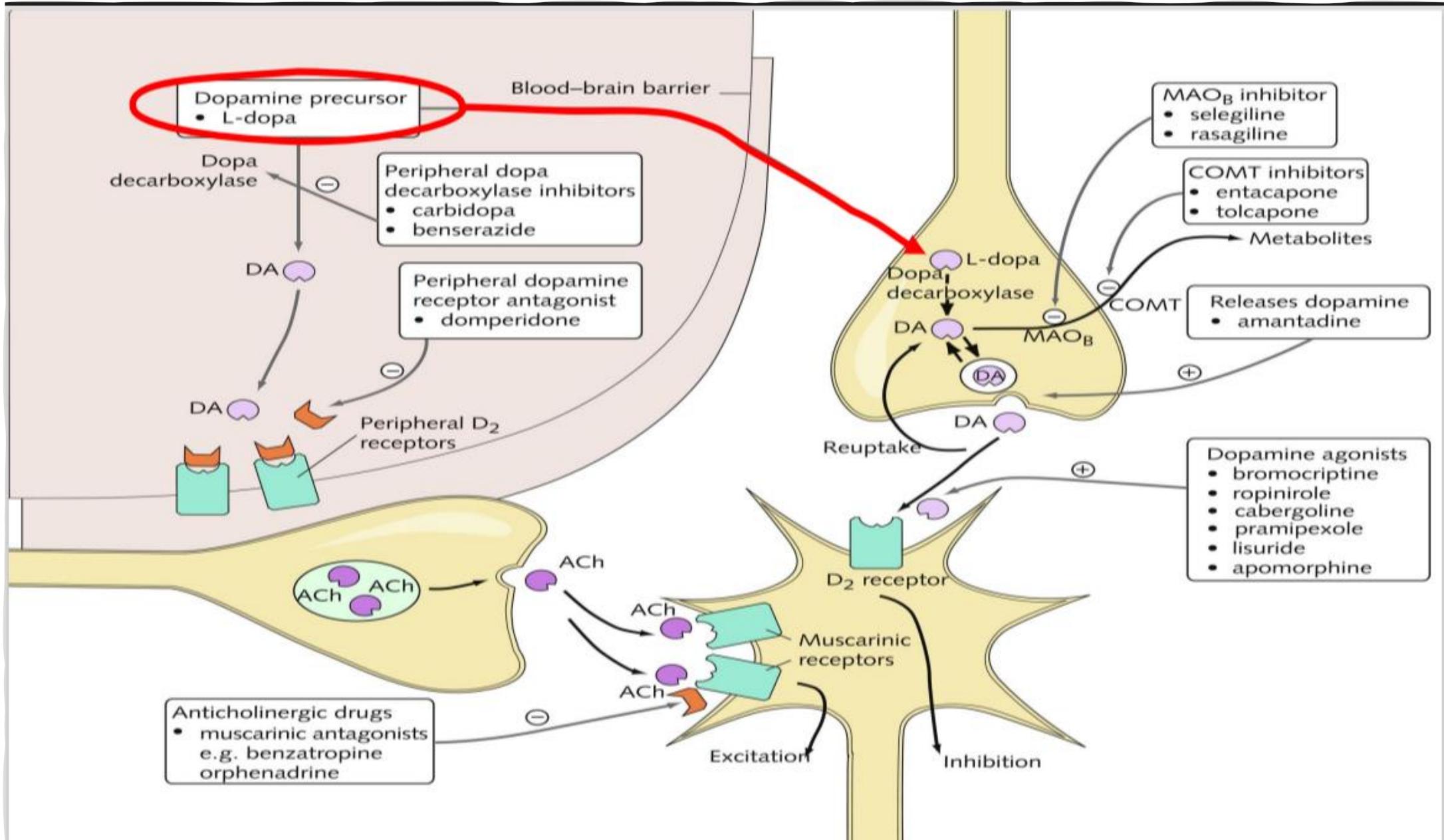
A 38-year-old man complained to his physician that the drug he was taking was effective in relieving his anxiety but caused a disturbing adverse effect. The patient had been recently diagnosed with a social anxiety disorder and started treatment with **venlafaxine** 2 weeks ago. Which of the following **adverse effects** did the patient most likely experience?

- A. Obstinate constipation
- B. Negligible orgasm during intercourse
- C. Urge urinary incontinence
- D. Dizziness and vertigo upon standing
- E. Dry mouth, most of the day
- F. Difficulty in near vision



SIDE EFFECTS OF LEVODOPA

- ✓ **D**yskinesia
- ✓ **O**n-off phenomenon
- ✓ **P**sychosis
- ✓ **A**BP drop
- M**outh dryness
- I**nsomnia
- ✓ **N**ausea/vomiting
- E**xcessive daytime sleepiness



Question

A 62-year-old man complained to his physician of **facial grimacing, lip smacking, and rocking of the trunk** that occurred 1 to 2 hours after taking his prescribed medication. The man, who suffered from Parkinson disease, had been receiving **an antiparkinsonian drug** for 3 years. Which of the following drugs most likely caused the adverse effects reported by the patient?

- A. Selegiline
- B. Levodopa
- C. Entacapone
- D. Amantadine
- E. Benztropine

Question

Tolcapone may be of value in patients being treated with levodopa-carbidopa because it

- (A) Activates COMT
- (B) Decreases the formation of 3-O-methyldopa
- (C) Inhibits monoamine oxidase type A
- (D) Inhibits neuronal reuptake of dopamine
- (E) Releases dopamine from nerve endings

Question

With respect to pramipexole, which of the following is most accurate?

- (A) Activates brain dopamine D2 receptors**
- (B) Effective as monotherapy in mild parkinsonism**
- (C) May cause postural hypotension**
- (D) Not an ergot derivative**
- (E) All of the above**

Thank you

