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PHARMACOLOGY

ASSESSMENT #2

Pharmacology Assessment #2:

1. A 6-year-old Caucasian boy with a history of recurrent respiratory infections, failure to thrive, and failure to pass meconium for 72 hours after birth has genotyping performed in order to be considered for a novel treatment for his condition. Gene sequencing shows a G551D mutation in the *CFTR* gene, in which glycine (G) in position 551 is replaced with aspartic acid (D). He does not carry a Phe508del (ΔF508; deletion of phenylalanine at position 508) mutation. Which of the following agent(s) may be used in this patient as a result of these findings?

A) Dornase-alfa
B) Guaifenesin
C) Ivacaftor
D) Lumacaftor + Ivacaftor
E) Elexacaftor+ Ivacaftor + Tezacaftor

The answer is C.

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Drug names	Mechanism of action
Ivacaftor	CFTR potentiator (↑ opening/activity of channel at cell surface)
Lumacaftor	CFTR corrector (↑ shuttling of defective channel to cell surface)
Tezacaftor	CFTR corrector
Elexacaftor	CFTR corrector
Formulations used in clinical practice	When to use
Ivacaftor	**Patients >6 yrs of age with at least one copy of the *G551D-CFTR* mutation**
Lumacaftor + Ivacaftor	Patients who are homozygous for the Phe508del (ΔF508) mutation
Elexacaftor+ Ivacaftor + Tezacaftor	Patients age ≥ 12 years who have ≥ 1 F508del mutation

This patient has cystic fibrosis (CF), an autosomal recessive disorder on chromosome 7 caused by a defective chloride channel.[1]

CF is characterized by chronic bacterial respiratory infections, fat malabsorption secondary to exocrine pancrease insufficiency, infertility in males due to congenital bilateral absence of the vas deferens (CBAVD), and elevated concentrations of chloride in sweat.[2, 3]

Ivacaftor[4, 5, 6, 7]

- One type of mutation responsible for CF, the G551D missense mutation, leads to a glycine that is replaced by an aspartic acid at position 551.
- This enables the cystic fibrosis transmembrane regulator (CFTR) channel to make it to the cell surface, in contrast to sequestration in the RER/cytosol. The CFTR channel is still defective; it's just merely at the correct location on the cell surface.
- Ivacaftor is a CFTR modulator/potentiator that binds to this misfolded channel and increases the probability it will open.
- **Ivacaftor is approved for use in patients >6 yrs of age with at least one copy of the *G551D-CFTR* mutation.**

Lumacaftor/ivacaftor[8, 9]

- Approved for the treatment of CF in patients who are homozygous for the Phe508del (ΔF508) mutation.
- Lumacaftor works by increasing the trafficking of CFTR proteins to the cell surface. Ivacaftor works by enabling the opening of what would otherwise be a dysfunctional chloride channel.[8]

Elexacaftor/ivacaftor/tezacaftor[10, 11, 12, 13, 14]

- Approved by the US FDA for the treatment of cystic fibrosis in patients age ≥ 12 years who have ≥ 1 F508del mutation in the CFTR gene.[10, 12]
- Tezacaftor and elexacaftor are similar to lumacaftor. They are known as "correctors" and help traffic the defective CFTR channel to the cell surface.[11, 13, 14]

Dornase-alfa is a recombinant deoxyribonuclease used in the treatment of CF. It functions as a mucolytic.[15, 16]

Guaifenesin is an over-the-counter mucous expectorant that may be used in CF, although there is no evidence that it is effective for any form of lung disease.[17]

Bottom line: Ivacaftor is approved as a monotherapy CFTR potentiator in patients with at least one G551D mutation. This mutation leads to the misfolded CFTR channel making it to the cell surface instead of sequestration in the RER. Lumacaftor/ivacaftor and elexacaftor/ivacaftor/tezacaftor are combination therapies used in patients with the ΔF508 mutation. Elexacaftor is a potentiator similar to ivacaftor. Lumacaftor and tezacaftor are CFTR correctors that facilitate the trafficking of the channel to the cell surface.

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Lumacaftor + Ivacaftor	Patients who are homozygous for the Phe508del (ΔF508) mutation
Elexacaftor+ Ivacaftor + Tezacaftor	Patients age ≥ 12 years who have ≥ 1 F508del mutation

1) https://ghr.nlm.nih.gov/gene/CFTR

2) https://www.ncbi.nlm.nih.gov/books/NBK546620/

3) https://www.nejm.org/doi/10.1056/NEJMe020070

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3626070/

5) https://err.ersjournals.com/content/22/127/66

6) https://www.ncbi.nlm.nih.gov/pubmed/24656117

7) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4272825/

8) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6650604/

9) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5495103/

10) https://www.ncbi.nlm.nih.gov/m/pubmed/31784874/

11) https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32597-8

12) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5768901/

13) https://pubchem.ncbi.nlm.nih.gov/compound/CFTR-corrector-1

14) https://www.ncbi.nlm.nih.gov/pubmed/30073878

15) https://www.ncbi.nlm.nih.gov/pubmed/27043279

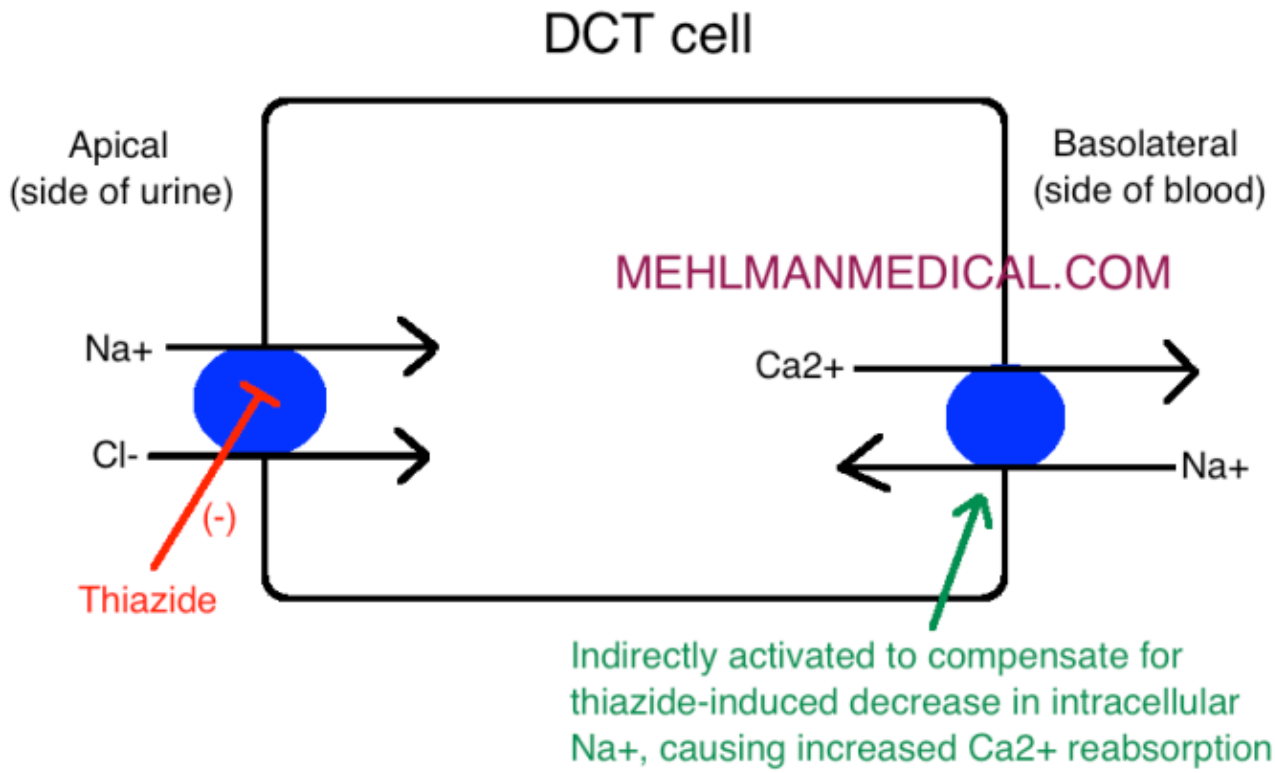
16) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2727891/

17) https://www.ncbi.nlm.nih.gov/pubmed/17594730

2. A 55-year-old man presents with shooting groin pain unlike anything he has ever experienced in his life. He is afebrile and stable. A non-contrast urologic CT shows a small ureteral calculus. The physician recommends copious fluid intake and simple analgesia with the hopes of spontaneous passage. The patient doesn't like this idea and demands medication to decrease the risk of recurrence. The physician discusses with the patient that occasionally diuretic therapy may be attempting to decrease recurrence, however he does not recommend it as this time. Which of the following best describes the target of the diuretic the physician is referring to?

A) Apical; early-distal convoluted tubule (DCT); Na/Cl antiporter
B) Apical; early-DCT; Na/Cl symporter
C) Apical; late-DCT; Na/Cl antiporter
D) Apical; late-DCT; Na/Cl symporter
E) Basolateral; early-DCT; Na/Cl antiporter
F) Basolateral; early-DCT; Na/Cl symporter
G) Basolateral; late-DCT; Na/Cl antiporter
H) Basolateral; late-DCT; Na/Cl symporter

The answer is B.



A general rule about the USMLE is that the more common/quotidian something is (i.e., thiazides are super-common), the more specific of a question they tend to ask about it.

Symporters move ions or solutes in the same direction across a membrane; antiporters move them in the opposite direction.[1]

Apical means on the side of the urine; basolateral means on the side of the blood.[2]

Thiazide diuretics decrease urinary calcium and are frequently used to prevent recurrence of nephro- and ureterolithiasis in patients with hypercalciuria.[3, 4, 5]

They inhibit the Na^+/Cl^+ symporter on the apical membrane of the early-DCT (distal convoluted tubule).[6]

Blockage of the Na^+/Cl^+ symporter causes an increase in Na^+ and water retention in the lumen and therefore a decrease in DCT intracellular Na^+. This causes a compensatory increase in activity of the basolateral Na^+/Ca^{2+} symporter, resulting in increased calcium reabsorption into the interstitium in exchange for Na^+ secretion into the cell.[7, 8]

Chlorthalidone, indapamide, and hydrochlorothiazide (HCTZ) are thiazide diuretics used to decrease stone recurrence.[4]

Bottom line: Thiazides inhibit the Na^+/Cl^+ symporter on the apical membrane of the early-DCT. They decrease urinary calcium and are therefore frequently used to prevent recurrence of nephro- and ureterolithiasis in patients with hypercalciuria.

1) https://books.google.co.jp/books?id=8gpuDwAAQBAJ&pg

2) https://www.ncbi.nlm.nih.gov/books/NBK21502/

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3088497/

4) https://cjasn.asnjournals.org/content/5/10/1893

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3229098/

6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3350128/

7) https://www.ncbi.nlm.nih.gov/books/NBK532918/

8) https://www.ncbi.nlm.nih.gov/pubmed/3330837

3. A 19-year-old man being treated with chemotherapy for testicular cancer presents to hospital with tinnitis and high-frequency hearing loss. His creatinine is 1.8 mg/dL. Diuresis with 0.9% NaCl is initiated. Administration of which of the following agents may have prevented these findings?

A) Mesna
B) N-acetylcysteine
C) Leucovorin
D) Dexrazoxane
E) Amifostine

The answer is E.

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Chemotherapeutic agent	Toxicity (USMLE-important)	Mitigating / cytoprotective agent
Cisplatin	Ototoxicity; nephrotoxicity	Amifostine
Cyclophosphamide	Hemorrhagic cystitis	Mesna
Acetaminophen	Hepatotoxicity	N-acetylcysteine
Methotrexate	Bone marrow, pulmonary fibrosis, hepato- / nephrotoxicity	Leucovorin (folinic acid)
Doxorubicin (adriamycin)	Dilated cardiomyopathy	Dexrazoxane

This man is being treated with **cisplatin,** a platinum-based compound that is one of the first-line chemotherapeutic agents used for testicular cancer.[1]

It is well-known to damage the cochlear stereocilia, thereby causing **ototoxicity.**[2] It is also associated with **nephrotoxicity.**[3]

In an aqueous environment, the chloride ligands of cisplatin are replaced by water molecules. This generates a positively charged electrophilic moiety that damages DNA.[4, 5, 6]

Hydration is essential for all patients to prevent cisplatin-induced nephrotoxicity: [7]

- "Specifically, short-duration, low-volume, outpatient hydration with magnesium supplementation and mannitol forced diuresis (in select patients) represent best practice principles for the safe use of cisplatin."[8]

Amifostine is a cytoprotective adjuvant that decreases incidence of cisplatin-induced toxicity if administered prior to and during cisplatin infusion.[9, 10]

Mesna decreases the risk of hemorrhagic cystitis in patients being treated with cyclophosphamide.[11]

N-acetylcysteine decreases the incidence of severe hepatotoxicity caused by acetaminophen overdose. It regenerates reduced glutathione.[12]

Leucovorin "rescue" (folinic acid) may be used to mitigate myelosuppression, gastrointestinal toxicity, neurotoxicity, and acute kidney injury in patients receiving methotrexate.[13, 14, 15]

Dexrazoxane is a free-radical chelator that decreases the risk of dilated cardiomyopathy in patients receiving doxorubicin.[16]

Bottom line:

MEHLMANMEDICAL.COM		
Chemotherapeutic agent	Toxicity (USMLE-important)	Mitigating / cytoprotective agent
Cisplatin	Ototoxicity; nephrotoxicity	Amifostine
Cyclophosphamide	Hemorrhagic cystitis	Mesna
Acetaminophen	Hepatotoxicity	N-acetylcysteine
Methotrexate	Bone marrow, pulmonary fibrosis, hepato- / nephrotoxicity	Leucovorin (folinic acid)
Doxorubicin (adriamycin)	Dilated cardiomyopathy	Dexrazoxane

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5835297/

2) https://www.ncbi.nlm.nih.gov/pubmed/15721567/

3) https://journals.sagepub.com/doi/abs/10.1177/019262338601400215

4) https://www.pnas.org/content/113/41/11507

5) https://www.ncbi.nlm.nih.gov/pubmed/4831344/

6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3153174/

7) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5423518/

8) ***The Oncologist*** 2017;22:609–619

9) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4022215/

10) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2504739/

11) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4219308/

12) http://www.saudijgastro.com/article.asp?issn

13) https://www.ncbi.nlm.nih.gov/pubmed/8507221

14) http://theoncologist.alphamedpress.org/content/early/2016/08/05/theoncologist.2015-0164.full.pdf

15) https://theoncologist.alphamedpress.org/content/11/6/694.full

16) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4168851/

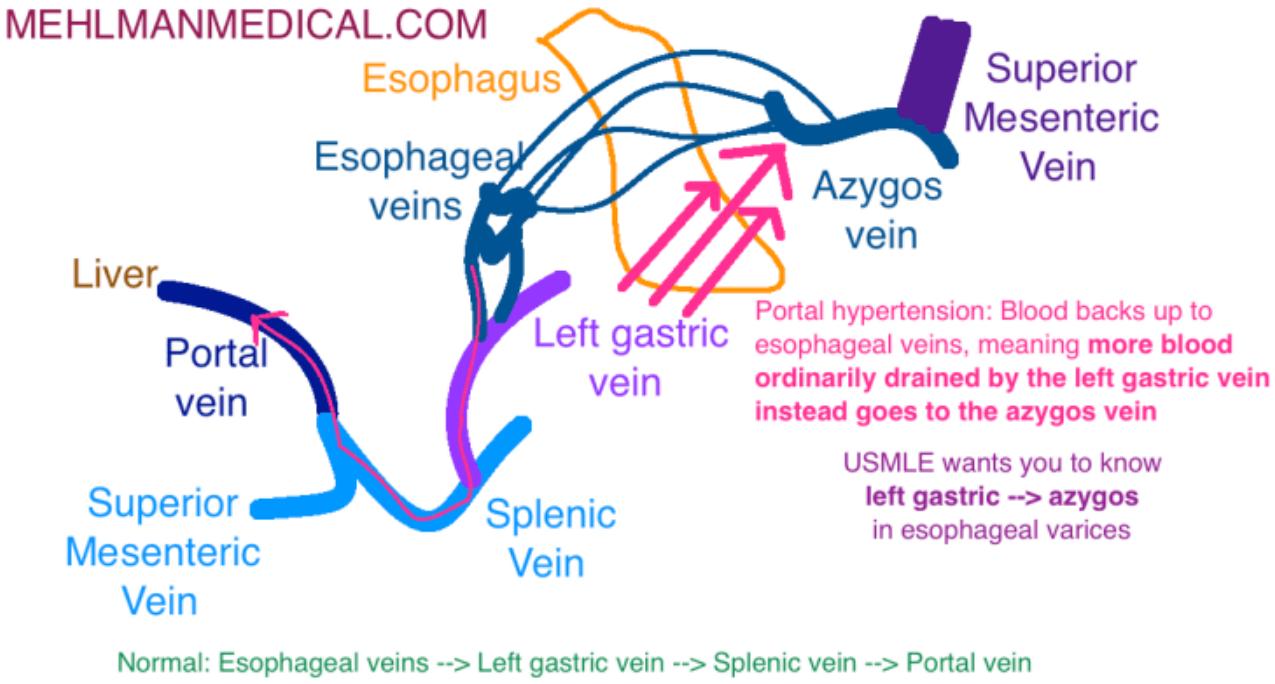
4. A 43-year-old man presents to emergency with a 5-day history of hematemesis and hematochezia on a background of chronic alcoholism and hepatitis C. His skin tone is pale and he is sudoretic (hyperhydrotic). HR is 135 bpm, RR 12, and BP 85/38 mm Hg. The liver edge is palpable 4 cm below the right costal margin. Palmar erythema is salient. After adequate hemodynamic resuscitation with 0.9% NaCl and packed RBCs, he undergoes emergent upper GI endoscopic treatment. He is also administered pharmacologic therapy to directly address his presenting pathology. Which of the following might be an effect of receiving this pharmacologic therapy?

A) Decreased renin release
B) Decreased glucagon release
C) Increased blood glucose
D) Increased thyroid-stimulating hormone release

The answer is B.

This patient has **esophageal varices** secondary to chronic liver disease. Varices are detected in ~50% of individuals with cirrhosis.[1]

Varices are a result of increased portal venous pressure.[2] This leads to increased pressure in the esophageal veins due to a congestion of the venous circulation:



Octreotide, a somatostatin analogue, is used in the treatment of esophageal varices.[3]

Treatment of acute variceal hemorrhage[3]

Immediate:

- Hemodynamic resuscitation (i.e., fluids, blood)
- Antibiotics
- **Octreotide**

Next 12-24 hours:

- Confirm diagnosis with upper endoscopy
- Perform endoscopic variceal ligation (EVL; "rubber banding") or sclerotherapy

Somatostatin inhibits the release of glucagon. This causes decreased, not increased, blood glucose.[4,5] Somatostatin also decreases, not increases, thyroid-stimulating hormone release.[6] It has no effect on the renin-angiotensin-aldosterone system (RAAS).[7]

Bottom line: Octreotide is a somatostatin analogue used in the acute treatment of esophageal varices. Somatostatin decreases blood glucose. Varices are caused by increased portal pressure, with a backup of blood to the esophageal veins. As a result, more blood ordinarily drained by the left gastric vein is shunted to the azygos vein. The USMLE likes this latter anatomical point.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3362051/

2) https://aasldpubs.onlinelibrary.wiley.com/doi/abs/10.1002/hep.1840050313

3) https://www.guidelinecentral.com/summaries/esophageal-varices/#section-420

4) https://diabetes.diabetesjournals.org/content/25/7/550

5) https://www.ncbi.nlm.nih.gov/pubmed/1278605

6) https://www.ncbi.nlm.nih.gov/books/NBK538327/

7) https://www.ncbi.nlm.nih.gov/pubmed/947943

5. A 54-year-old man has a four-month history of nocturnal dry cough and burning sensation in his chest, particularly if he lies down after meals. He has been trying out different medications that he's found around the drug store to treat his condition. He has also been experiencing occasional diarrhea. Which of the following agents might be responsible for his bowel symptoms?

A) Magnesium hydroxide
B) Aluminum hydroxide
C) Calcium carbonate
D) Omeprazole
E) Cimetidine

The answer is A.

Magnesium hydroxide, aluminum hydroxide, and calcium carbonate are all over-the-counter (no prescription needed) antacids.[1]

Magnesium is classically associated with diarrhea.[2,3]

Aluminum is associated with constipation.[3]

Calcium carbonate has no definite gastrointestinal motor effect.[3] However it is associated with rebound acid hypersecretion.[4]

Omeprazole, a proton-pump inhibitor, may increase the risk of diarrhea, however it is not available over-the-counter.[5] Regardless, magnesium is a well-established cause of diarrhea.

Cimetidine, an H2-blocker, is not a notable cause of diarrhea.

Bottom line: For the USMLE, with respect to antacid treatments: Magnesium can cause diarrhea. Aluminum can cause constipation. Calcium can cause rebound acid hypersecretion.

1) https://www.sciencedirect.com/science/article/pii/B9780323074452000112

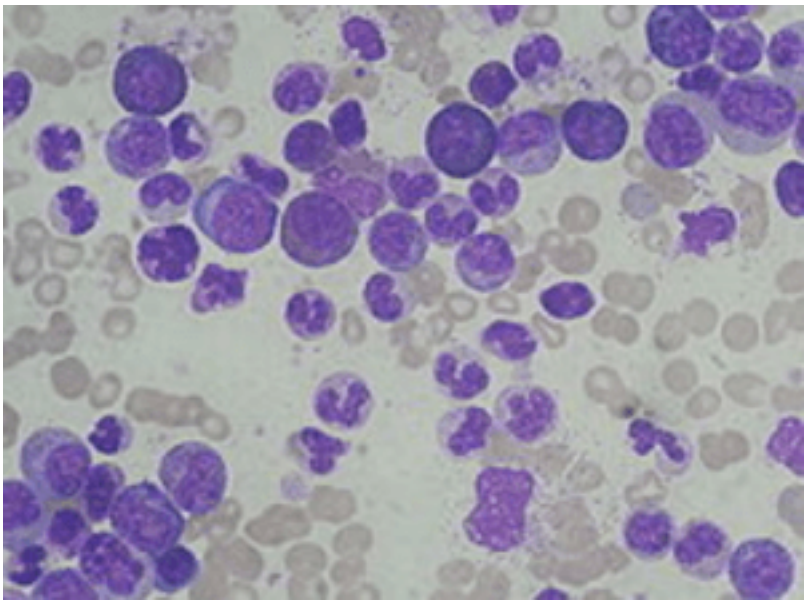
2) https://www.nejm.org/doi/full/10.1056/NEJM199104113241502

3) https://www.ncbi.nlm.nih.gov/pubmed/6858402

4) https://www.nejm.org/doi/10.1056/NEJM196810242791702

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3954014/

6.



A 35-year-old woman comes to the physician because of a 9-kg (20-lb) weight loss over the past four months. The spleen tip is palpable 5 cm below the left costal margin. Laboratory studies show:

Hematocrit: 47%
Leukocyte count: 25,500/mm^3
Segmented neutrophils: 52%
Bands: 13%
Metamyelocytes: 6%
Eosinophils: 2%
Basophils: 3%
Lymphocytes: 14%
Myelocytes: 10%
Platelet count: 600,000/mm3

After approximately 48 months of aggressive chemotherapy, he develops progressive dyspnea. Chest x-ray (CXR) shows a reticulonodular pattern. FEV_1/FVC is normal. Which of the following agents is most likely responsible for these findings?

A) Bleomycin
B) Busulfan
C) Doxorubicin
D) Prednisone
E) Imatinib

The answer is B.

This patient has chronic myelogenous leukemia (CML).

Busulfan, an alkylating agent which may be used in the treatment of CML[1], **causes pulmonary fibrosis.**[2]

Pulmonary fibrosis classically presents with reticular opacities (i.e., a reticulonodular pattern) on CXR.[3] This is colloquially referred to as "honeycombing."[4, 5]

FEV1/FVC may be **normal or increased** in restrictive lung disease. This is supported by Cleveland Clinic.[6] FEV1/FVC is decreased in obstructive lung disease.[7]

Imatinib, a tyrosine kinase inhibitor[8], is the **gold standard** treatment for CML.[9] **It causes fluid retention / edema.**[10]

Bleomycin is also known to cause pulmonary fibrosis. It is not a classic treatment for CML.[11, 12]

Doxorubicin, which is a treatment for Hodgkin lymphoma, causes dilated cardiomyopathy.[13, 14]

Prednisone may be used as an attempted mitigator / *treatment* for pulmonary fibrosis.[15]

Bottom line: Busulfan and bleomycin cause pulmonary fibrosis. Imatinib causes fluid retention / edema. Doxorubicin causes dilated cardiomyopathy. FEV1/FVC may be normal or increased in restrictive lung disease. "Reticular" or "reticulonodular" means "honeycombing," which refers to pulmonary fibrosis on imaging.

1) https://www.nejm.org/doi/full/10.1056/NEJM199403243301204

2) https://www.amjmed.com/article/0002-9343(61)90229-7/

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3408732/

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3579994/

5) https://radiopaedia.org/articles/reticular-and-linear-pulmonary-opacification

6) https://www.clevelandclinicmeded.com/live/owork/us-state/MDpres2/16.0830.Dweik.Pulm.A.PFTs.CME.v2.pdf

7) https://www.ncbi.nlm.nih.gov/books/NBK540970/

8) https://www.ncbi.nlm.nih.gov/pubmed/12528769

9) https://www.ncbi.nlm.nih.gov/pubmed/12637616

10) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2785832/

11) https://www.ncbi.nlm.nih.gov/pubmed/28836192

12) https://www.ncbi.nlm.nih.gov/pubmed/18188725

13) https://www.ncbi.nlm.nih.gov/pubmed/7636541

14) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2848530/

15) https://www.atsjournals.org/doi/10.1513/pats.200602-016TK

7. A 64-year-old man with a 50-pack-year history of smoking has 10-kg (22-lb) weight loss over the past four months. He has worsening cough with specks of blood. Chest x-ray shows a 3-cm central cavitating lesion. Biopsy is performed and shows advanced stage bronchogenic squamous cell carcinoma. Among the various treatment options, the physician considers a drug called erlotinib, which has demonstrated efficacy in treating non-small cell lung cancer. Which of the following best describes the molecular target of this agent?

A) Vascular endothelial growth factor (VEGF)
B) Bcr-Abl tyrosine kinase
C) Serine-threonine kinase
D) Epidermal growth factor receptor (EGFR) tyrosine kinase
E) Topoisomerase I
F) Topoisomerase II

The answer is D.

Erlotinib is an EGFR tyrosine kinase inhibitor used in the treatment of non-small cell lung cancer.[1]

Imatinib inhibits bcr-abl tyrosine kinase in the treatment of chronic myelogenous leukemia (CML).[2]

Sorafenib is a novel multikinase inhibitor, which inhibits tyrosine kinases as well as serine/threonine kinases, in the treatment of renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC).[3, 4]

Bevacizumab is a VEGF inhibitor used in the treatment of metastatic colorectal cancer.[5]

Irinotecan and topotecan are topoisomerase I inhibitors used in the treatment of colorectal cancer.[6]

Etoposide and teniposide are topoisomerase II inhibitors used in the treatment of various cancers.[6, 7]

Bottom line: Erlotinib is an EGFR tyrosine kinase inhibitor used in the treatment of non-small cell lung cancer.

1) https://www.ncbi.nlm.nih.gov/pubmed/23906302

2) https://www.ncbi.nlm.nih.gov/pubmed/20537386

3) https://www.ncbi.nlm.nih.gov/pubmed/18955668

4) https://www.ncbi.nlm.nih.gov/pubmed/24135988

5) https://www.ncbi.nlm.nih.gov/pubmed/16842197

6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3251848/

7) https://cancerres.aacrjournals.org/content/61/17/6555.short

8. A 57-year-old man with a 10-year history of hepatitis C is enrolled in a treatment study. After commencing treatment, his laboratory results are as follows:

Total bilirubin: 3.3 mg/dL (normal range: <1.2)
Direct bilirubin: 0.2 mg/dL (NR: < 0.3)
Reticulocyte count: 9.1% (NR: 0.5-2.5)
Hematocrit: 38.5% (male NR: 40-54)

Which of the following is the most likely causative agent?

A) Ritonavir
B) Entecavir
C) Glecaprevir
D) Sofosbuvir
E) Ribavirin

The answer is E.

Ribavirin, an RNA polymerase inhibitor that may be used in the treatment of hepatitis C, can cause hemolytic anemia.[1,2,3]

This is evidenced by this patient's elevated indirect bilirubin (i.e., an increase in total without an increase in direct) and reticulocyte count.

Ritonavir is a protease inhibitor used in the treatment of HIV. Because it is a P-450-inhibitor, it is sometimes used as a "booster" agent to maintain serum levels of other drugs. It has been trialed in hepatitis C regimens for this reason.[4] However it is not associated with hemolysis.[5]

Entecavir is a DNA polymerase inhibitor used in the treatment of hepatitis B.[6,7]

Glecaprevir is a hepatitis C NS3/4A protease inhibitor.[8] Hemolysis may be seen if combined with ribavirin.[9]

Sofosbuvir is a hepatitis C NS5B nucleotide polymerase inhibitor.[10] Hemolysis may be seen if combined with ribavirin.[11]

Bottom line: Ribavirin is an RNA polymerase inhibitor used in the treatment of hepatitis C. It causes hemolytic anemia.

1) https://www.ncbi.nlm.nih.gov/books/NBK548115/

2) https://www.ncbi.nlm.nih.gov/pubmed/11964896

3) http://www.jbc.org/content/276/49/46094.full

4) https://www.ncbi.nlm.nih.gov/pubmed/25846301

5) https://www.ncbi.nlm.nih.gov/pubmed/11724090

6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2387288/

7) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1866160/

8) https://www.ncbi.nlm.nih.gov/pubmed/29084747

9) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5740381/

10) https://www.ncbi.nlm.nih.gov/pubmed/24790644

11) https://www.ncbi.nlm.nih.gov/pubmed/31009550

9. An 8-year-old boy is brought to the physician by his mother for several episodes of unusual "daydreaming" over the past three weeks in which he will suddenly stop all activity and stare into space with a blank look. Sometimes it appears as though his eyelids flutter. These episodes generally last less than ten seconds. His teacher has also reported observing similar episodes. One year ago, he was treated for a tonic-clonic seizure. Which of the following best describes the most appropriate pharmacologic therapy for this patient?

A) Inhibition of thalamic T-type calcium channels
B) Inhibition of sodium channels
C) Inhibition of sodium channels + increase GABA
E) Inhibition of GABA reuptake

The answer is C.

This is a favorite USMLE "trick" question.

The "daydreaming" episodes are classic for absence (petit mal) seizures, which usually manifest as a vacant stare lasting about 10 seconds. There is usually no confusion, headache, or drowsiness afterward. Signs and symptoms of absence seizures include:[1]

- Sudden stop in motion without falling
- Lip smacking
- Eyelid flutters
- Chewing motions
- Finger rubbing
- Small movements of both hands

The optimal monotherapy for children and adolescents with absence seizures is ethosuximide[2], which blocks thalamic T-type calcium channels.[3]

However, if absence and generalized tonic-clonic seizures coexist, valproic acid is preferred.[2,4] Ethosuximide is considered to be less efficacious for tonic-clonic seizures.[2]

Valproic acid blocks sodium channels and increases GABA.[5]

Phenytoin, carbamazepine, and lamotrigine block neuronal voltage-gated Na^+ channels.[6]

Tiagabine is a selective GABA reuptake inhibitor.[7]

Bottom line: Ethosuximide is the optimal monotherapy therapy for patients with absence seizures. However if absence and generalized tonic-clonic seizures coexist, valproic acid is preferred. This is one of the "trick" questions on the USMLE, as most students will jump on ethosuximide as soon as they identify an absence seizure in the vignette.

1) https://www.mayoclinic.org/diseases-conditions/petit-mal-seizure/symptoms-causes/syc-20359683

2) https://www.ncbi.nlm.nih.gov/pubmed/28195639

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC320973/

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2912003/

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3766376/

6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2981395/

7) https://www.ncbi.nlm.nih.gov/pubmed/16420077

10. A 27-year-old woman experiences reduced visual acuity and color vision in her left eye. This is accompanied by general facial weakness, numbness, and dysarthria. The symptoms resolve fully within 24 hours. Three months later she begins experiencing muscle spasticity, balance problems, and the urge to run to the bathroom. She undergoes an MRI which reveals white matter lesions in her brain and spinal cord. An agent with which of the following mechanisms of action might be effective in treating her spasticity?

A) Muscarinic agonist
B) Muscarinic antagonist
C) Nicotinic agonist
D) Nicotinic antagonist
E) GABA-A agonist
F) GABA-A antagonist
G) GABA-B agonist
H) GABA-B antagonist
I) Glutamate agonist
J) Glutamate antagonist
K) Mu-opioid agonist
L) Kappa-opioid agonist

The answer is G.

This patient has relapsing-remitting multiple sclerosis.

Optic neuritis and urge incontinence, as seen in this patient, are common presenting features.[1]

MRI is the gold standard for diagnosis.[2] CNS white matter lesions are characterized by multifocal areas of myelin sheath destruction, oligodendrocyte death, axonal and neuronal damage, and activation of glial cells.[3]

NKG2C-expressing CD4 T cells are present in white matter lesions and kill human oligodendrocytes.[4]

Baclofen, a $GABA_B$ receptor agonist, is used to treat spasticity in multiple sclerosis.[5, 6]

This drug might sound weird and low-yield, but the USMLE really likes it. And they want you to know that it **agonizes,** not antagonizes, GABA **B**, not A.

Bottom line: Baclofen is used to treat spasticity in multiple sclerosis. It is a $GABA_B$ receptor agonist.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6177731/

2) https://www.ncbi.nlm.nih.gov/pubmed/8274111

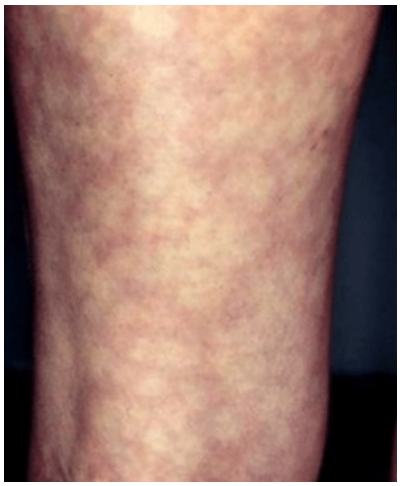
3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5052065/

4) https://www.ncbi.nlm.nih.gov/pubmed/23396942/

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2014648/

6) https://www.ncbi.nlm.nih.gov/pubmed/24289845

11.



A 70-year-old man being treated for Parkinson disease develops the above appearance of his legs. Which of the following agents is most likely responsible?

A) Amantadine
B) Levodopa/carbidopa
C) Bromocriptine
D) Pergolide
E) Pramipexole
F) Ropinirole
G) Cabergoline
H) Selegiline
I) Tolcapone

The answer is A.

This patient has **livedo reticularis,** a cutaneous sign characterized by a blotchy and lace-like, reddish-blue to purple appearance.

Amantadine, a dopamine reuptake inhibitor sometimes used in Parkinson disease, can cause livedo reticularis.[1,2]

Is is believed that livedo reticularis is a physiological response provoked by depletion of catecholamine stores in peripheral nerve terminals.[3]

Levodopa/carbidopa is a frequently used formulation in Parkinson disease. Dopamine does not cross the blood-brain barrier (BBB), but L-dopa does.[4] Carbidopa, an L-dopa decarboxylase inhibitor, decreases the amount of L-dopa converted to dopamine peripherally so that more can cross the BBB, where it is then converted to dopamine.[5]

Bromocriptine, pergolide, pramipexole, ropinirole, and cabergoline are all dopamine receptor agonists that may be used in Parkinson disease.[6]

Selegiline is a selective monoamine oxidase B (MAO-B) inhibitor used in Parkinson disease.[7]

Tolcapone, a catechol-O-methyltransferase (COMT) inhibitor used in Parkinson disease, decreases the metabolism of L-dopa so that more is available to cross the BBB.[8]

Bottom line: Amantadine causes livedo reticularis.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1796527/

2) https://www.sciencedirect.com/science/article/pii/B9780444521668500108

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1796527/

4) https://www.nature.com/articles/228358a0

5) https://www.ncbi.nlm.nih.gov/books/NBK482140/

6) https://www.ncbi.nlm.nih.gov/pubmed/18303487/

7) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4289953/

8) https://www.ncbi.nlm.nih.gov/books/NBK548573/

12. A 71-year-old woman is brought to the physician by her brother because of a 4-year history of worsening memory impairment and difficulty finding words. Her brother says that she has been angry at the suggestion that she may have a progressive impairment, but others have also noticed a decline in her general housekeeping and ability to maintain financial affairs. She appears well-groomed, alert, and friendly. Her neurological examination and psychiatric screen are both unremarkable. She scores a 22/30 on the Mini-Mental State Exam (MMSE). Her brother self-pays for an MRI that shows diffuse cerebral atrophy. A medication with which of the following mechanisms of action may provide initial benefit for this patient?

A) Direct muscarinic receptor agonism
B) Direct muscarinic receptor antagonism
C) Inhibition of acetylcholinesterase
D) Regeneration of acetylcholinesterase
E) Glutamate (NMDA) receptor agonism

The answer is C.

Donepezil, galantamine, and rivastigmine are all **acetylcholinesterase inhibitors** approved for use in the treatment of mild-moderate Alzheimer disease (AD).[1]

Cholinergic neurons located in the basal forebrain, particularly in the nucleus basalis of Meynert, are severely lost in AD. Therefore an acetylcholinesterase inhibitor functions to increase cholinergic transmission.[2]

Memantine, a glutamate (NMDA) receptor antagonist, may be used for moderate-severe AD.[1]

Pralidoxime regenerates active acetylcholinesterase. It is used in organophosphate poisoning and is unrelated to AD.[3]

Bottom line: Donepezil, galantamine, and rivastigmine are all acetylcholinesterase inhibitors used in mild-moderate AD. Memantine is a glutamate (NMDA) receptor antagonist used in moderate-severe AD.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4369281/

2) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4787279/

3) https://www.atsdr.cdc.gov/csem/csem.asp?csem=11&po=23

13. A 23-year-old girl experiences periodic pounding unilateral headaches. She self-medicates with acetaminophen and ibuprofen, although these have been modestly effective at best. An agent with which of the following mechanisms of action may provide benefit as an abortive therapy for future episodes?

A) 5-HT1A/D receptor agonism
B) 5-HT1A/1D receptor antagonism
C) 5-HT1C receptor agonism
D) 5-HT1C receptor antagonism
E) 5-HT1B/D receptor agonism
F) 5-HT1B/D receptor antagonism

The answer is E.

Sumatriptan is a 5-$HT_{1B/1D}$ serotonin receptor agonist.[1]

It is the first-line abortive therapy for moderate to severe migraines, or mild to moderate migraines that have not responded to adequate doses of simple analgesics.[2]

5-$HT_{1B/1D}$ serotonin receptor agonism is believed to alleviate migraine pain via multiple mechanisms, including vasoconstriction of cerebral blood vessels, inhibition of vasoactive neuropeptide release by trigeminal nerves, and inhibition of nociceptive neurotransmission.[1]

It should be noted that **combination simple analgesics** (i.e., non-prescription combinations containing **acetaminophen, aspirin, and caffeine**) are effective first-line therapy for mild to moderate migraines and should be used by patients prior to triptans.[2] This patient has not experienced relief with these over-the-counter medications however.

Bottom line: Sumatriptan is a 5-$HT_{1B/1D}$ serotonin receptor agonist used as abortive migraine therapy. It may be used in patients not responding to simple analgesic combinations of acetaminophen, aspirin, and caffeine.

1) https://jamanetwork.com/journals/jamaneurology/fullarticle/782346

2) https://www.aafp.org/afp/2011/0201/p271.html

14. A 55-year-old man is diagnosed with prostatic adenocarcinoma and started on hormonal therapy. Which of the following is most appropriate for this patient?

A) Leuprolide
B) Triptorelin
C) Leuprolide then flutamide
D) Triptorelin then flutamide
E) Flutamide then leuprolide
F) Flutamide + leuprolide commenced together

The answer is F.

The benefit of anti-androgenic hormonal therapy in the treatment of prostate cancer is uncontroversial.

Dihydrotestosterone causes increased prostatic cellular proliferation, decreased apoptosis, and increased angiogenesis.[1]

Flutamide is an androgen receptor antagonist. **Leuprolide and -relins (e.g., goserelin, triptorelin)** are gonadotropin-releasing hormone (GnRH) receptor agonists.[2]

GnRH receptor agonists, *given daily and continuously,* cause desensitization of the GnRH receptor and effectively act as antagonists.[3]

However, the initial administration of a GnRH receptor agonist will cause a transient increase in luteinizing hormone and androgen levels prior to the desensitization. Therefore in theory, flutamide should be given prior to GnRH agonist therapy. However in clinical practice, they are commenced together:

- "Flutamide is indicated in combination with an LHRH-agonist (e.g., leuprolide) as initial therapy in metastatic (stage D2) prostate cancer. The usual dose is 250 mg po tid given at eight-hour intervals and started concurrently with the LHRH-agonist."[4]
- "Pretreatment with flutamide increased the serum testosterone level, but the testosterone surge after leuprorelin [leuprolide] administration was almost the same…Simultaneous administration of flutamide with a GnRH agonist is sufficient to prevent flare-up phenomena."[5]

If the USMLE were to ever force you into a corner where you need to select a definitive sequence, **choose flutamide then leuprolide,** but if one of the other options is **simultaneous administration, choose this latter option instead.**

Bottom line: In the treatment of prostatic adenocarcinoma, flutamide and leuprolide are commenced together. In the USMLE question, if you must choose a linear sequence, the answer is flutamide then leuprolide. But if simultaneous administration is also an option, this latter choice is correct.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1578721/

2) https://www.ncbi.nlm.nih.gov/pubmed/2118417

3) https://www.ncbi.nlm.nih.gov/pubmed/6417315

4) https://www.ncbi.nlm.nih.gov/pubmed/2193461

5) https://www.ncbi.nlm.nih.gov/pubmed/11316974

15. A 32-year-old IV drug user is commenced on empiric antibiotic therapy for acute bacterial endocarditis. He develops severe oliguria and dark urine. The agent most likely responsible demonstrates which of the following molecular inhibition and binding patterns?

A) 50S ribosomal subunit; 23s RNA of peptidyl transferase cavity; blocks peptidyl transferase; prevents tRNA from binding to A site
B) 50S ribosomal subunit; 23s RNA of peptidyl transferase cavity; blocks peptidyl transferase; prevents tRNA from binding to A and P sites
C) 50S ribosomal subunit; 23s RNA of peptidyl transferase cavity; does not block peptidyl transferase; blocks tunnel that channels nascent peptides away from peptidyl transferase center
D) 50S ribosomal subunit; 23S rRNA nucleotides; prevents formation of initiation complex
E) 30S ribosomal subunit – inhibits formation of initiation complex and causes misreading of mRNA
F) 30S ribosomal subunit – prevents aminoacyl-tRNA from binding to the A site

The answer is E.

Empiric treatment for endocarditis[1,2]

- Vancomycin or ampicillin/sulbactam, PLUS an aminoglycoside (e.g., gentamicin)
- **Add rifampin in patients with prosthetic valves**

This patient has acute tubular necrosis (ATN) due to gentamicin.

Aminoglycosides such as gentamicin are well-established causative agents of acute tubular necrosis (ATN) and ototoxicity.[3,4]

They bind to the 30S ribosomal subunit, thereby inhibiting formation of the initiation complex and causing misreading of the mRNA.[5]

With respect to the 50S ribosomal subunit inhibitors, all bind to the 23S ribosomal RNA (rRNA) at the peptidyl transferase cavity. Chloramphenicol and clindamycin block peptidyl transferase; macrolides do not.[6]

Chloramphenicol: "50S ribosomal subunit; 23S rRNA of peptidyl transferase cavity; blocks peptidyl transferase; prevents tRNA from binding to A site."[6]

Clindamycin: "50S ribosomal subunit; 23S rRNA of peptidyl transferase cavity; blocks peptidyl transferase; prevents tRNA from binding to A and P sites."[6]

Macrolides (e.g., erythromycin): "50S ribosomal subunit; 23S rRNA of peptidyl transferase cavity; does not block peptidyl transferase; blocks tunnel that channels nascent peptides away from peptidyl transferase center."[6]

Linezolid: "50S ribosomal subunit; 23S rRNA nucleotides; prevents formation of initiation complex."[7,8]

Tetracycline: "Inhibits 30S ribosomal subunit – prevents aminoacyl-tRNA from binding to the A site."[9]

Mnemonic: "Buy **AT** 30. **CCEL** at 50." ("Buy at 30. Sell at 50.")
– **A**minoglycosides, **T**etracyclines are 30S; **C**hloramphenicol, **C**lindamycin, **E**rythromycin (macrolides), **L**inezolid are 50S.

Bottom line: Aminoglycosides cause nephrotoxicity (acute tubular necrosis) and ototoxicity. The 30S ribosomal subunit inhibitors are aminoglycosides and tetracyclines. The high-yield 50S inhibitors are clindamycin, chloramphenicol, and macrolides. Knowing which ones are 30S vs 50S is exceedingly HY for the USMLE Step 1. The more specific mechanisms of action are occasionally asked and are worth memorizing if you have any desire for a 250+.

1) https://www.aafp.org/afp/2012/0515/p981.html

2) https://www.ncbi.nlm.nih.gov/pubmed/19713420

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC89104/

4) https://www.ncbi.nlm.nih.gov/pubmed/17266591

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5187519/

6) https://www.ncbi.nlm.nih.gov/pubmed/11677599 (https://www.weizmann.ac.il/Structural_Biology/faculty_pages/Yonath/Nat10.01.pdf)

7) https://watermark.silverchair.com/dkg249.pdf?token=AQECAHi208BE49Ooan9kkhW

8) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3264260/#__sec3title

9) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC99026/

16. A 54-year-old comes to the physician because of a 5-month history of diffuse muscle cramping. Physical examination shows diffuse muscle atrophy, fasciculations, and a left foot-drop. His deep tendon reflexes are brisk. Sensory examination is unremarkable. The physician considers a relatively novel treatment agent believed to function as a free radical scavenger, in addition to reducing lipid peroxides and hydroxyl radicals. Which of the following pharmacologic therapies is being considered?

A) Edaravone
B) Riluzole
C) Pyridostigmine
D) Dexrazoxane
E) Amifostine

The answer is A.

This patient has amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), a progressive neuromuscular disease characterized by **degeneration of motor neurons in the brain and spinal cord.**[1]

In order to diagnose ALS in a USMLE vignette, 19 times out of 20, there is:

1. A mix of upper motor neuron (UMN) and lower motor neuron (LMN) findings.[2]
2. No sensory abnormalities.[2]

This patient has apparent muscle hypertonia and brisk reflexes (both UMN), as well as fasciculations (LMN).

Edaravone, a novel agent used in the treatment of ALS[3, 4, 5, 6], carries a mechanism of action best described as:

- "Antioxidant. Edaravone is thought to be a free radical scavenger, and it reportedly eliminates lipid peroxides and hydroxyl radicals."[3]
- "The etiology of amyotrophic lateral sclerosis (ALS) is unknown. Oxidative stress may be one of the major mechanisms involved. In vitro and in vivo data of edaravone suggest that it may possess broad free radical scavenging activity and protect neurons, glia, and vascular endothelial cells against oxidative stress."[4]
- "Although the exact mechanism of action of edaravone in the treatment of ALS is unknown, its therapeutic effect may be due to its known antioxidant properties; oxidative stress is a part of the process that kills neurons in patients with ALS."[5]
- "Edaravone is a strong antioxidant that prevents oxidative stress from inducing motor neuron death in ALS patients. Being a potent free radical scavenger, it has been shown to inhibit nitration of tyrosine residues in the cerebrospinal fluid and improve motor functions in mouse models of ALS."[6]

Riluzole is a glutamate (NMDA) receptor antagonist that may be used in the treatment of ALS.[7]

Pyridostigmine is an acetylcholinesterase inhibitor used in the treatment of myasthenia gravis.[8]

Dexrazoxane is a free radical chelator used to reduce the risk of doxorubicin-associated dilated cardiomyopathy.[9]

Amifostine is a free radical chelator used to reduce the risk of cisplatin-associated nephro- and ototoxicity.[10]

Bottom line: ALS is the answer if 1) there is mix of UMN + LMN findings, and 2) there are no sensory abnormalities. Edaravone is a free radical scavenger used to treat ALS.

1) https://www.nejm.org/doi/full/10.1056/NEJMra1603471

2) https://www.aafp.org/afp/1999/0315/p1489.html

3) https://www.cell.com/cell/pdf/S0092-8674(17)31198-4.pdf

4) https://www.ncbi.nlm.nih.gov/pubmed/28872907

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5737249/

6) https://www.ncbi.nlm.nih.gov/pubmed/29998226

7) https://www.ncbi.nlm.nih.gov/pubmed/8959995

8) https://www.ncbi.nlm.nih.gov/pubmed/21815707

9) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4168851/

10) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2504739/

17. A 68-year-old man with benign prostatic hyperplasia desires medication to improve his urinary outflow. Digital rectal exam demonstrates marked prostatic enlargement. Which of the following would be most effective at improving this patient's urinary symptoms?

A) Alpha-1 agonist alone
B) Alpha-1 antagonist alone
C) 5-alpha-reductase inhibitor alone
D) Alpha-1 agonist + 5-alpha-reductase inhibitor
E) Alpha-1 antagonist + 5-alpha-reductase inhibitor

The answer is E.

Treatment of benign prostatic hyperplasia (BPH)[1]

Alpha-1-blocker monotherapy[1]

- **Alfuzosin, doxazosin, tamsulosin,** and **terazosin** are all appropriate first-line agents for BPH.
- They do not alter the natural progression of the disease.

5-alpha-reductase inhibitor monotherapy[1]

- **Dutasteride** and **finasteride** are appropriate agents for BPH associated with demonstrable prostatic enlargement.
- BPH disease progression may be slowed through a reduction in the risk of acute urinary retention and the need for surgical intervention.

Combination alpha-1-blocker + 5 alpha-reductase inhibitor[1]

- Appropriate and effective treatment strategy for BPH associated with prostatic enlargement.
- **Clinical trial results have shown that combination therapy significantly improves symptom scores and peak urinary flow compared with either monotherapy.**
- Delays disease progression.

This patient has marked prostatic enlargement and would benefit from a 5-alpha-reductase inhibitor. However because combination therapy with an alpha-1-antagonist would provide him benefit superior to either agent used as monotherapy, a regimen such as tamsulosin + finasteride would be most effective for him.

Bottom line: Combination therapy with an alpha-1-antagonist and 5-alpha-reductase inhibitor is superior to either used as monotherapy in the treatment of BPH. Alpha-1-antagonists do not alter disease progression and may be used in any male with lower urinary tract symptoms. 5-alpha-reductase inhibitors slow disease progression and are only used in patients with demonstrable prostatic enlargement.

1) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2950766/

18. A 28-year-old woman presents with a two-month history of worsening dyspnea. Chest x-ray (CXR) shows increased prominence of vascular markings. Cardiac exam demonstrates a loud S2. She says she occasionally gets painful fingers that change color in the cold. Examination of her hands shows healing ulcerations of the skin secondary to spontaneous exfoliation from calcium deposits. Her appearance is remarkable for scattered dilated facial capillaries. Which of the following might be an effective treatment for her pulmonary symptoms?

A) Albuterol
B) Azathioprine
C) Bupropion
D) Bosentan
E) Buspirone

The answer is D.

This is an exceedingly HY drug for the USMLE.

This patient has pulmonary hypertension secondary to CREST syndrome (limited scleroderma; limited systemic sclerosis).

CREST

- **Calcinosis**[1]
  - Cutaneous condition in which calcium salts are deposited in the skin
- **Raynaud phenomenon**[2]
  - Due to transient cessation of blood flow to the digits of the hands or feet.
  - An attack of Raynaud's phenomenon is classically manifested as triphasic color changes.
  - The white phase is due to excessive vasoconstriction and cessation of regional blood flow.
  - This phase is followed by a cyanotic phase, as the residual blood in the finger desaturates.
  - The red phase is due to hyperemia as the attack subsides and blood flow is restored.
- **Esophageal dysmotility**[3]
  - Associated with symptoms of gastroesophageal reflux disease (GERD)
  - ↓ peristalsis of the distal esophagus
  - ↓ lower esophageal sphincter tone
- **Sclerodactyly**[4]
  - Tightening of the skin of the fingers and toes
- **Telangiectasias**[5]
  - Dilated cutaneous blood vessels

Pulmonary arterial hypertension is a known sequela of CREST syndrome / limited scleroderma.[6]

Endothelin-1 is a potent endogenous vasoconstrictor and smooth-muscle mitogen[6] that is over-expressed in patients with primary pulmonary hypertension[7,8] and scleroderma.[9]

Bosentan is an endothelin-1 receptor antagonist effective in treating pulmonary hypertension in patients with primary pulmonary hypertension and scleroderma.[10]

Albuterol is a beta-2 agonist used as the first-line abortive therapy for asthma.[11]

Azathioprine is an immunosuppressant. It is metabolized into 6-mercaptopurine, which is a purine synthesis inhibitor.[12]

Bupropion is both an anti-depressant and smoking cessation agent. It inhibits dopamine and norepinephrine reuptake, with little serotonergic effect.[13]

Buspirone is a serotonin 5-HT1A receptor agonist used a second-line treatment for generalized anxiety disorder; SSRIs are first-line.[14]

Bottom line: Bosentan is an endothelin-1 receptor antagonist effective in treating pulmonary hypertension in patients with primary pulmonary hypertension and scleroderma. **This is an exceedingly HY drug for the USMLE.**

1) https://www.ncbi.nlm.nih.gov/books/NBK448127/

2) https://www.ncbi.nlm.nih.gov/pubmed/16444858

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5825946/

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170368/

5) https://www.ncbi.nlm.nih.gov/books/NBK430875/

6) https://www.ncbi.nlm.nih.gov/pubmed/3707629

7) https://insights.ovid.com/european-clinical-investigation-supplement/ejcis/1996/04/001

8) https://www.nejm.org/doi/pdf/10.1056/NEJM199306173282402

9) https://www.jstage.jst.go.jp/article/internalmedicine1992/33/10/33_10_579/

10) https://www.nejm.org/doi/full/10.1056/NEJMoa012212

11) https://www.ncbi.nlm.nih.gov/pubmed/9228352

12) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC152947/

13) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2528204/

14) https://www.ncbi.nlm.nih.gov/books/NBK531477/

19. A 45-year-old woman runs 10 miles a day and was recently treated for a metatarsal stress fracture. She is 5’8″ (173 cm) and weighs 96 lbs (43.6 kg). She has not had a menstrual period in four months. She states life is not worth living and that she has had zero interest in socializing with friends for the past six months. She wakes up around 4am every day and cannot fall back asleep, despite saying she would like to sleep longer. Which of the following medications is most appropriate for this patient?

A) Sertraline
B) Desvenlafaxine
C) Lithium
D) Buspirone
E) Amitriptyline
F) Mirtazapine
G) Clonidine

The answer is F.

This patient has anorexia nervosa with depression.

Her BMI is 14.6 and she has had a metatarsal stress fracture, a common finding in anorexia due to osteoporosis from decreased estrogen secondary to paucity of adipose tissue.[1,2]

She also has **terminal insomnia,** which is highly reflective of depression.[3] This is the inability to stay asleep, rather than an inability to fall asleep.

Mirtazapine, an alpha-2 antagonist, is a first-line treatment for patients with anorexia and depression.[4,5] It stimulates appetite and causes weight gain, which may sometimes be rapid.[6]

Sertraline, a selective serotonin reuptake inhibitor (SSRI), is also a first-line medication for this patient and is certainly appropriate in practice.[7] However because this patient also has anorexia, the robust appetite-stimulating effects of mirtazapine make the latter a superior choice.

Desvenlafaxine is a serotonin-norepinephrine reuptake inhibitor (SNRI) used for depression. Desvenlafaxine has been shown to cause a small but statistically significant decrease in weight compared to placebos.[8] In fact, anorexia is one of its adverse effects.[9] This would not be an appropriate choice for a patient with anorexia.

Lithium is the first-line treatment for bipolar disorder.[10]

Buspirone is an agonist at serotonin 5HT1A receptors. It is a second-line treatment for generalized anxiety disorder after SSRIs.[11]

Amitriptyline is a tricyclic antidepressant (TCA), which works by blocking the reuptake of both serotonin and norepinephrine. It is effective for depression but is not first-line because of its multitude of adverse effects.[12] It notably causes cardiotoxicity and anti-cholinergic side-effects.[13] **However it is the first-line treatment for diabetic neuropathic pain.**[14] This latter point is high-yield.

Clonidine is an alpha-2 agonist that may be used for attention deficit and hyperactivity disorder (ADHD).[15] It may also be used as an anti-hypertensive and for Tourette disorder.[16]

Bottom line: Mirtazapine is an alpha-2 antagonist used first-line for patients who have both anorexia and depression.

1) https://www.ncbi.nlm.nih.gov/pubmed/7668964

2) https://www.archives-pmr.org/article/S0003-9993

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5678925/

4) https://www.ncbi.nlm.nih.gov/pubmed/17687663

5) https://www.ncbi.nlm.nih.gov/pubmed/23229075

6) https://neuro.psychiatryonline.org/doi/pdfplus/10.1176

7) https://www.nejm.org/doi/full/10.1056/NEJMoa052963

8) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2882808/

9) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2899788/

10) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5125816/

11) https://www.ncbi.nlm.nih.gov/books/NBK531477/

12) https://www.ncbi.nlm.nih.gov/pubmed/17636748

13) https://www.ncbi.nlm.nih.gov/books/NBK537225/

14) https://www.aafp.org/afp/2010/0715/p151.html

15) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3926778/

16) https://www.ncbi.nlm.nih.gov/books/NBK459124/

20. A 42-year-old man who processes bear pelts in Umiat, Alaska has had a six-month history of weakness, fatigue, and anterograde amnesia. He has also had subtle muscle twitches and shaking every few minutes. Serum studies detect the presence of a heavy metal in high amounts. Which of the following is the most appropriate treatment?

A) Deferoxamine
B) Dimercaprol
C) Penicillamine
D) Trientine
E) EDTA

The answer is B.

MEHLMANMEDICAL.COM	
Heavy metal poisoning	**Chelator treatment**
Mercury	Dimercaprol; Succimer
Iron	Deferoxamine; Deferasirox; Deferiprone
Copper	Penicillamine; Trientine
Lead	EDTA; Dimercaprol; Succimer

This man has mercury poisoning, which is also known colloquially as Mad Hatter Disease.

Mercury has long been associated with those who work in fur trades, as mercury can be used to generate a sheen for pelts and hats.[1, 2]

Call it weird/obscure all you want, but 1) Alaska is still in the United States, and 2) heavy metal poisonings are exceedingly HY on the USMLE.

Mercury poisoning[3]

- "At low-level exposures, nonspecific symptoms like weakness, fatigue, anorexia, weight loss, and gastrointestinal disturbance have been described."
- "Higher exposure levels are associated with mercurial tremor: fine muscle fasciculations punctuated every few minutes by coarse shaking."
- "Erethism may also be observed: severe behavior and personality changes, emotional excitability, loss of memory, insomnia, depression, fatigue, and in severe cases delirium and hallucination. Gingivitis and copious salivation have been described."

The first-line treatments for mercury poisoning are dimercaprol and succimer, which are both chelating agents.[4]

Deferoxamine, deferasirox, and deferiprone are iron chelators used to treat transfusional siderosis, which is iron overload secondary to chronic blood transfusions, e.g., for thalassemia. Serial phlebotomy, in contrast, is used to control iron levels in hereditary hemochromatosis.[5, 6, 7]

Penicillamine and trientine are copper chelators used in Wilson disease.[8, 9]

EDTA is a chelator used to treat lead poisoning. Succimer and dimercaprol may also be used.[10]

Bottom line: Heavy metal poisonings are exceedingly HY on the USMLE. Know their treatments.

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Heavy metal poisoning	**Chelator treatment**
Mercury	Dimercaprol; Succimer
Iron	Deferoxamine; Deferasirox; Deferiprone
Copper	Penicillamine; Trientine
Lead	EDTA; Dimercaprol; Succimer

1) https://www.bmj.com/content/bmj/287/6409/1961.full.pdf

2) https://books.google.co.jp/books?id=YaINUh1BkJUC&pg

3) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3253456/

4) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4055906/

5) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3012763/

6) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5139945/

7) https://www.ncbi.nlm.nih.gov/pubmed/22565013

8) https://www.ncbi.nlm.nih.gov/pubmed/22327203

9) https://www.ncbi.nlm.nih.gov/pubmed/1887758

10) https://www.ncbi.nlm.nih.gov/books/NBK548099/

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