Antianxiety & Antidepressant drugs

Classification of sedative-hypnotic drugs

1-Benzodiazepines:	• Diazepam
2-Barbiturates:	• Phenobarbital
3-Other anxiolytic drugs:	• Buspirone
4- Other newer hypnotic drugs:	• Zolpidem, Zaleplon, Eszopiclone, Ramelteon
5-Antihistamines:	• Diphenhydramine

Classification of Antidepressant drugs:

I. The amine reuptake inhibitors	• Tricyclic antidepressants (TCAs) • Selective serotonin reuptake inhibitors (SSRIs) • Serotonin and norepinephrine reuptake inhibitors (SNRIs) • Norepinephrine reuptake inhibitors (NRIs) → maprotiline
II. The multi-action drugs (atypical antidepressants)	
III. monoamine oxidase inhibitors (MAOIs) (Last option)	

Case 1

- *A 35-year-old woman comes to her physician complaining of not being able to sleep for the past week.*
- *She is prescribed zolpidem to be taken at bedtime.*

1) Classify zolpidem and what is its mechanism of action?

2) What are the advantages of zolpidem?

- ***Answers:***

Q1	• *Zolpidem is* ***new agent have largely replaced older benzodiazepines*** *for the treatment of insomnia.* • ***MOA:*** *the same as benzodiazepine but have a different allosteric binding site*
Q2	• ***Advantage of newer drugs as hypnotics :*** a) *Less adverse effects than the older benzodiazepine* b) *Less tolerance and dependence.* c) *Shorter duration of action so less sedation and hangover.* d) *More selective on GABA A receptors*

Case 2

- *A 23-year-old male college student is brought to the ER because he cannot be aroused.*
- *The patient has a history of depression, and he has been acting depressed over his classes lately. He has a prescription for lorazepam for anxiety and insomnia.*

1) You suspected lorazepam overdose, What drug is used in treating a benzodiazepine toxicity and describe its mechanism?

- ***Answers:***

Q1	• ***Flumazenil*** ➢ *Competitive antagonist at **benzodiazepine receptors.*** ➢ *Speed recovery from benzodiazepines effects in anesthetic & diagnostic procedures.*

Case 3

- *A 39-year-old woman is taking fluoxetine for major depression*

1) What is the mechanism of action?

2) What are the adverse effects?

- ***Answers:***

Q1	• ***Mechanism of Action:*** ➢ *SSRIs selectively block the neuronal reuptake of 5HT → causing immediate ↑ in the synaptic concentration of 5HT.*
Q2	• ***Adverse effects:*** ➢ ***Nervousness, dizziness, and insomnia** → decrease with continued use* ➢ *Occasionally cause male **sexual dysfunction** → priapism and impotence → major cause of discontinuation.* ➢ *SSRIs should not be used with MAOIs → the combination can **serotonergic syndrome.***

Case 4

- *A 48-year-old man has developed depression after the death of his wife.*
- *He is prescribed venlafaxine.*

1) What is the mechanism of action?

2) What side effects might this patient expect with venlafaxine?

- ***Answers:***

Q1	• ***Mechanism of Action:*** ➢ *SNRIs block the neuronal reuptake of 5HT & NE → causing immediate ↑ in the synaptic concentration of 5HT & NE.*
Q2	• ***Adverse effects*** *→ like that of SSRIs*

MCQ

1. *A 43-year-old man with severe hepatic cirrhosis requires a sedative for insomnia. Which of the following sedatives would be the best choice for this patient?* *a. Phenobarbital* *b. Diazepam* *c. Lorazepam* *d. Secobarbital* *e. Flurazepam*	**C**
2. *32-year-old woman is taking ramelteon for chronic insomnia. Ramelteon binds to:* *A. melatonin receptors M1 and M2.* *B. muscarinic receptors M3.* *C. nicotinic receptors.* *D. α1-adrenergic receptors.* *E. D2 dopaminergic receptors.*	**A**

3. 24-year-old stockbroker has developed a "nervous disposition." He is worries about minor matters, and sometimes complains of stomach cramps. There is no history of drug abuse. Diagnosed as suffering from generalized anxiety disorder, he is prescribed buspirone. The patient should be informed to anticipate *(A) A need to continually increase drug dosage because of tolerance* *(B) A significant effect of the drug on memory* *(C) Additive CNS depression with alcoholic beverages* *(D) That the drug is likely to take a week or more to begin working* *(E) That if he stops taking the drug abruptly, he will experience withdrawal signs*	***D***
4. Which of the following best describes the mechanism of action of benzodiazepines? *a) Activate GABAB receptors in the spinal cord* *b) Block glutamate receptors in hierarchical neuronal pathways in the brain* *c) Increase frequency of opening of chloride ion channels coupled to GABAA receptors* *d) Inhibit GABA transaminase to increase brain levels of GABA* *e) Stimulate release of GABA from nerve endings in the brain*	***C***

5. An 82-year-old woman, otherwise healthy for her age, has difficulty sleeping. Triazolam is prescribed for her at one half of the conventional adult dose. Which statement about the use of triazolam in this elderly patient is accurate? *a) Ambulatory dysfunction is unlikely to occur in elderly patients taking one half of the conventional adult dose* *b) Hypertension is a common adverse effect of benzodiazepines in elderly* *c) OTC cold medications may antagonize the hypnotic effects of the drug* *d) The patient may experience amnesia, especially if she also consumes alcoholic beverages* *e) Triazolam does not cause rebound insomnia on abrupt discontinuance*	***D***
6. A 40-year-old woman has sporadic attacks of intense anxiety with marked physical symptoms, including hyperventilation, tachycardia, and sweating. If she is diagnosed as suffering from a panic disorder, the most appropriate drug to use is *(A) Alprazolam* *(B) Eszopiclone* *(C) Flurazepam* *(D) Propranolol* *(E) Ramelteon*	***A***

7. A 34-year-old male patient who was prescribed citalopram for depression has decided he wants to stop taking the drug. When questioned, he said that it was affecting his sexual performance. You find out that he is also trying to overcome his dependency on tobacco products. If you decide to reinstitute drug therapy in this patient, the best choice would be *(A) Amitriptyline* *(B) Bupropion* *(C) Fluoxetine* *(D) Imipramine* *(E) Venlafaxine*	***B***
8. A patient under treatment for a major depressive disorder is brought to the emergency department after ingesting 30 times the normal daily therapeutic dose of imipramine. Which of the following would be least useful? *a) Administer bicarbonate and potassium chloride (to correct acidosis and hypokalemia)* *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*	***C***

9. Concerning the proposed mechanisms of action of antidepressant drugs, which statement is accurate? *a) Bupropion inhibits NE and 5-HT reuptake into nerve endings in the CNS* *b) Chronic treatment with tricyclic antidepressants leads to downregulation of presynaptic autoreceptors* *c) Decreased levels of NE and 5-HT in cerebrospinal fluid is a characteristic of depressed patients before drug therapy* *d) Nefazodone activates 5-HT receptors in the CNS* *e) Selegiline selectively decreases the metabolism of serotonin*	***B***
10. Which of the following is an antidepressant that is acting as an antagonist at 5-HT2 receptors and widely used in (low doses) for the management of insomnia? *(A) Estazolam* *(B) Flurazepam* *(C) Trazodone* *(D) Triazolam* *(E) Zolpidem*	***C***

11. 76-year-old female patient was treated with a benzodiazepine for several weeks after the death of her husband, but she did not like the daytime sedation it caused even at low dosage. Living independently, she has no major medical problems. Because her depressive symptoms are not reduced, you decide on a trial of an antidepressant medication. Which of the following drugs would be the most appropriate choice for this patient? *(A) Amitriptyline* *(B) Citalopram* *(C) Mirtazapine* *(D) Phenelzine* *(E) Trazodone*	***B***
12. Which of the following drugs is most likely to be of value in obsessive compulsive disorders? *(A) Amitriptyline* *(B) Bupropion* *(C) Clomipramine* *(D) Trazodone* *(E) Venlafaxine*	***C***

Analgesics

- **Def:**
  - *Drugs that relieve pain **without** altering consciousness and **without** affecting its cause.*

- **Classified into:**
  - ***Opioids (Narcotic analgesics)***
  - ***Non-opioids:***
    - *Non-steroidal anti-inflammatory (NSAIDs) e.g Aspirin , ibuprofen*
    - *Analgesic antipyretics: e.g. paracetamol*

Narcotic analgesics

- **Classification:**

Strong μ agonists	Weak/moderate μ agonists	Partial μ agonists / Mixed agonist-antagonists
• Morphine • Meperidine • Methadone • Fentanyl	• Codeine • Oxycodone • Hydrocodone	• Pentazocine → partial μ agonist & κ agonist • Buprenorphine → partial μ agonist & κ antagonist

- ***Pharmacological effects:***

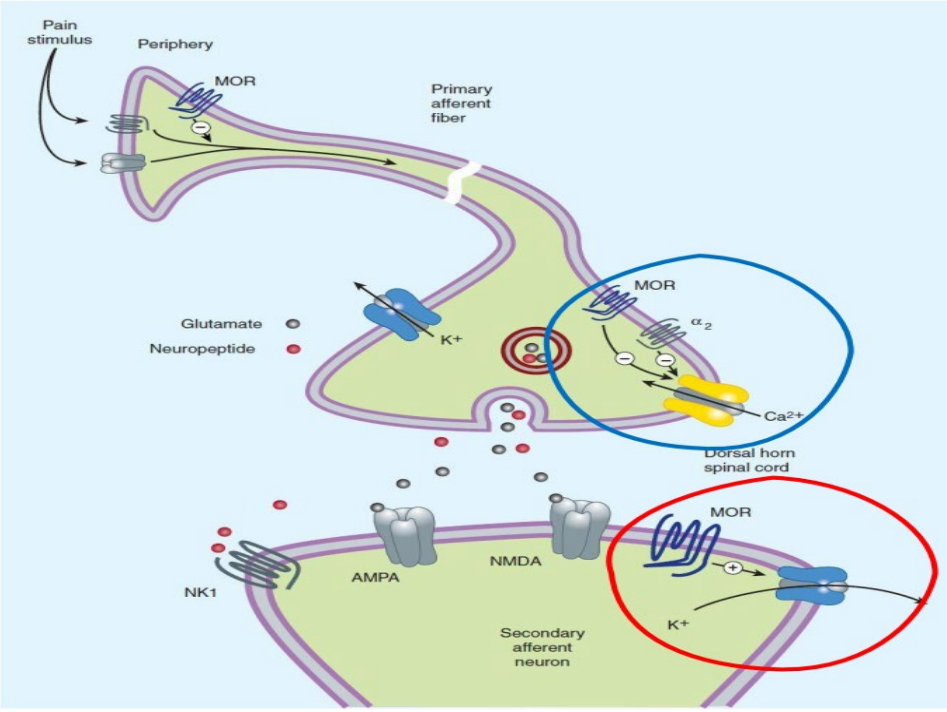
CNS:	• *Analgesia* • *Euphoria* • *Sedation* • *Inhibition of cough reflex (codeine)* • *Tolerance and dependence* • *Respiratory depression* • *Miosis (pinpoint pupil)*
GIT:	• *Constipation* • *Increased biliary sphincter tone and pressure* • *Nausea and vomiting*
Others:	• *CVS: Vasodilation and hypotension* • *Flushing & pruritis* • *Prolongation of labor (except meperidine)* • *Urine retention*

Case 1

- *A 22-year-old man is brought to the emergency room following an injury to his knee. Although he is in considerable pain, it is relieved by a small dose of morphine.*
- *He reports that his pain is still present, but it is less bothersome.*
- *He says the morphine 'feels good'.*

1) What is the mechanism of action for morphine and other opiate ligands to produce analgesia?

Receptors:	• ***There are three major opioid receptor subtypes:*** ***1. μ (MOP)*** ➢ *responsible for most of the analgesic effects of opioids* ➢ *and for major adverse effects* ***2. δ (DOP).*** ***3. κ (KOP)*** → *contribute to analgesia at the spinal level*
MOA:	***1) supraspinal analgesia :*** ➢ *by activation of pain control system* ***2) spinal analgesia :*** ➢ ***presynaptic inhibition*** *by inhibition of Ca Channel and decreasing chemical transmitter release* ➢ ***postsynaptic inhibition*** *by K efflux and hyperpolarization*



2) What are the adverse effects that should be taken into account when treating chronic pain with opiates?

- *Respiratory depression*
- *↑ intracranial tension → CI in patients with closed-head injury*
- *Nausea and vomiting → direct stimulation of the chemoreceptor trigger zone.*
- *Miosis (pupil constriction) → direct stimulation of the Edinger-Westphal nucleus of the oculomotor nerve.*
- *Constipation → increases smooth muscle tone & decreases peristalsis.*
- *Exacerbation of pain in patients with biliary dysfunction or a gallbladder attack. Why??*
- *Pruritis, flushing & bronchospasm → due to histamine release from mast cells.*
- *Tolerance and Dependence*

Case 2

- *A 19-year-old man is brought to the emergency room with a suspected heroin overdose, He is unresponsive and his respiration is depressed.*
- *He was discharged from 30 days in a detoxification program.*
- *Naloxone is administered intravenously.*

1) What is naloxone and why is it effective in this patient?

2) What precautions must be taken with the administration of naloxone?

- ***Answers:***

Q1	• *Naloxone is a pure competitive antagonist that quickly (in seconds to minutes) displaces opioids already bound to receptors and reverses respiratory depression.*
Q2	• ***Should be used cautiously*** *because it also can precipitate withdrawal in dependent subjects.* • *The duration of action of naloxone is relatively short, and it often must be given* ***repeatedly or by continuous infusion.***

Case 3

- *A 30-year-old man has been abusing morphine for some time.*
- *Gradually, He started to increase the dose to achieve the desired effect, until he was found dead in the street.*

1) What is your comment?

➢ ***Tolerance to opioid analgesics***

Definition of Tolerance:	• *A decrease in the pharmacologic effect of opioid analgesics observed after chronic/long-term/repeated drug administration.*

Mechanism:	• *Pharmacodynamic tolerance to all opioid analgesics **(cross-tolerance).*** • *Primarily results from **down-regulation of opioid μ receptors** with repeated opioid administration.* • *Tolerance develops to most of the effects of opioids but not to **miosis and constipation.***

2) What regimen do you recommend for the treatment of opioid dependence?

➢ ***Treatment of opioid dependence:***

	Phase 1	Phase 2
Description	• *Medically supervised opioid withdrawal (detoxification)*	• *Opioid replacement, maintenance, or substitution therapy*
used drugs:	***1) Longer acting opioid agonists:*** *methadone & buprenorphine* ***2) Alpha-2 adrenergic agonists:*** *clonidine.*	***1) Agonists:*** *buprenorphine and methadone.* ***2) Antagonists:*** *naltrexone*

NB:

- ***Naltrexone*** → *As opioid antagonists precipitate withdrawal in patients actively using opioids, medically supervised withdrawal is necessary prior to initiation of naltrexone*

- **Adjunct drugs:**

1) ***Alpha-2 adrenergic agonists (clonidine)*** → *to decrease anxiety associated with opioid withdrawal.*
2) ***Benzodiazepines or other sedating drugs*** → *to treat anxiety and insomnia associated with opioid withdrawal.*
3) ***Anti-diarrheal and antiemetic drugs***
4) ***NSAIDs (naproxen)*** → *to relieve pain.*

Case 4

- *Following surgery for a hip replacement, a 64-year-old woman is treated with a parenteral opiate for pain.*
- *Upon release from the hospital, she is given a prescription for oral oxycodone for pain.*
- *Three days after discharge she is complaining of constipation.*

1) What is the cause of her constipation?

2) What are opioid agonists used as antidiarrheal drugs?

- ***Answers:***

Q1	• *Opioid agonists increase smooth muscle tone & decrease peristalsis.*
Q2	• *Loperamide & Diphenoxylate*

Case 5

- *A 17-year-old boy is brought to the emergency room following an injury to his arm while playing football.*
- *He is administered meperidine by intramuscular injection for pain.*

1) What is meperidine and how does it act as an analgesic?

- ***Answers:***

Q1	• ***Full μ opioid receptor agonist.*** • *The major use of meperidine is for* ***analgesia.*** • ***Equianalgesic*** *compared with morphine,* • *Does not cause* ***constipation or increase biliary pressure*** *→ used in pancreatitis.* • *Does not prolong* ***labor*** *→ used for analgesia in labor.* • *Has atropine like action → ↑ HR → used in* ***inferior MI*** • ***Only short courses are allowed*** *→ accumulation of a toxic metabolite (normeperidine) might cause seizures in patients with renal failure.*

MCQ

1. A 42-year-old man with chronic pain is brought to the emergency room because of over-sedation and respiratory depression while using fentanyl patches. He is given intravenous naloxone. **He is not given oral naloxone because naloxone:** *A. is not absorbed from the GI tract.* *B. undergoes first-pass metabolism in the liver.* *C. is metabolized to an inactive metabolite in the GI lining.* *D. is excreted unchanged in the urine.* *E. is destroyed by the stomach*	**B**
2. A 47-year-old woman is recovering from a hysterectomy. Her physician prescribes an opioid analgesic as needed for postoperative pain. Opioids can cause many effects in addition to analgesia including constipation, respiratory depression, euphoria, miosis, and drowsiness. With prolonged use, tolerance develops to most of these effects. **Which of the following effects persists despite tolerance?** *A. Analgesia* *B. Constipation* *C. Drowsiness* *D. Euphoria* *E. Nausea and vomiting*	**B**

3. A 48-year-old man is being treated with a long-acting opiate for pain associated with terminal cancer. He is also prescribed a transmucosal fentanyl formulation (lollipop) for "breakthrough" pain. ***The transmucosal formulation is an effective analgesic because it:*** *a) avoids first-pass metabolism of fentanyl.* *b) delivers fentanyl directly to opiate receptors in the mouth.* *c) avoids constipation.* *d) avoids respiratory depression.* *e) avoids nausea and vomiting that is associated with the systemic use of fentanyl.*	***A***
4. A 53-year-old man is requesting meperidine for his chronic back pain. His physician is hesitant to use meperidine for the treatment for chronic pain because of *A. metabolite toxicity.* *B. poor oral absorption.* *C. increased addiction potential.* *D. patient non-compliance.* *E. likelihood that meperidine will be diverted for sale on the street*	***A***
5. The morphine metabolite that may be responsible for most of morphine's analgesic activity is: *A. desmethylmorphine* *B. morphine-6-glucuronide* *C. morphine sulfate* *D. N-acetylmorphine* *E. hydroxymorphine*	***B***

6. Which drug does not activate opioid receptors and has been proposed as a maintenance drug in treatment programs for opioid addicts? *A. Fentanyl* *B. Naloxone* *C. Buprenorphine* *D. Naltrexone* *E. Codeine*	***D***

Anti-epileptic Drugs

Seizures

- **Definition:**
  - ***abnormal electrical activity*** *in the brain that may lead to involuntary movements and sensations, which are* ***accompanied by*** *characteristic changes on electroencephalography (EEG).*
- **Classification of seizures:**

Partial (focal),	Generalized
originate at ***a specific focus*** *and do not spread to involve other cortical areas.*	*arise in* ***both cerebral hemispheres****, and accompanied by* ***loss of consciousness.***

- **Classification of anticonvulsant drugs:**

I. Drugs that inhibit Voltage-gated Na+ channels:	• *Phenytoin & Fosphenytoin* • *Carbamazepine & Oxcarbazepine* • *Valproic acid* • *Topiramate* • *Lamotrigine* • *Zonisamide*
II. Drugs that inhibit T-type Ca++ channels:	• *Ethosuximide*
III. Drugs that potentiate GABA activity:	• ***Stimulate GABA/Cl- receptor complex:*** ➢ *Phenobarbital & Primidone* ➢ *Clonazepam, Diazepam & Lorazepam* • ***Block GABA reuptake:*** *Tiagabine* • ***GABA-mimetics:*** ➢ *Gabapentin* ➢ *Pregabalin* • ***Decrease GABA degradation:*** *Vigabatrin*

▪ Clinical uses of anti-convulsant drugs:

Seizure type	1st choice	2nd choice
Partial and generalized tonic clonic seizures	• *Carbamazepine* • *Sodium valproate*	• *Lamotrigine* • *Phenytoin* • *Gabapentin* • *Vigabatrin* • *Phenobarbital*
Absence seizures	• *Ethosuximide (children)* • *Sodium valproate (adults)* • *Lamotrigine*	
Status epilepticus	• *Lorazepam* • *Diazepam*	• *Phenytoin or fosphenytoin* • *Phenobarbital*

▪ Status Epilepticus Treatment:

1. Benzodiazepines	• ***Treatment of choice*** • *The most used → Lorazepam or diazepam (IV).* • *Recently, midazolam (IM) is tried with equal effectiveness.*
2. IV fosphenytoin or phenytoin	• ***A 2nd therapy** if seizures continue.*
3. IV Phenobarbital	• ***An acceptable 2nd therapy** if seizures continue.*

▪ Antiepileptic drugs during pregnancy

- *It is recommended to use the **lowest possible doses** of anticonvulsant drugs during pregnancy.*
- ***Lamotrigine and Levetiracetam** present the lowest level of risk to the fetus considered for use in pregnancy.*
- *If possible, valproate, phenobarbital, and topiramate **should be avoided.***

Case 1

- *A 12-year-old girl has her first tonic-clonic seizure while at school.*
- *Her seizure was preceded by lip smacking and lasted about 1 minute during which she lost consciousness, she was started on carbmazepine.*

1) What is the mechanism of action of carbmazepine?

2) What are the side effects of carbmazepine?

- ***Answers:***

Q1	• *They block the voltage-gated Na+ channels.*
Q2	• ***CNS:*** *Nystagmus, ataxia, diplopia - sedation and vertigo.* • *Allergic reactions, e.g., rash* • ***Hematological effects****, e.g., aplastic anemia* • ***Endocrine effects****, e.g., ↑ ADH secretion → water retention and hyponatremia* • ***Teratogenic effects.***

Case 2

- *An 8-year-old boy presents to the emergency department after seizure-like activity. During class, the teacher noted that the boy stare off for about 45s.*
- *He has done this three times in the past. He would not respond to her during the episode and was confused for about 1 min following it.*

1) What is the most appropriate first-line therapy for this child?

2) what is the mechanism of action of this drug?

3) what are the adverse effects of this drug?

- ***Answers:***

Q1	• *Ethosoximide*
Q2	• *Blocks the low-threshold T-Type Ca++ channels in the thalamus*
Q3	• *Gastrointestinal upset.* • *Drowsiness and mood swings.* • *Rarely, it causes serious bone marrow depression.*

MCQ

1. 28-year-old man is being treated with phenytoin for tonic-clonic seizures. His drug plasma concentration is in the low therapeutic range, and he is still having occasional seizures. ***His dose is increased slightly. Within 2 weeks he is ataxic, lethargic, and has nystagmus.*** ***A repeat of his plasma concentration shows that he is now slightly above the upper limit of the therapeutic range.*** ***The reason for the dramatic rise in his plasma concentration following a modest increase in his dose is most likely because of:*** *A. renal failure.* *B. liver failure.* *C. zero order elimination.* *D. metabolic acidosis.* *E. poor GI absorption of Ca.*	**C**

2. *A 29-year-old woman is being treated with valproic acid for simple partial seizures. She is at risk for developing a rise in her plasma:* *A. calcium.* *B. hepatic transaminases.* *C. blood urea nitrogen (BUN).* *D. potassium.* *E. glucose.*	**B**
3. *A 32-year-old woman is being treated with vigabatrin because her complex seizures have been refractory to all other therapies. Vigabatrin is reserved for use in patients such as this although its availability is restricted due to:* *A. renal failure.* *B. liver failure.* *C. heart failure.* *D. vision loss.* *E. hearing loss.*	**D**
4. *A 16-year-old boy is brought to the urgent care clinic after suffering an episode of lip smacking followed by stiffness and convulsions.* ***His mother explains that this is the third such attack in the past 2 years and that each attack has lasted about a minute.*** ***The pediatrician prescribes carbamazepine control his seizures.*** ***What is the mechanism of action of this agent:*** *A. Inhibition of calcium channels.* *B. Inhibition of potassium channels.* *C. Inhibition of sodium channels.* *D. Potentiation of GABA receptors.* *E. Stimulation of chloride channels.*	**C**

5. An 8-year-old boy presents to the emergency department after seizure-like activity. During class, the teacher noted that the boy stare off for about 45 s. He has done this three times in the past. ***He would not respond to her during the episode and was confused for about 1 min following it.*** ***What is the most appropriate first-line therapy for this child?*** *A. Carbamazepine.* *B. Ethosoximide.* *C. Lamotrigine.* *D. Phenytoin.* *E. Valproic acid.*	***B***
6. A 15-year-old boy presents to clinic for follow-up for his tonic-clonic seizures. He reports that he has not had a seizure in the past 6 months. ***A complete blood count is performed and shows megaloblastic anemia.*** ***The physician told the patient that this was most likely a side effect of his antiseizure medication.*** ***What is the must likely medication he was taking:*** *A. Lamotrigine.* *B. Ethosuximide.* *C. Phenobarbital.* *D. Phenytoin.* *E. Valproic acid.*	***D***

7. 33-year-old woman with seizure disorder, Bipolar disorder, and trigeminal neuralgia presents to her primary care physician for follow-up and treatment She has no new complaints. ***Which of the following medications may serve to treat all of her earlier mentioned problems?*** *A. Carbamazepine.* *B. Ethosuximide.* *C. Fellsamate.* *D. Gabapentin.* *E. Lacosamide.*	***A***
8. Which antiepileptic drug is most likely to elevate the plasma concentration of other drugs administered concomitantly ? *A. Carbamazepine.* *B. Clonazepam.* *C. Phenobarbital.* *D. Phenytoin.* *E. Valproic acid.*	***E***
9. With chronic use in seizure states, the adverse effects of this drug include coarsening of facial features, hirsutism, and gingival hyperplasia: *A. Carbamazepine.* *B. Zonisamide.* *C. Ethosuximide.* *D. Tiagabine.* *E. Phenytoin.*	***E***

10. A 45-year-old man with a history of alcohol abuse was brought to the emergency department after having a seizure. The patient had a witnessed seizure lasting approximately 10 minutes. Upon arrival, he was found to be in status epilepticus. ***What is the first drug of choice?*** *A . Phenobarbital.* *B. Lorazepam.* *C. Lamotrigine.* *D. Valproate.*	***B***