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Web-Based Pharmacology Cases for Cardiovascular System 1 and Renal System 1

Abstract

Undergraduate medical education is constantly evolving to develop new, effective, engaging teaching methods. An integrated medical school curriculum correlates the basic and clinical sciences beginning in the first year in order to engage students, develop clinical reasoning skills, and prepare them for their clinical experiences. Contextualization, in which clinical case examples are used to illustrate basic science principles, is one strategy used to achieve this goal. In addition to changes in the structure of medical school curricula, the platforms by which educational material is delivered are also rapidly changing. Web-based applications, including podcasts and virtual interactive cases, provide endless opportunities to present information in efficient and interesting formats and encourage self-directed learning by students.

Pharmacology is an area of preclerkship education that is particularly challenging to medical students. One reason for this is the fact that students begin learning clinical pharmacology in the first year, prior to learning detailed pathophysiology of the diseases being treated; without clinical context, learning pharmacology can feel little more than memorization of names and mechanisms. The UCSD School of Medicine Integrated Scientific Curriculum addresses these challenges by through a two-pass curriculum, whereby pharmacology is introduced with physiology and basic pathophysiology in Year 1, and reiterated with pathophysiology as the focus in Year 2; however, pharmacology still remains a difficult subject for many medical students. Cardiovascular System 1 (CS1) and Renal System 1 (RS1) have been identified as courses in the first-year curriculum that would benefit from additional supplemental pharmacology resources.

Background & Rationale

Medical education in the modern age is an ever-evolving entity. Medical schools are constantly updating their curricula to better prepare students for their futures in the medical field. Two important concepts central to medical education today are the transition to “integrated” curricula and the utilization of electronic resources to supplement the core teaching material.

The transition of many curricula from a “traditional” 2+2 format, in which the first 2 years of preclinical basic science education is largely separate from the final 2 years of clinical education, to an “integrated” format, in which basic and clinical sciences are intertwined throughout the 4 years, has been an important shift for many undergraduate medical education programs.[1] An integrated curriculum, in addition to integrating different basic science disciplines as they pertain to each organ system (e.g., physiology, pharmacology, histology, etc.), aims to draw connections between basic science principles and their clinical applications beginning in the first year, a strategy that helps students learn how to approach and solve clinical problems and prepares them

for clinical experiences.[2] Furthermore, the integrated curriculum aims to develop critical-thinking skills that will allow students to apply the concepts learned in the preclinical years to the clinical clerkships and beyond.[3]

One of many strategies implemented in an integrated curriculum is contextualization of basic science concepts, whereby basic science concepts are applied to a clinical scenario in order to demonstrate their application in medical practice. Contextualization allows students to correlate the information they are learning in their preclinical courses to scenarios they would be likely to see in the clinical setting. Examples of contextualization include the widely implemented problem-based learning (PBL), in which small groups of students led by a tutor work through a clinical case together in order to demonstrate both basic science and clinical concepts.[1] In addition to helping students learn to apply basic science concepts to clinical problems, the integrated approach and case-based learning provide an educational platform that students find engaging. Furthermore, students perceive that these methodologies help them better understand and retain information presented.[4]

Medical education curricula today are rapidly evolving to implement a variety of different web-based learning platforms, collectively titled "e-learning." Medical students today tend to prefer interactive and self-directed learning opportunities, as opposed to traditional strictly lecture-based teaching.[5] Additionally, students desire access to a variety of online resources, such as podcasts, interactive tutorials, and patient simulations.[6] The availability of such online content allows students to individualize their education by identifying resources that will be beneficial to them, and to work through the material at a pace that is conducive to their own learning.[7] However, despite students' preferences for web-based and self-directed learning, these tools must be implemented strategically into medical school curricula. When compared head-to-head, strictly web-based learning is not superior to didactic lectures in terms of acquisition of knowledge, and e-learning alone lacks other important aspects of medical education including the promotion of interactions with faculty and peers.[5,6] E-learning is therefore not meant to replace lecture-based learning, but to provide students with resources they can utilize in a way that allows them to tailor their studies to fit their personal needs and enhance their education.

Several challenges have been identified in regard to basic pharmacology teaching in the undergraduate medical curriculum. Students often struggle to retain the wide breadth of information about each medication. One reason for this challenge is that students are expected to learn information about drugs before learning in detail about the diseases they are meant to treat.[8] Additionally, during the preclinical years the traditional medical curriculum often spends little time teaching students about therapeutic decision-making in the clinical setting.[9] Problem-based learning and contextualized learning of pharmacology is an effective way to counter these challenges. It allows students to apply basic principles to real-life clinical scenarios, begin to understand the disease states that they will be treating rather than simply memorizing drug names and facts, and work through the decision-making process in a step-by-step manner.[8,9] It follows that context-based lessons in pharmacology, presented as an interactive web-based resource for self-directed learning, would be an interesting and effective adjunct to pharmacology lectures for medical students in the preclinical years.

Objectives & Methods

The primary objective for this project is to develop a collection of interactive web-based pharmacology modules to supplement learning of first-year medical students and second-year pharmacy students in Cardiovascular System 1 (CS1) and Renal System 1 (RS1) courses in Year 1 of UC San Diego School of Medicine's Integrated Scientific Curriculum (ISC). These modules will provide students with an additional resource to assist in preparation for examinations and future clinical practice, as well as encourage students to apply basic science knowledge of pharmacology to clinical case scenarios and clinical decision-making.

In order to achieve the above objective, the CS1 and RS1 lectures and required pharmacology were first reviewed. Focusing on the core ("bold") drug classes and specific medications, the pharmacology material for each course was organized based on indication (e.g., hypertension, myocardial infarction). The pharmacology modules were then written, with each focusing on 1-2 indications and the core drug classes and medications used for the indication. Each module begins as a clinical case presentation and description of the disease process involved, followed by questions relating to the relevant medications. The modules in total cover at least all of the following principles for each of the core drug classes and medications: name, suffix common to the drug class (if applicable), mechanism of action, indication(s), and adverse effects.

Achievements & Future Considerations

The pharmacology modules resulting from this project will provide future first-year medical students and second-year pharmacy students with a relevant study resource to assist in the mastery of cardiovascular and renal pharmacology. The case presentations will provide clinical context and promote understanding of the disease states being treated, and help students learn to apply pharmacologic principles in clinical scenarios. Additionally, since the modules will be available via a web-based application, students will have the opportunity to use the cases at their own pace as they see fit to supplement their studies, not only in CS1 and RS1 but also when reviewing these drugs in the future. For example, these modules will be useful to second-year medical students during the Year 2 CS and RS courses (CS2 and RS2, respectively) and when studying for Step 1 of the USMLE. The Pharmacology Cases for CS1 and RS1 are included in Appendix A and Appendix B, respectively. In the future, the cases will be made available to students via the UCSD School of Medicine online portal for the respective courses. Additionally, modules may be amended in the future to integrate core principles of physiology as they relate to the clinical cases and pharmacology.

References

1. Kulasegaram KM, Martimianakis MA, Mylopoulos M, Whitehead C, Woods NN. Cognition Before Curriculum: Rethinking the Integration of Basic Science and Clinical Learning. *Acad Med.* 2013;88(10):1578-85. doi:10.1097/ACM.0b013e3182a45def

2. Balla JI, Biggs JB, Gibson M, Chang AM. The application of basic science concepts to clinical problem-solving. *Med Educ.* 1990;24(2):137-147. doi:10.1111/j.1365-2923.1990.tb02512.x
3. Abraham RR, Subramanya U, Sharmila T, Ramnarayan K. Clinically oriented physiology teaching: strategy for developing critical-thinking skills in undergraduate medical students. *Adv Physiol Educ.* 2004;28(3):102-104. doi:10.1152/advan.00001.2004
4. Thistlethwaite JE, Davies D, Ekeocha S, Kidd JM, MacDougall C, Matthews P, Purkis J, Clay D. The effectiveness of case-based learning in health professional education. A BEME systematic review: BEME Guide No. 23. *Med Teach.* 2012;34(6):e421-e444. doi:10.3109/0142159X.2012.680939
5. Chumley-Jones HS, Dobbie A, Alford CL. Web-based Learning: Sound Educational Method or Hype? A Review of the Evaluation Literature. *Acad Med.* 2002;77(10):S86-S93. https://journals.lww.com/academicmedicine/Fulltext/2002/10001/Web_based_Learning__Sound_Educational_Method_or.28.aspx
6. Hopkins L, Hampton BS, Abbott JF, Buery-Joyner SD, Craig LB, Dalrymple JL, Forstein DA, Graziano SC, McKenzie ML, Pradham A, Wolf A, Page-Ramsey SM. To the point: medical education, technology, and the millennial learner. *Am J Obstet Gynecol.* 2018;218(2):188-192. doi:10.1016/j.ajog.2017.06.001
7. Ruiz JG, Mintzer MJ, Leipzig RM. The Impact of E-Learning in Medical Education. *Acad Med.* 2006;81(3):207-212. https://journals.lww.com/academicmedicine/Fulltext/2006/03000/The_Impact_of_E_Learning_in_Medical_Education.2.aspx
8. Michel MC, Bischoff A, Jakobs KH. Comparison of problem- and lecture-based pharmacology teaching. *Trends Pharmacol Sci.* 2002;23(4):168-170. doi:10.1016/S0165-6147(00)01940-4
9. Richir MC, Tichelaar J, Geijteman ECT, de Vries TPGM. Teaching clinical pharmacology and therapeutics with an emphasis on the therapeutic reasoning of undergraduate medical students. *Eur J Clin Pharmacol.* 2008;64(2):217-229. doi:10.1007/s00228-007-0432-z

Appendix 1: Cardiovascular System 1 (CS1) Pharmacology Cases

Asthma

J is a 7-year-old girl who presents to her pediatrician with her father due to "difficulty breathing."

J's father explains that several times per week she complains that "it feels hard to breathe." The episodes often occur when she is playing, and she has trouble keeping up with her friends because she often has to stop to catch her breath. In addition, she occasionally wakes up due to coughing at night. J's father notes that these symptoms have been occurring for approximately 1 year, but seem to have worsened recently with the change in seasons. J's past medical history is significant for eczema.

On physical exam, J is breathing comfortably on room air without tachypnea or use of accessory respiratory muscles. On auscultation, she has good air movement bilaterally with mild scattered end-expiratory wheezes throughout the lung fields.
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J's pediatrician suspects asthma.

Asthma is a condition characterized by chronic airway inflammation, hyperresponsiveness to irritants, and reversible bronchoconstriction. Common presenting symptoms are cough, wheezing, shortness of breath, and chest tightness. Symptoms are often triggered by specific stimuli, such as upper respiratory infections, environmental allergens, or exercise. Additionally, patients with asthma may have evidence of other allergic disease – when present together, asthma, atopic dermatitis (eczema), and allergic rhinitis comprise the so-called "allergic triad."
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J's pediatrician orders *spirometry*, which confirms his suspicion of asthma. J's father asks how the condition is treated. J's pediatrician explains that the therapeutic options in asthma target chronic airway inflammation and reversible bronchoconstriction. Inhaled corticosteroids are the most commonly used agents to reduce chronic airway inflammation (you will learn more about the use of inhaled corticosteroids in Pulmonary System I & II). The use of an additional inhaled medication reduces the reversible bronchoconstriction seen in asthma.

a) What receptors are present in the bronchioles that can be targeted in the treatment of asthma? To what class of receptors do they belong?

β_2 receptors and M_3 receptors are both present on the bronchial smooth muscle. Both are G protein-coupled receptors (GPCRs).

b) What class of medications targeting β_2 receptors is employed in the treatment of asthma? What is the suffix common to this class of medication? Give an example.

β_2 agonists are commonly used in the first-line treatment of asthma. Most β_2 agonists share the suffix "***-terol***." Examples include ***albuterol***, salmeterol, formoterol, and metaproterenol.

c) What is the mechanism of action of β_2 agonists in the treatment of asthma?

β_2 agonists bind to β_2 receptors on bronchial smooth muscle. β_2 receptors couple to G_s, and stimulation by the agonist results in increased intracellular cAMP and subsequent smooth muscle relaxation, leading to bronchodilation.

d) What are common adverse effects of β_2 agonists?

Common adverse effects of β_2 agonists are tremor, CNS effects (anxiety, apprehension), and cardiac stimulation (tachycardia, palpitations).

e) What are the mechanisms underlying tremor and cardiac stimulation caused by β_2 agonists?

Tremor is caused by stimulation of β_2 receptors on skeletal muscle. Cardiac stimulation is caused by stimulation of β_1 receptors in the heart; there is some cross-reactivity with β_1 receptors as the β_2 agonists are not 100% selective.

f) What class of medications targeting M_3 receptors is employed in the treatment of asthma? What is their mechanism of action?

mAChR antagonists can be used in the treatment of asthma. The antagonist binds to M_3 receptors on bronchial smooth muscle. M_3 receptors couple to G_q; under normal circumstances, ACh binds to the receptor, resulting in increased intracellular [Ca^{2+}] and subsequent smooth muscle contraction. Blockade of M_3 receptors on bronchial smooth muscle by mAChR antagonists prevents this stimulation, decreasing parasympathetic tone to the bronchioles and resulting in bronchodilation.

mAChR antagonists are not used in the first-line treatment of asthma; rather, they are used as long-term maintenance therapy and are added to the treatment regimen if patients are not adequately controlled on first-line therapy. Tiotropium is the only mAChR antagonist that is currently approved for the treatment of asthma, though others (e.g., ipratropium) are used off-label in clinical practice.

References:
https://www.uptodate.com/contents/asthma-in-children-younger-than-12-years-initial-evaluation-and-diagnosis

https://www.uptodate.com/contents/asthma-in-children-younger-than-12-years-epidemiology-and-pathophysiology

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COPD; BPH

Mr. R is a 60-year-old man who presents to his primary care physician with a chief complaint of "shortness of breath."

Mr. R has had increasing shortness of breath on exertion for the several years. He reports that he has had a "smoker's cough" for many years, but over the past year he has been coughing up white-colored sputum, especially in the morning. He has not had fevers, blood-tinged sputum, or weight loss during this time. Mr. R's past medical history is significant for hypertension and benign prostatic hyperplasia (BPH). He currently takes losartan (AT_1 receptor blocker [ARB]) to control his blood pressure. He has smoked 2 packs of cigarettes daily for 30 years.

On physical exam, he is seated comfortably, speaking in full sentences without difficulty, and has good oxygen saturation on room air. His lungs are mildly hyperresonant on percussion, the expiratory phase is prolonged, and scattered faint expiratory wheezes are heard on auscultation.
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Mr. R's physician suspects *chronic obstructive pulmonary disease* (*COPD*).

COPD is characterized by the progressive destruction of the lung parenchyma and chronic inflammation of the small airways, leading to obstruction of airflow. Patients typically present with insidious onset of shortness of breath, chronic cough, and sputum production. On physical exam, patients may have prolonged expiration, as air is *trapped* in the lung by obstructive small airway disease, and expiratory wheezing. With disease progression, patients may exhibit hyperresonance to percussion of the lung fields and/or a "barrel chest" appearance due to destruction of lung parenchyma and air trapping. Findings such as "pursed-lip" breathing in an attempt to help "stent" the airways open, evidence of respiratory distress at rest such as "tripoding" (leaning forward with the hands supported on the knees) and use of accessory muscles of respiration, or low oxygen saturation may be seen in very severe disease or in the setting of an acute exacerbation. The most important risk factor for the development of COPD is a history of cigarette smoking.

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Mr. R's physician orders spirometry, which shows an obstructive pattern of lung disease and supports the diagnosis of COPD.

Mr. R's physician counsels Mr. R regarding smoking cessation, explaining that quitting smoking is one of the most important factors in preventing progression of the disease. In addition, he wishes to start medical management of the condition.

a) Which of the following classes of medications are used in the treatment of COPD? More than one answer may be correct. Give an example of each.

i. α_1 agonists
ii. α_1 antagonists
iii. α_2 agonists
iv. β_1 agonists
v. β_1 antagonists
vi. β_2 agonists
vii. mAChR agonists
viii. mAChR antagonists

β_2 agonists (iv) and mAChR antagonists (viii) are used in the treatment of COPD. Examples of β_2 agonists used in COPD include ***albuterol***, salmeterol, formoterol, metaproterenol, and olodaterol. Most share the common suffix "***-terol***." Examples of mAChR antagonists used in COPD include ***ipratropium***, tiotropium, aclidinium, umeclidinium, and glycopyrrolate.

b) What is the mechanism of action of β_2 agonists and mAChR antagonists in the treatment of COPD?

β_2 agonists stimulate β_2 receptors on bronchial smooth muscle, resulting in bronchodilation and relief of small airway obstruction. mAChR antagonists block M_3 receptors on bronchial smooth muscle and secretory glands, blocking parasympathetic tone to the lungs and resulting in bronchodilation and decreased secretions.

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Mr. R's physician prescribes ***ipratropium***, an inhaled mAChR antagonist.

c) What are the possible adverse effects of ipratropium? Recall Mr. R has a history of hypertension and BPH; what about his history is important for his physician to note when prescribing ipratropium and why?

Possible side effects of mAChR antagonists such as ipratropium are predictable from the effects of decreasing parasympathetic tone to various effector organs. Such adverse effects include dry mouth (xerostomia), constipation, urinary retention, tachycardia, and attacks of angle-closure glaucoma in susceptible individuals. Other anticholinergic adverse effects include drowsiness and confusion (especially in elderly patients or patients with underlying cognitive dysfunction).

Mr. R has a history of *benign prostatic hyperplasia* (*BPH*), caused by proliferation of the cells in the prostate. The prostate is a gland that is located around the urethra in males, and hyperplasia of the prostate can cause obstruction of the urethra. BPH is common in elderly men, and symptoms include urinary frequency, urinary urgency, nighttime awakenings to urinate, difficulty starting/maintaining a stream of urine, and straining to urinate. Importantly, patients with BPH are at risk of *acute urinary retention* as an adverse effect of anticholinergic drugs, and these medications should be used with caution in such patients.

d) What class of medications targeting the autonomic nervous system is used in the treatment of BPH? What suffix is common to this class of medication?

Certain α_1 antagonists are used in the treatment of BPH. All α_1 antagonists share the common suffix "***-osin***." Examples include doxazosin, terazosin, and tamsulosin (these drugs are not "bold" on the Cardiovascular System I drug list).

e) What is the primary mechanism of action of α_1 antagonists in the treatment of BPH?

α_1 antagonists bind to α_1 receptors in the prostate and the neck of the bladder, resulting in relaxation of the smooth muscle and subsequent relief the obstruction of the urethra. (Note that studies suggest that α_1 antagonists also induce apoptosis of smooth muscle cells in the prostate, therefore also contributing to long-term relief of the obstruction of BPH.)

References:
https://www.uptodate.com/contents/chronic-obstructive-pulmonary-disease-definition-clinical-manifestations-diagnosis-and-staging

https://www.uptodate.com/contents/medical-treatment-of-benign-prostatic-hyperplasia

https://www.ncbi.nlm.nih.gov/pubmed/12629407

Mycetism

Ms. A is a healthy 25-year-old female who presents to the Emergency Department with a chief complaint of "food poisoning." She had been camping with her friends, and developed abdominal cramping and diarrhea within one hour of eating dinner this evening. For dinner she ate chicken with wild celery and wild mushrooms she foraged on a hike. She states her friends cooked fish they caught in the creek for dinner, and they do not have any symptoms.
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The attending in the ED suspects Ms. A's symptoms are due to *mycetism*, or mushroom poisoning, caused by *muscarine* present in some species of mushrooms.

a) What receptors does muscarine act on, and where are they located?

Muscarine is an agonist at mAChRs; in fact, mAChRs got their name because they are selectively stimulated by muscarine. mAChRs are located at all parasympathetic neuroeffector junctions (NEJs), cholinergic sympathetic NEJs, and on vascular smooth muscle and endothelial cells (non-innervated).

b) What are the subtypes of mAChR? Briefly, what is the molecular mechanism stimulated by an agonist binding to the receptors and the ultimate result?

There are 5 subtypes of mAChR (M_1-M_5). All are G protein-coupled receptors (GPCRs). For this course (an for understanding the most important clinical uses of drugs that target mAChRs), we will focus on M_2 and M_3.

M_2 receptors couple to G_i. Stimulation of the receptor leads to a decrease in intracellular cAMP and effects on ion channels, including activation of K^+ channels leading to an increase in efflux of K^+ from the cell and inhibition of Ca^{2+} channels leading to a decrease in Ca^{2+} influx into the cell.

M_3 receptors couple to G_q. Stimulation of the receptor leads to an increase in intracellular [Ca^{2+}]. This can have one of several ultimate effects depending on cell type, including smooth muscle contraction, exocytosis of secretory granules, or synthesis of nitric oxide (NO).

c) For each organ, what subtype of mAChR mediates the predominant response? What is the effect of stimulation of the receptor on each organ?

i. GI tract
ii. Urinary tract
iii. Bronchioles
iv. Eye
v. Secretory glands
vi. Heart
vii. Blood vessels

i. GI tract: M_3. Stimulation of receptors on smooth muscle results in increased GI motility and defecation.
ii. Urinary tract: M_3. Stimulation results in increased bladder tone and urination.
iii. Bronchioles: M_3. Stimulation of receptors on bronchial smooth muscle results in bronchoconstriction.
iv. Eye: M_3. Stimulation of receptors on pupillary constrictor muscle results in miosis. Stimulation of receptors on ciliary muscle results in contraction of the ciliary muscle and accommodation for near vision.
v. Secretory glands: M_3. Stimulation of receptors on secretory glands in various locations results in salivation, bronchial secretion, nasal secretion, lacrimation (tearing), and diaphoresis (sweating). Note that diaphoresis due to stimulation of M_3 receptors on sweat glands is the result of *sympathetic cholinergic* transmission.
vi. Heart: M_2. Stimulation of receptors in the sinoatrial (SA) node results in decreased heart rate. Stimulation of receptors in the atrioventricular (AV) node results in slowed AV conduction.
vii. Blood vessels: M_3. Stimulation of receptors on vascular smooth muscle results in vasoconstriction. Stimulation of receptors on endothelial cells results in increased synthesis of NO, which then diffuses to adjacent vascular smooth muscle cells, causing vasodilation. As long as the endothelium is intact, NO-mediated vasodilation is the dominant effect. Note that these receptors are not innervated, and their physiologic role is not understood. However, their presence has important pharmacologic implications as exogenous drugs can act on these receptors.

d) How does the mechanism of action of muscarine explain Ms. A's symptoms? What other symptoms might you expect Ms. A to be experiencing? What signs might you expect to find on physical examination? What abnormalities might be present on ECG?

Ms. A is presenting with abdominal cramping and diarrhea. Muscarine stimulates M_3 receptors on GI smooth muscle, resulting in smooth muscle contraction, and subsequent increased GI motility and abdominal cramping. Muscarine also stimulates M_3 receptors on secretory glands in the GI tract, resulting in increased GI secretions. The combination of increased GI motility and increased GI secretions leads to diarrhea.

Ms. A might be expected to be experiencing additional symptoms due to the effects of muscarine on other organ systems. Such possible symptoms include increased salivation, lacrimation, diaphoresis, chest tightness or wheezing (due to increased bronchial secretions and bronchoconstriction), blurry vision at distance (due to inability to accommodate for far distance), decreased peripheral visual acuity in low light (due to pupillary constriction), and dizziness/lightheadedness (due to bradycardia, AV block, or hypotension).

Possible findings on physical exam include evidence of increased secretions (lacrimation, salivation, diaphoresis), wheezing (due to increased bronchial secretions and bronchoconstriction), bradycardia, hypotension, hyperactive bowel sounds (due to increased GI motility), miosis, and evidence of dehydration (e.g., dry mucous membranes, decreased capillary refill; due to fluid losses from diarrhea).

Possible abnormalities on ECG include bradycardia and AV block.
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Ms. A begins to complain of lightheadedness. An ECG is obtained, which demonstrates bradycardia and AV block.

e) What medication can be administered to treat Ms. A's condition? What is its mechanism of action?

Atropine can be administered to treat mycetism, as well as bradycardia and AV block in the acute care setting not associated with mycetism. Atropine is a mAChR antagonist. It competes with ACh (and, in the case of mycetism, with muscarine) for binding to mAChRs.

f) What are the predictable adverse effects of atropine?

The adverse effects of mAChR antagonists such as atropine can be predicted from the effects of decreasing cholinergic tone to various effector organs. Such effects include dry mouth (xerostomia), urinary retention (especially in elderly men with BPH), constipation, and attacks of angle-closure glaucoma in susceptible patients. mAChR antagonists can also cause confusion (especially in elderly patients or patients with underlying cognitive dysfunction) and drowsiness.

References:
https://www.uptodate.com/contents/clinical-manifestations-and-evaluation-of-mushroom-poisoning

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Overactive bladder

Ms. H is a 62-year-old male who presents to his primary care physician with a chief complaint of "urinary incontinence."

For the last two months, Ms. H has had frequent strong urges to urinate throughout the day. She wakes up 3-4 times nightly to urinate as well. There have been several episodes of urinary incontinence where she has had a sudden urge to urinate and was unable to reach the restroom in time. Her physical exam is normal.

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Ms. H's physician suspects she is suffering from *overactive bladder* (*OAB*).

OAB is caused by hyperactivity of the bladder detrusor muscle. Etiologies include neurologic disorders (e.g., spinal cord injury, multiple sclerosis), pelvic surgery, bladder outlet obstruction (e.g., benign prostatic hyperplasia in men), foreign bodies within the bladder (e.g., bladder stones), altered bladder microbiome, or it may be idiopathic. Patients with OAB present with urinary urgency, frequent small-volume voids throughout the day, and nocturia (waking at night to urinate). Patients may also experience episodes of urinary incontinence associated with urges if unable to reach a restroom in time (termed *urgency incontinence*).

Note that when bladder dysfunction is caused by disorders of the central or peripheral nervous system, it is often termed *neurogenic bladder*; neurogenic bladder can be classified as either *flaccid* (characterized by detrusor underactivity) or *spastic* (characterized by detrusor hyperactivity).

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a) Which of the following classes of medications targeting the autonomic nervous system are used in the treatment of OAB? More than one answer may be correct. Give an example of each.

i. mAChR agonists
ii. mAChR antagonists
iii. α_1 agonists
iv. α_2 agonists
v. α antagonists
vi. β_1 agonists
vii. β_2 agonists
viii. β_3 agonists
ix. β antagonists

mAChR antagonists (ii; e.g., ***oxybutynin***, tolterodine, trospium, darifenacin, solifenacin, fesoterodine) and β_3 agonists (viii; e.g., mirabegron) are used in the treatment of OAB.

b) What is the mechanism of action of the mAChR antagonists such as oxybutynin in the treatment of OAB?

These medications bind nonselectively to mAChRs. They bind to and inhibit M_3 receptors on the bladder detrusor muscle, inhibiting smooth muscle contraction.

(Note that tolterodine is functionally selective for mAChRs in the bladder, and darifenacin and solifenacin are relatively selective for M_3 over M_2 receptors.)

c) What are the adverse effects of oxybutynin?

The adverse effects of oxybutynin and other mAChR antagonists are predictable by their effects at other cholinergic NEJs. They include xerostomia, urinary retention (especially in men with benign prostatic hyperplasia), constipation, confusion (especially in elderly patients or patients with underlying cognitive dysfunction), drowsiness, and attacks of acute angle-closure glaucoma in susceptible patients.

d) What is the mechanism of action of β_3 agonists in the treatment of OAB?

β_3 agonists stimulate β_3 receptors on bladder smooth muscle, resulting in detrusor relaxation. (β_3 receptors, like all β receptors, couple to G_s, and have a role in lipolysis and thermogenesis in addition to bladder smooth muscle relaxation.)

References:
https://www.uptodate.com/contents/lower-urinary-tract-symptoms-in-men

https://www.uptodate.com/contents/chronic-complications-of-spinal-cord-injury-and-disease

https://www.uptodate.com/contents/treatment-of-urgency-incontinence-overactive-bladder-in-women

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Urinary retention

Ms. V is a 71-year-old female who presents to her primary care physician with a chief complaint of "urinary incontinence."

For the past year Ms. V has had to strain to urinate and notes that the stream of urine is slower than it used to be. She cannot feel when her bladder is full as well as she previously could. In the last two months, she has noticed that her underwear is often wet with small amounts of urine. Ms. S has a past medical history of type 2 diabetes mellitus diagnosed 20 years ago, for which she takes metformin and glipizide. On physical exam, sensation to pinprick is absent in her feet bilaterally, and a smooth nontender suprapubic mass is noted on palpation of the abdomen.
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Ms. V's physician suspects she is suffering from *urinary retention*.

Urinary retention is caused by underactivity of the bladder detrusor muscle, obstruction of the bladder outlet or urethra, or a combination of both. In this module, we will focus on *detrusor underactivity*. Etiologies of detrusor underactivity include age, diabetes mellitus (due to damage to sensory and motor neurons), a variety of neurologic disorders, and medications with anticholinergic adverse effects (e.g., anticholinergic drugs, antihistamines). Patients with chronic urinary retention often present with slow urine stream, straining to urinate, and may complain about inability to feel when their bladder is full. Patients may also experience episodes of urinary incontinence (termed *overflow incontinence*) due to leakage of urine from a full bladder. Physical exam may be notable for a palpable distended bladder. Diagnosis is confirmed by measuring an elevated volume of urine in the bladder after the patient attempts to empty their bladder (*post-void residual*).

Note that when bladder dysfunction is caused by disorders of the central or peripheral nervous system, it is often termed *neurogenic bladder*; neurogenic bladder can be classified as either *flaccid* (characterized by detrusor underactivity) or *spastic* (characterized by detrusor hyperactivity).
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Ms. V's physician uses ultrasound imaging to measure a post-void residual, which confirms the diagnosis of urinary retention.

a) What medication can be used to treat urinary retention? What class of medication is it?

Bethanechol, a mAChR agonist, can be used in the treatment of urinary retention (although it is not commonly used, as its efficacy is limited).

Note that bethanechol is indicated for use in both acute urinary retention (such as post-operatively or post-partum) and for use in chronic urinary retention due to neurologic dysfunction (i.e., flaccid neurogenic bladder). It has not been shown to be effective in the treatment of chronic urinary retention of other etiologies. Additionally, a patient with this degree of bladder distention (a bladder palpable above the pelvis likely contains at least a liter of urine) would likely be treated initially with bladder catheterization to decompress the bladder prior to the use of medication.

b) What is the mechanism of action of bethanechol in the treatment of urinary retention?

Bethanechol binds nonselectively to mAChRs. In the bladder detrusor muscle, it stimulates M_3 receptors (coupled to G_q), resulting in increased intracellular [Ca^{2+}] and subsequent smooth muscle contraction and bladder emptying.

c) What are the adverse effects of bethanechol and other mAChR agonists?

Adverse effects of bethanechol and other mAChR agonists can be predicted by the effects of stimulating mAChRs on various effector organs. These include abdominal cramping, diarrhea, nausea/vomiting, diaphoresis, hypersalivation, lacrimation, urinary urgency, and visual disturbances.

d) What are other indications for the use of mAChR agonists?

Other indications for use of mAChR agonists are conditions in which an increase in parasympathetic activity is beneficial. These include: postoperative ileus (***bethanechol***), xerostomia (pilocarpine), glaucoma (carbachol, pilocarpine), and bronchoprovocation (methacholine; the "methacholine challenge" is used for the diagnosis of asthma).

e) What conditions are contraindications to the use of bethanechol and other mAChR agonists? Why?

mAChR agonists are contraindicated in patients with asthma or COPD because they can trigger bronchoconstriction and exacerbate these conditions.

mAChR agonists are also contraindicated in patients with obstruction of the urinary or gastrointestinal tract, as contraction of smooth muscle against a fixed obstruction can cause damage to these structures.

References:
https://www.uptodate.com/contents/chronic-urinary-retention-in-women

https://www.uptodate.com/contents/lower-urinary-tract-symptoms-in-men

https://www.uptodate.com/contents/chronic-complications-of-spinal-cord-injury-and-disease

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Narcolepsy

Mr. I is a 24-year-old previously healthy male who presents to his primary care physician with a chief complaint of "fatigue."

He reports feeling tired during the day for several years. He was previously able to manage his daytime sleepiness with frequent short naps, but he recently started at a new job and is now having trouble fulfilling his responsibilities. He has even started to have episodes where he suddenly falls asleep at his desk or during meetings. There have been no changes in his sleep; he sleeps for 7-8 hours each night and feels well rested in the morning. On further questioning about his sleep, he notes that when he is falling asleep he occasionally sees or hears very vivid images or sounds, and sometimes when falling asleep or upon awakening he is unable to move his arms and legs for a couple of minutes. On exam, he appears comfortable. His vital signs are within normal limits and BMI is 22. Physical exam, including complete neurologic exam, is normal.
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Mr. I's physician suspects he may be suffering from *narcolepsy*. He undergoes a sleep study, and results are consistent with the diagnosis.

Narcolepsy is a neurologic disorder characterized by chronic daytime sleepiness. The etiology of narcolepsy involves decreased levels of the CNS neurotransmitters orexin-A and orexin-B, which stimulate neurons in the hypothalamus in the brain. Patients generally have good nighttime sleep quality and feel refreshed in the morning. Daytime sleepiness can be so severe that patients suddenly fall asleep at inappropriate times during the day ("sleep attacks"), and sleepiness is temporarily improved with short naps throughout the day. Classic features of narcolepsy also include sleep paralysis (complete paralysis of voluntary muscles for up to a couple of minutes when falling asleep or immediately upon awakening), hypnogogic hallucinations (vivid visual, auditory, and/or tactile hallucinations when falling asleep), and cataplexy (sudden episodes of partial or generalized muscle paralysis lasting less than two minutes, often precipitated by laughter or excitement).
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a) What drug that targets the autonomic nervous system can be used in the treatment of narcolepsy? To what class of medication does this drug belong?

Amphetamine is used in the treatment of narcolepsy. It is an amphetamine-like indirect sympathomimetic.

b) What is the mechanism of action of amphetamine?

Amphetamine is transported into adrenergic nerve terminals via the norepinephrine transporter (NET), and then into synaptic vesicles by the vesicular monoamine transporter (VMAT). This causes displacement of NE from the synaptic vesicles, allowing NE to escape the nerve terminal and enter the junctional space, resulting in increased stimulation of postsynaptic cells. In narcolepsy, increased noradrenergic stimulation in the CNS helps to alleviate daytime sleepiness. Additionally, amphetamine may reduce sleep paralysis, hypnogogic hallucinations, and cataplexy.

c) What are the primary adverse effects of amphetamine?

The primary adverse effects of amphetamine are the result of increased noradrenergic stimulation of various effector organs. Elevated blood pressure, elevated heart rate, and cardiac arrhythmias are possible due to increased sympathetic stimulation of the heart and of the contraction of vascular smooth muscle. Insomnia, headaches, and anxiety are possible due to increased CNS stimulation.

d) What are other indications for the use of amphetamine?

Amphetamine is used in the treatment of attention deficit hyperactivity disorder (ADHD). It is also a drug of abuse.

References:
https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-narcolepsy-in-adults

https://www.uptodate.com/contents/treatment-of-narcolepsy-in-adults

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Eye redness due to ocular irritation; Rhinorrhea due to allergic or nonallergic rhinitis; Nasal congestion

Ms. W is a 27-year-old female with a history of hay fever. With the change of the seasons from summer to fall, she has noticed an increase in her symptoms of eye redness and rhinorrhea. She presents to her primary care physician to ask about medications to help relieve her symptoms.

a) What class of medications targeting the autonomic nervous system is used in the treatment of ocular redness due to irritation? What is the suffix common to these medications?

Nonselective α agonists are used in the treatment of ocular redness. The suffix common to these medications is "***-zoline***." Examples include oxymetazoline and tetrahydrozoline. For this indication, these medications are administered as topical ophthalmic drops.

b) What is the mechanism of action of the nonselective α agonists in the treatment of ocular redness?

α agonists stimulate α_1 receptors on blood vessels on the surface of the eye (note that they are applied topically and therefore act locally), resulting in constriction of these vessels.

c) What class of medications targeting the autonomic nervous system is used in the treatment of rhinorrhea due to allergic rhinitis? Give an example.

mAChR antagonists (e.g., ***ipratropium***) are used in the treatment of rhinorrhea due to both allergic and nonallergic rhinitis. For this indication, ipratropium is administered as a topical nasal spray.

d) What is the mechanism of action of ipratropium in the treatment of rhinorrhea?

Ipratropium blocks M_3 mAChRs on secretory glands in the nasal cavity, resulting in decreased nasal secretions.
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Ms. W experiences good relief of her allergic symptoms using the treatments discussed previously. In the winter, she returns to her primary care physician with several days of fever, cough, and nasal congestion, consistent with viral upper respiratory infection. Her physician explains that management is supportive while her body clears the infection. Ms. W wonders if there is a medication that can help relieve her nasal congestion.

e) Which of the following classes of medications are used in the treatment of nasal congestion? More than one answer may be correct. Give an example of each.

i. Amphetamine-like indirect sympathomimetics
ii. Reuptake inhibitor indirect sympathomimetics
iii. Endogenous catecholamines
iv. α agonists

v. α antagonists
vi. β agonists
vii. β antagonists
viii. mAChR agonists
ix. mAChR antagonists

Amphetamine-like indirect sympathomimetics (i; e.g., pseudoephedrine) and α agonists (iv; α_1 selective (e.g., ***phenylephrine***), nonselective ("***-zolines***," e.g., oxymetazoline, tetrahydrazoline) are used in the treatment of nasal congestion.

f) What is the mechanism of action of pseudoephedrine (an amphetamine-like indirect sympathomimetic) in the treatment of nasal congestion?

Pseudoephedrine is transported into synaptic vesicles (via NET, VMAT), where it displaces NE from the vesicles. Free NE can then enter the junctional space to act on adrenergic receptors. NE stimulates α_1 receptors on blood vessels in the nasal mucosa, resulting in vasoconstriction and subsequent decrease of mucosal edema that contributes to nasal congestion.

g) What is the mechanism of action of α agonists (phenylephrine and the "-zolines") in the treatment of nasal congestion?

These medications stimulate α_1 receptors on blood vessels in the nasal mucosa, resulting in vasoconstriction and subsequent decrease of mucosal edema. (Note that these medications are administered topically as nasal spray. Phenylephrine is available in oral formulation, but the latter is no more effective than placebo.)

h) What are the primary adverse effects of phenylephrine?

The primary adverse effects of phenylephrine include elevation of blood pressure (due to systemic stimulation of α_1 receptors with subsequent increase in systemic vascular resistance) and rebound rhinorrhea on discontinuation after using the medication for an extended period of time. For this reason, use of phenylephrine is generally limited to 3 days or less, and should not be considered for chronic relief of congestion.

References:
https://www.uptodate.com/contents/conjunctivitis

https://www.uptodate.com/contents/pharmacotherapy-of-allergic-rhinitis

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Glaucoma; Ophthalmologic exam

Ms. E is an 80-year-old female who presents to the ophthalmologist for follow up of open-angle glaucoma.

Ms. E was diagnosed with open-angle glaucoma on a routine ophthalmologic screening exam 5 years ago, which revealed increased intraocular pressure (IOP) and "cupping" of the optic nerve on fundoscopic exam. She reports feeling well, and she has not noticed any changes in her vision since her last visit to the ophthalmologist. Today, the ophthalmologist will do a complete ophthalmologic examination, including

visual acuity and visual field testing, tonometry (measurement of IOP), and fundoscopic exam, and will discuss medications with Ms. E.
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Glaucoma is a group of diseases characterized by optic nerve neuropathy secondary to increased intraocular pressure (IOP), including open-angle glaucoma, acute angle-closure glaucoma, and developmental/congenital glaucoma. Here, we will discuss *open-angle glaucoma*. See Case Studies: Autonomic Pharmacology small group session for discussion of *acute angle-closure glaucoma*.

Open-angle glaucoma is characterized by chronically elevated IOP, which leads to gradual optic nerve damage. Elevation of IOP in open-angle glaucoma is caused by an imbalance between the rates of production and drainage of aqueous humor (the fluid that fills the anterior and posterior chambers of the eye). Damage to the optic nerve eventually leads to visual field loss and later to central vision loss, decreased visual acuity, and even blindness. However, most patients are diagnosed by routine screening exam and are asymptomatic at the time of diagnosis. Characteristic findings on exam are increased IOP and changes to the optic disc (the portion of the optic nerve visualized on fundoscopic exam).

a) What pharmacologic strategies are employed in the treatment of glaucoma?

The only pharmacologic approach proven to prevent optic nerve damage and vision loss in open-angle glaucoma is a reduction of IOP. This can be achieved by either (a) decreasing the rate of aqueous humor production or (b) increasing the rate of aqueous humor drainage.

b) Which of the following classes of medication are employed in the treatment of glaucoma? More than one answer may be correct.

i. α_1 agonists
ii. α_2 agonists
iii. α antagonists
iv. β agonists
v. β antagonists
vi. mAChR agonists
vii. mAChR antagonists
viii. Anti-ChEs
ix. Eicosanoids
x. Eicosanoid antagonists

α_2 agonists (ii; e.g., brimonidine, apraclonidine), β antagonists (v; e.g., timolol), mAChR agonists (vi; e.g., carbachol, pilocarpine), anti-ChEs (viii; e.g., physostigmine, echothiophate), and eicosanoids (ix; e.g., latanoprost, bimatoprost, travoprost, unoprostone, tafluprost) are used in the treatment of glaucoma.

c) What is the mechanism of action of each aforementioned class of medication in the treatment of glaucoma?

The precise mechanism of α_2 agonists in the treatment of glaucoma is poorly understood. Topical application results in constriction of blood vessels in the eye, leading to reduced aqueous humor production (in contrast to systemic application of α_2 agonists, which results in vasodilation by decreasing sympathetic vascular tone). α_2 agonists also appear to increase aqueous humor outflow from the anterior chamber.

β antagonists block β_2 receptors on the ciliary body, resulting in decreased aqueous humor production.

mAChR agonists stimulate M_3 receptors on the pupillary constrictor and ciliary muscles, resulting in increased patency of the aqueous humor outflow tract and subsequent increased aqueous humor drainage from the anterior chamber.

Anti-ChEs inhibit AChE at cholinergic NEJs. In the eye, this results in stimulation of the pupillary constrictor and ciliary muscles, resulting in increased aqueous humor drainage as above.

Eicosanoids, specifically $PGF_{2\alpha}$ prodrugs/analogs, stimulate FP receptors in the eye, resulting in increased drainage of aqueous humor from the anterior chamber.

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Ms. E's ophthalmologist begins her exam. Her visual acuity is unchanged, and visual field testing shows slight interval decrease in peripheral vision compared to her last visit. Tonometry shows an interval decrease in IOP on her current medication regimen. In order to thoroughly visualize the fundus, Ms. E's ophthalmologist will use topical medication to dilate her pupils.

d) Which of the following classes of medications targeting the autonomic nervous system are used to produce mydriasis (pupillary dilatation) for the ophthalmologic exam? More than one answer may be correct.

i. α_1 agonists
ii. α_2 agonists
iii. α antagonists
iv. β agonists
v. β antagonists
vi. mAChR agonists
vii. mAChR antagonists
viii. Anti-ChEs
ix. Eicosanoids
x. Eicosanoid antagonists

α_1 agonists (i) and mAChR antagonists (vii) are used to produce mydriasis for ophthalmologic exam.

e) What is an example of an α_1 agonist used for ophthalmologic exam? What is its mechanism of action for this indication?

Phenylephrine is an α_1 agonist used for ophthalmologic exam. Phenylephrine stimulates α_1 receptors on the pupillary dilator muscle, resulting in mydriasis.

f) What is the mechanism of action of mAChR antagonists for ophthalmologic exam?

mAChR antagonists (e.g., homatropine, cyclopentolate, tropicamide) block M_3 receptors on the pupillary constrictor muscle, resulting in mydriasis. They also block M_3 receptors on the ciliary muscle, resulting in cycloplegia (inability to accommodate for near vision).

References:

https://www.uptodate.com/contents/open-angle-glaucoma-epidemiology-clinical-presentation-and-diagnosis

https://www.uptodate.com/contents/open-angle-glaucoma-treatment

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4523637/

Pheochromocytoma; Postoperative ileus

Ms. S is a previously healthy 36-year-old woman who presents to her primary care physician with a chief complaint of "palpitations."

She reports a 2-month history of episodes where she suddenly feels her heart racing. When this occurs, she also feels anxious, sweaty, and develops a mild headache. She cannot think of anything that triggers the episodes, which often occur at rest. She tries to sit down and do deep-breathing exercises, but this does not seem to help. The episodes tend to last for approximately thirty minutes before self-resolving. After the symptoms resolve, she feels very tired and often has to lie down for a while. Her vital signs in the office are within normal limits and her complete physical exam is normal.
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One of the possibilities on the differential diagnosis compiled by Ms. S's physician is a *pheochromocytoma*.

Pheochromocytomas are rare catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla. (Less commonly, such tumors can arise from the paravertebral sympathetic ganglia; tumors in this location are termed *paragangliomas*.) Pheochromocytomas are symptomatic in approximately 50% of cases. The classic presentation is a triad of headache, tachycardia, and diaphoresis (although a minority of patients present with the complete triad). Episodes are typically paroxysmal, meaning they occur suddenly with rapid intensification. Patients can additionally have hypertension and other symptoms attributable to increased circulating catecholamines, such as tremor, palpitations, and panic-like symptoms. Pheochromocytomas in asymptomatic individuals are discovered incidentally on abdominal imaging, or on autopsy.
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Ms. S's physician orders a 24-hour urine collection to measure the level of *urinary fractionated metanephrines*, metabolites produced by breakdown of epinephrine and excreted into the urine. Her level of urinary metanephrines returns elevated, confirming a *biomedical diagnosis* of a catecholamine-secreting tumor. Her physician next orders a CT scan of the abdomen and pelvis, which reveals a 5-cm mass located in the right adrenal gland.

Ms. S is referred to the Endocrine Surgery clinic to discuss treatment of her pheochromocytoma. The surgeon explains that surgical removal is the definitive treatment, but that it is important to start a medication prior to the surgery to prevent dangerous intraoperative complications.

a) What class of medications is used in the preoperative management of pheochromocytoma? Give an example.

Nonselective α receptor antagonists are used in the preoperative management of pheochromocytoma. Examples include ***phentolamine*** and phenoxybenzamine.

(Note that methyltyrosine, an inhibitor of tyrosine hydroxylase that decreases catecholamine synthesis, can also be used in the preoperative treatment of pheochromocytoma. However, due to severe adverse effects, this medication is not first-line and is used only in patients refractory to other therapies. Methyltyrosine is not a "bold" drug in Cardiovascular System I.)

b) What is the purpose of using an α receptor antagonist prior to surgery?

Patients are started on α antagonists prior to surgical removal of pheochromocytoma to prevent hypertensive crisis intraoperatively. During surgery, there is a risk of massive secretion of catecholamines into the bloodstream, which can result in dangerous elevation of blood pressure caused by α_1-mediated vasoconstriction. Administering an α antagonist prior to the surgery helps to prevent this possible complication.

c) Ms. S is instructed to begin taking phentolamine 10 days prior to the scheduled surgery. What major adverse effect should she be aware of? What is the mechanism of this adverse effect?

The primary adverse effect of α antagonists is *orthostatic hypotension*. Orthostatic hypotension is a significant decrease in blood pressure on standing. Symptoms result from decreased blood flow to the brain and include lightheadedness, dizziness, and/or syncope (fainting).

Under normal circumstances, standing from a seated position triggers a response called the *baroreceptor reflex* (*BRR*), in which a small decrease in blood pressure results in increased sympathetic and decreased parasympathetic outflow to the cardiovascular system. This results in (a) α_1-mediated vasoconstriction and (b) β_1-mediated cardiac stimulation that act to maintain blood pressure.

When α receptors are blocked by a medication such as phentolamine, α_1-mediated vasoconstriction is inhibited in response to the BRR. As a result, blood pressure is not able to be maintained on standing and the patient becomes hypotensive. Additionally, as the blood pressure drops, further increased sympathetic outflow results in β_1-mediated *reflex tachycardia*.

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Ms. S is admitted for surgery, and a laparoscopic adrenalectomy is successfully performed by a transabdominal approach. Ms. S is admitted to the floor for recovery.

On the fourth postoperative day, Ms. S is noted to have abdominal distention and discomfort. She has been attempting to eat small amounts of food, but feels nauseated after eating and has vomited several times. She also has not had a bowel movement since before her surgery. Her vital signs are within normal limits, and on physical exam her abdomen is distended and mildly tender.

The team orders an abdominal x-ray, which shows diffusely dilated loops of bowel without evidence of focal bowel obstruction.

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The team concludes Ms. S most likely has *postoperative ileus*. Postoperative ileus is caused by a lack of coordinated gastrointestinal motility following surgery, resulting in obstipation (inability to pass stool or gas), abdominal pain, distention, and/or oral intolerance with nausea and vomiting. Risk factors include intraabdominal surgery and use of opioid pain medications following surgery.

d) What class of medication can be used in the treatment of postoperative ileus? Give an example.

mAChR agonists are used in the treatment of postoperative ileus. ***Bethanechol*** is an example. However, note that bethanechol is not commonly used clinically as postoperative ileus usually resolves with time in the absence of operative complications.

e) What is the mechanism of action of bethanechol in the treatment of postoperative ileus?

Bethanechol binds nonselectively to mAChRs, activating the receptors. In the gastrointestinal tract, binding to M_3 receptors (coupled to G_q) causes increased intracellular $[Ca^{2+}]$ and subsequent smooth muscle contraction, resulting in increased GI motility.

References:
https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-pheochromocytoma

https://www.uptodate.com/contents/treatment-of-pheochromocytoma-in-adults

https://www.uptodate.com/contents/mechanisms-causes-and-evaluation-of-orthostatic-hypotension

https://www.uptodate.com/contents/postoperative-ileus

Hypertension 1

Ms. Y is a 40-year-old female who presents to her primary care physician to follow up regarding her blood pressure. At her last visit, her blood pressure was measured at 145/90. She bought an automated blood pressure cuff and has been measuring her blood pressure daily at home, with measurements ranging from (140-155)/(85-95). She reports feeling well and has no complaints. Ms. Y has no significant past medical history and takes no medications. In the office, her blood pressure is 150/90. Her physical exam, including complete cardiovascular exam, is normal.
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Ms. Y's physician diagnoses her with *hypertension*.

Hypertension, diagnosed when a patient has blood pressure ≥130/80 in the office and on home measurements, is a very prevalent disease in the United States. Hypertension may be *primary* (sometimes referred to as *essential hypertension*) or *secondary* to another disease process (note that primary hypertension is much more common than secondary hypertension). In this module we will focus on *primary hypertension*; you will learn about secondary causes of hypertension in later courses. Primary hypertension is typically asymptomatic, making screening important. Risk factors for primary hypertension include age, obesity, family history, heavy alcohol consumption, high-salt diet, sedentary lifestyle, and African American ethnicity. Diagnosis and treatment of hypertension are important because hypertension is an important risk factor for a variety of other conditions, including left ventricular hypertrophy (LVH), heart failure, stroke (ischemic vs. hemorrhagic), coronary artery disease (e.g., myocardial infarction), and chronic kidney disease.
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Ms. Y's physician would like to start her on an antihypertensive medication. The physician explains that there are many medications that can be used in the treatment of hypertension. Some antihypertensive agents, while not generally first-line options, target the autonomic nervous system.

a) Which of the following classes of medications targeting the autonomic nervous system can potentially be used in the treatment of hypertension? More than one answer may be correct. Give an example of each.

i. α_1 agonists
ii. α_2 agonists
iii. α_1 antagonists
iv. β_1 agonists
v. β_2 agonists
vi. β antagonists
vii. mAChR agonists
viii. mAChR antagonists

The following autonomic drugs can be used in the treatment of hypertension:

α_2 agonists (ii), e.g., ***clonidine***, ***methyldopa***
α_1 antagonists (iii), e.g., ***prazosin***, doxazosin, terazosin (common suffix "***-osin***")
β antagonists (vi), e.g., ***propranolol***, ***metoprolol***, ***atenolol***, ***carvedilol***

Note that these agents are not used in the first-line treatment of hypertension. Some specific instances in which these drugs may be used include:

- β antagonists, α_1 antagonists, and clonidine may be added to a medication regimen as a second or third agent if hypertension is has failed to respond to the use of other medications.
- Methyldopa may be used in pregnancy (many other antihypertensive agents are not safe to use in pregnancy), though it is not the first-line choice for use in pregnancy.
- α_1 antagonists may be advantageous to use in combination for refractory hypertension in men with comorbid benign prostatic hyperplasia (BPH), as it can treat the symptoms of BPH as well.
- Cardioselective β antagonists (e.g., carvedilol) may be used in the setting of comorbid heart failure.

b) What is the mechanism of action of the α_2 agonists in the treatment of hypertension?

(Note that methyldopa is a *prodrug*, and its pharmacologic effects are due to its active metabolite, methylNE.)

α_2 agonists stimulate α_2 receptors in the medulla oblongata in the brain, resulting in decrease in sympathetic tone to the body. Decreased sympathetic tone to the blood vessels and heart result in vasodilation and decreased inotropic state, respectively, both of which contribute to a decrease in blood pressure.

c) What are the primary adverse effects of the α_2 agonists?

The primary adverse effects of the α_2 agonists are drowsiness and xerostomia (dry mouth).

d) What is the mechanism of action of the α_1 antagonists in the treatment of hypertension?

α_1 antagonists block α_1 receptors on blood vessels. This causes vasodilation, resulting in decreased systemic vascular resistance and subsequent decrease in blood pressure.

e) What is the primary adverse effect of the α_1 antagonists?

The primary adverse effect of the α_1 antagonists is orthostatic hypotension with reflex tachycardia. For an explanation of the mechanism of this adverse effect, see the module on pheochromocytoma.

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Medications targeting the autonomic nervous system are generally not used as first-line agents in the treatment of hypertension. They are instead used in *combination therapy* when the first-line agents alone do not produce adequate blood pressure control. However, there are some clinical situations in which these medications may provide additional benefit and therefore may be preferred.

f) In what comorbid conditions would using a β antagonist be beneficial?

Certain β antagonists improve survival in patients with *heart disease with reduced ejection fraction* (HFrEF; ***metoprolol***, ***carvedilol***, and bisoprolol) and in patients who have had *myocardial infarction*.

β antagonists are also used in the treatment of other diseases such as *atrial fibrillation* and *atrial flutter* (to control ventricular rate), *angina pectoris*, and *migraines* (for prophylaxis, these will be introduced in Mind, Brain, and Behavior I).

References:
https://www.uptodate.com/contents/overview-of-hypertension-in-adults

https://www.uptodate.com/contents/choice-of-drug-therapy-in-primary-essential-hypertension

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Hypertension 2

Mr. D is a 63-year-old male with a history of hypertension and type 2 diabetes mellitus who presents to his primary care physician to discuss initiation of treatment for hypertension.

Mr. D has had elevated blood pressure for many years, but has been hesitant to start medication because he didn't want to take pills for something that doesn't make him feel sick. However, Mr. D's most recent lab tests show an elevation in his serum *creatinine* (a marker of kidney function) and a small amount of protein in his urine, concerning for *chronic kidney disease*. In light of a conversation with his physician following these lab results about how hypertension and diabetes both contribute to CKD and how treatment of his hypertension can help to slow the progression of kidney damage, he is now interested in learning more about the available options.
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a) What are the classes of medication targeting the autonomic nervous system can potentially be used in the treatment of hypertension? Give an example of each.

β antagonists (e.g., ***propranolol***, ***metoprolol***, ***atenolol***, ***carvedilol***), α_1 antagonists (e.g., ***prazosin***, doxazosin, terazosin (common suffix "***-osin***")), and α_2 agonists (e.g., ***clonidine***, ***methyldopa***) are used in the treatment of hypertension. The use of these medications in the treatment of hypertension is detailed in the Hypertension 1 module.

b) In addition to the autonomic drugs, which of the following classes of medication are used in the treatment of hypertension?

i. Angiotensin-converting enzyme inhibitors (ACEIs)
ii. AT receptor agonists
iii. AT_1 receptor blockers (ARBs)
iv. Direct renin inhibitors (DRIs)
v. Dihydropyridine (DHP) calcium channel blockers (CCBs)
vi. Non-DHP CCBs
vii. Organic nitrates

ACEIs (i), ARBs (iii), DRIs (iv), DHP CCBs (v), and non-DHP CCBs (vi) are used in the treatment of hypertension.

c) Give an example of a DHP and a non-DHP CCB. What is the mechanism of action of the CCBs in the treatment of hypertension?

Examples of DHP CCBs include ***amlodipine***, nifedipine, felodipine, isradipine, nicardipine, and nisoldipine (common suffix "***-dipine***"). Examples of non-DHP CCBs include ***verapamil*** and diltiazem.

CCBs inhibit L-type Ca^{2+} channels (LTCCs) on vascular smooth muscle and cardiac cells, reducing Ca^{2+} influx into the cells. Reduced intracellular [Ca^{2+}] in vascular smooth muscle causes vasodilation, resulting in decreased systemic vascular resistance and consequent decreased blood pressure. Reduced intracellular [Ca^{2+}] in the myocardium causes a decrease in inotropic state, also resulting in decreased blood pressure.

(Remember the differences between the two categories of CCBs. Vasodilation is more prominent with DHPs than non-DHPs, and decreased cardiac contractility is significant with non-DHPs but minimal with DHPs.)

d) Give an example of an ACEI, ARB, and DRI. What are the suffixes common to the ACEIs and ARBs?

Examples of ACEIs include ***enalapril***, captopril, benazepril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril (common suffix "***-pril***").
Examples of ARBs include ***losartan***, candesartan, eprosartan, irbesartan, olmesartan, telmisartan, and valsartan (common suffix "***-sartan***").
Aliskiren is the only DRI that is currently available.

e) What pathway do the ACEIs, ARBs, and DRIs act on? Describe this pathway and the steps on which each medication acts.

ACEIs, ARBs, and DRIs act on the *renin-angiotensin system* (*RAS*).

The enzyme renin is secreted into the blood by the *granular cells* of the kidney. Renin catalyzes the conversion of *angiotensinogen* to *angiotensin I* (*Ang I*). *Angiotensin-converting enzyme* (*ACE*) then catalyzes the conversion of Ang I to the active enzyme *angiotensin II* (*Ang II*). Renin secretion is increased by β_1 adrenergic stimulation, decreased stretch of renal baroreceptors (renal baroreceptor mechanism; note, however, that in contrast to the carotid sinus and aortic baroreceptors the renal baroreceptor mechanism is a local effect that does not involve sensory neurons), and reduced sodium chloride delivery to the the macula densa (the tubular epithelial cells located just proximal to the distal convoluted tubule; the regulation of renin secretion by this mechanism will be discussed in more detail in Renal System I). Renin secretion is decreased by elevated concentrations of angiotensin II (negative feedback effect). Ang II acts to increase the blood pressure by several mechanisms, mediated primarily by binding to AT_1 receptors (the actions of Ang II will be discussed in more detail in the Vasoactive Mediators lecture and Cardiovascular Pharmacology lecture).

DRIs (aliskiren is the only example that currently is available) inhibit the action of renin, preventing conversion of angiotensinogen to Ang I, and thereby preventing the generation of Ang II. (Note that this is the rate-limiting step in Ang II production). ACEIs inhibit the action of ACE, preventing conversion of Ang I to Ang II. ARBs block AT_1 receptors, resulting in blockade of the actions of Ang II. All three mechanisms inhibit Ang II action, resulting in blood pressure reduction.

f) What are the primary adverse effects of ACEIs, ARBs, and DRIs?

There are several adverse effects that are common to ACEIs, ARBs, and DRIs due to the similarities in their mechanism of action. All can cause hyperkalemia (elevated serum potassium) due to decreased potassium secretion by the kidney (in Renal System I, you will learn why this adverse effect is predictable). The use of these medications in patients with decreased renal perfusion (e.g., renal artery stenosis) can cause decreased kidney function, since RAS activity is very important to maintain renal

blood flow in these patients. Additionally, these medications are teratogenic, and are therefore contraindicated in pregnancy.

ACEIs and ARBs can both cause hypotension, especially in patients with elevated renin levels at baseline. ACEIs can also cause cough and angioedema, due to inhibition of the metabolism of *bradykinin* by ACE. DRIs additionally can cause mild GI effects (e.g., nausea, cramping).

g) What part of Mr. D's history is important in helping to guide the choice of antihypertensive agent?

Mr. D's most recent labs show elevated serum *creatinine*, indicative of chronic kidney disease (CKD), as well as the presence of protein in his urine (*proteinuria*). ACEIs or ARBs are the antihypertensive agents of choice for patients with CKD with proteinuria, as they protect the kidney and slow CKD progression by reducing intraglomerular pressure, among other effects. You will learn more about the mechanism of renal protection by ACEIs and ARBs in Renal System I. Furthermore, ACEIs and ARBs are shown to be beneficial in patients with CKD of any etiology (diabetic and non-diabetic CKD), even in the absence of comorbid hypertension.

Note that proteinuria is unlikely to develop in CKD due to hypertension alone, and is more commonly seen if there is coexistent glomerular injury (such as that resulting from diabetes). In this case, the cause of Mr. D's CKD is likely multifactorial from uncontrolled hypertension and diabetes, but the proteinuria is more likely the result of diabetes.

h) In addition to CKD, what are other indications for the use of ACEIs/ARBs?

ACEIs and ARBs are also used in the treatment of heart failure with reduced ejection fraction (HFrEF) and myocardial infarction. These medications are particularly helpful in these conditions because they inhibit detrimental Ang II-mediated cardiovascular remodeling and hypertrophy.

i) Of the above medications used in the treatment of hypertension, which drugs are first-line agents?

ACEIs, ARBs, and DHP CCBs are first-line choices in the treatment of hypertension. Non-DHP CCBs and β antagonists are not first-line choices, but are often employed in combination therapy if blood pressure control is not adequate on monotherapy, or if there are comorbid conditions for which a non-DHP or β antagonist would be beneficial (e.g., arrhythmia that can be treated by slowing AV conduction, angina pectoris, history of myocardial infarction).

Note that *thiazide diuretics* (e.g., hydrochlorothiazide, chlorthalidone) are also first-line agents in the treatment of hypertension. These medications will be introduced in Renal System I.

References:
https://www.uptodate.com/contents/overview-of-hypertension-in-adults

https://www.uptodate.com/contents/choice-of-drug-therapy-in-primary-essential-hypertension

https://www.uptodate.com/contents/antihypertensive-therapy-and-progression-of-nondiabetic-chronic-kidney-disease-in-adults

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Hypertensive emergency

Mr. P is a 33-year-old male who is brought to the Emergency Department by his wife, who says he is "confused."

Mr. P was in his normal state of health until shortly after dinner this evening, when he starting complaining of headache. His wife then noticed that he seemed disoriented and could not remember where he was or the events leading up to that point. Mr. P's wife notes that they were at a dinner party, where they indulged on wine and fancy cheeses. Mr. P has history of depression, for which he takes phenelzine (a monoamine oxidase (MAO) inhibitor). [MAO inhibitors are atypical antidepressants that are not used in the first-line treatment of depression, but may be used in patients who have not responded to first-line options or who have first-degree relatives that responded well to a MAOi.] In the ED, Mr. P's blood pressure is 190/130. On mental status exam, Mr. P is oriented to self but not to place, time, or situation. There are no focal deficits on neurologic exam. His cardiovascular exam is normal. The remainder of the physical exam is unremarkable.
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The ED physician diagnoses Mr. P with *hypertensive emergency*.

Hypertensive emergency is defined as significantly elevated blood pressure (≥180/120) with clinical evidence of end-organ damage. Examples of evidence of end-organ damage include encephalopathy (confusion), intracranial hemorrhage, pulmonary edema, acute kidney injury, and acute coronary syndrome (e.g., myocardial infarction). Hypertensive emergencies most commonly occur in patients with a history of hypertension, but may also occur in patients without underlying hypertension. There are a wide variety of possible causes (e.g., antihypertensive medication nonadherence, chronic kidney disease, head trauma with increased intracranial pressure, illicit drug use [e.g., cocaine, methamphetamine], endocrine abnormalities [e.g., pheochromocytoma, hyperthyroidism]). In this case, Mr. P's condition is most likely caused by the ingestion of tyramine-containing foods in the setting of MAO inhibitor use (i.e., *tyramine crisis*).

(Note that this case is an example of secondary hypertension [hypertension caused by a different disease process], rather than primary hypertension as discussed in the Hypertension 1 and Hypertension 2 modules.)

a) What is the mechanism of the development of tyramine crisis in patients taking an MAO inhibitor?

MAO is an enzyme present in adrenergic nerve terminals that metabolizes catecholamines. The MAO-A isoform present in the GI tract and liver acts to metabolize tyramine (an amino acid) that is absorbed from foods (found in aged cheeses, wine, cured meats, etc.). Blockade of MAO-A by MAO inhibitors such as phenelzine allows increased GI absorption of tyramine, which enters the bloodstream and acts as an amphetamine-like indirect sympathomimetic. Subsequent increased stimulation of α_1 receptors on vascular smooth muscle results in vasoconstriction and severe hypertension.
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The physician orders an ECG, chest x-ray, and labs to evaluate for any evidence of other end-organ damage, and wants to initiate treatment to bring down Mr. P's blood pressure in a controlled manner.

b) Which of the following classes of medications are used in the treatment of hypertensive emergency? Give an example.

i. ACE inhibitors
ii. Direct renin inhibitors

iii. Nitric oxide (NO) donors
iv. Cardiac glycosides

Nitric oxide (NO) donors (iii) are used in the treatment of hypertensive emergencies. Examples include ***nitroglycerin*** (an organic nitrate) and ***nitroprusside*** (an inorganic nitrate). In the setting of hypertensive emergency, it is preferred to give medications intravenously for more rapid onset of action and ease in titration to meet blood pressure goals. The rate of correction of the hypertension is important – it must be rapid enough to prevent further harmful effects of elevated blood pressure, but not too rapid as to cause damage due to poor perfusion of organs that have equilibrated to the high pressure by autoregulation. A general goal is to decrease the blood pressure by 10-20% in the first hour, then by an additional 5-15% over the next 23 hours.

Other medications such as dopamine receptor agonists, calcium channel blockers, and β antagonists (in particular *labetalol*, which has both anti-α and anti-β activity) are also used clinically in hypertensive emergency. The use of these drugs for this indication is beyond the scope of this course.

c) What is the mechanism of the NO donors in the treatment of hypertensive emergency?

NO molecules released by the NO donors activate soluble guanylyl cyclase (sGC) in vascular smooth muscle cells, promoting the production of cGMP and ultimately resulting in vasodilation. This decreases the blood pressure by two mechanisms – arterial vasodilation decreases systemic vascular resistance, and venous vasodilation decreases preload (and cardiac output).

d) What are the primary adverse effects of nitroglycerin?

The primary adverse effects of nitroglycerin are the result of systemic vasodilation and include headache, flushing, and hypotension or orthostatic hypotension with reflex tachycardia.

e) What are other indications for use of nitroglycerin?

Nitroglycerin is also used for the treatment of angina pectoris (including vasospastic angina), acute myocardial infarction, and acute heart failure.

f) What are the primary adverse effects of nitroprusside?

The primary adverse effects of nitroprusside are hypotension (due to systemic vasodilation) and cyanide toxicity (nitroprusside contains five cyanide groups for every NO; dosing guidelines must be followed to avoid toxicity, e.g., maximal infusion rates should not be continued for more than 10 minutes).

g) What are other indications for the use of nitroprusside?

Nitroprusside is also used for acute heart failure, and for the production of controlled hypotension during surgical procedures.

References:
https://www.ncbi.nlm.nih.gov/books/NBK470371/

https://www.uptodate.com/contents/evaluation-and-treatment-of-hypertensive-emergencies-in-adults

https://www.uptodate.com/contents/drugs-used-for-the-treatment-of-hypertensive-emergencies

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Angina pectoris 1

Ms. B is a 57-year-old female who presents to her primary care physician with a chief complaint of "chest discomfort."

Ms. B says she has had intermittent episodes of chest discomfort for the past several months. She feels a heavy, pressure-like sensation located behind her sternum. This occurs only during physical exertion and resolves with rest. The pressure radiates to her left shoulder and is sometimes associated with sweating and shortness of breath. Ms. B's past medical history is significant for hypertension and hypercholesterolemia. Her medications include enalapril (ACE inhibitor; first-line antihypertensive agent) and atorvastatin (cholesterol-lowering agent). She previously smoked 1 pack of cigarettes daily for 20 years, and quit 8 years ago. Ms. B denies any pain at this time. Her vital signs are significant only for a blood pressure of 130/85; a complete physical exam is unremarkable. An ECG obtained in the office is normal.
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Ms. B's history of pressure-like chest pain on exertion, with radiation to the left shoulder/arm and associated dyspnea and sweating are characteristic of *angina pectoris*.

Angina pectoris is the result of transient ischemia of the myocardium due to an imbalance between the oxygen demand and oxygen supply to the heart. This imbalance is most often caused by a partial occlusion (stenosis) of one or more coronary arteries supplying the myocardium. Under normal conditions, when the myocardial oxygen demand increases (for example, during exercise), the blood supply (and consequently the oxygen supply) increases appropriately by a phenomenon called autoregulation. However, when there is a stenosis of one or more coronary arteries, the ability of the coronary vasculature to increase myocardial oxygen supply may be insufficient to meet the demand during times of stress, leading to ischemia and chest pain. Important risk factors for coronary artery disease include hypertension, dyslipidemia (high LDL, low HDL, high triglycerides), obesity, smoking, poor diet, sedentary lifestyle, and family history.
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a) Knowing the pathophysiology, what general strategies can be employed in the pharmacologic treatment of angina pectoris?

Medications that decrease myocardial oxygen demand or increase myocardial oxygen supply (increase coronary blood flow) would both reduce oxygen supply/demand imbalance, thereby relieving symptoms of angina.

b) What class of medications targeting the autonomic nervous system is used in the treatment of angina pectoris? What is the mechanism of these drugs?

β receptor antagonists (both nonspecific and β_1 selective antagonists) are first-line agents in the treatment of angina pectoris. β receptor antagonists function by both decreasing myocardial oxygen demand and indirectly increasing myocardial oxygen supply.

i) Decreasing myocardial oxygen demand:
The most important determinants of myocardial oxygen demand are the following:

i. Heart rate
ii. Afterload/wall stress
iii. Inotropic state (contractility)

β_1 receptors are present in the sinoatrial node (SA node) as well as the myocardium. By decreasing sympathetic tone to the SA node and the myocardium, β antagonists function to reduce heart rate and inotropic state, respectively. β antagonists also have antihypertensive effects, leading to reduction in afterload on the heart. The mechanism for these antihypertensive effects is not completely understood and is likely multifactorial. Possible mechanisms will be discussed in the Case Studies: Cardiovascular Pharmacology small group session.

ii) Increasing myocardial oxygen supply:
Perfusion of the myocardium occurs primarily during diastole. By decreasing the heart rate, a larger fraction of the cardiac cycle is spent in diastole and the oxygen supply to the myocardium is consequently increased.

c) What is the suffix common to the β antagonists? Give an example of a nonselective antagonist, a β_1 selective antagonist, and a β antagonist with additional cardiovascular effects.

The suffix "***-lol***" is common to the β antagonists. Examples of nonselective β antagonists include ***propranolol***, nadolol, timolol, and pindolol. Examples of β_1 selective antagonists include ***metoprolol***, ***atenolol***, acebutolol, and bisoprolol. Examples of nonselective β antagonists with additional cardiovascular effects include ***carvedilol*** and labetalol. An example of a β_1 selective antagonist with additional cardiovascular effects is nebivolol.

d) Ms. B's physician wishes to prescribe propranolol, a nonselective β receptor antagonist. He first asks her if she has a history of asthma, COPD, peripheral vascular disease, or diabetes mellitus. Why does he ask about these conditions?

It is important to ask about these conditions before prescribing a β antagonist due to the medication's possible adverse effects.

Blockade of β_2 receptors on bronchial smooth muscle can cause bronchoconstriction, resulting in exacerbation of COPD or asthma. In fact, nonselective β antagonists are contraindicated in patients with a history of asthma. This effect is less pronounced with β_1-selective antagonists, however exacerbation of COPD or asthma is still possible due to cross-reactivity of the medication with β_2 receptors.

Blockade of β_2 receptors on vascular smooth muscle can impair epinephrine's vasodilator effects, e.g., in skeletal muscle during exercise. Patients with peripheral vascular disease (atherosclerotic disease of the peripheral arteries) often suffer from *intermittent claudication*, characterized by extremity pain with exercise due to transient ischemia. In theory, blockade of vascular β_2 receptors can lead to unopposed α_1-mediated vasoconstriction and worsening of symptoms of claudication. While no randomized controlled studies have shown significant change in symptoms of claudication with the use of β antagonists (because metabolic vasodilation and flow-induced vasodilation can compensate for the blockade of β_2 receptor-mediated vasodilation), they still should be used with caution in such patients. This effect is less pronounced with β_1-selective antagonists, however it is still possible due to cross-reactivity of the medication with β_2 receptors.

Blockade of β receptors can lead to decreased hypoglycemic awareness in patients with diabetes mellitus. Blockade of β_1 receptors in the heart and β_2 receptors on skeletal muscle prevent tachycardia and tremor, respectively, that normally acts as clues to the patient that their blood glucose is low. Additionally, blockade of β_2 receptors on hepatocytes (liver cells) prevents glycogenolysis, a process that normally counters hypoglycemia by quickly releasing more glucose into the blood. Note that while these effects are possible, they are not a contraindication to the use of β antagonists.

e) What are the other possible adverse effects of β antagonists?

β antagonists can cause heart failure, bradycardia, or AV block due to blockade of β_1 receptors in the heart; note that these medications are contraindicated in patients who have preexisting acute heart failure, bradycardia, or AV block. Other adverse effects include adverse metabolic effects (low HDL, high triglycerides), vivid dreams, fatigue, drowsiness, and sexual dysfunction.

f) What are the other common indications for use of β antagonists?

β antagonists are also used in the treatment of myocardial infarction, heart failure with reduced ejection fraction (HFrEF), cardiac arrhythmias, hypertension, glaucoma, essential tremor, performance anxiety, and migraine prophylaxis.

g) Are there other drug classes that are used in the treatment of angina?

Yes. Calcium channel blockers (CCBs) and organic nitrates are used in the treatment of angina. See the Angina Pectoris 2 module for a detailed description of the use of these medications in the treatment of angina.

References:
https://www.uptodate.com/contents/angina-pectoris-chest-pain-caused-by-myocardial-ischemia

https://www.uptodate.com/contents/overview-of-established-risk-factors-for-cardiovascular-disease

https://www.cochrane.org/CD005508/PVD_beta-blockers-for-peripheral-arterial-disease

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Angina pectoris 2; Vasospastic angina

Mr. Q is a 41-year-old male who presents to his primary care physician with a chief complaint of "chest discomfort."

He complains of deep, pressure-like substernal chest discomfort occurring about once per week for the last 6 months. The episodes typically occur very early in the morning and wake him from sleep, and are associated with pain radiating to his left arm, and sweating. He has never had these symptoms during exercise. Mr. Q has no significant past medical history. He has smoked 1 pack of cigarettes daily for 20 years. In the office, Mr. Q's vital signs are within normal limits. He currently denies pain. His physical exam, including complete cardiovascular exam, is normal. An ECG obtained in the office is normal.
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Mr. Q's physician explains that Mr. Q's symptoms are concerning for *angina pectoris*. He is sent for further evaluation of angina. Ambulatory ECG monitoring at home reveals ST-segment elevations during a recorded episode of chest pain, indicative of myocardial ischemia. He then undergoes coronary arteriography, which reveals no evidence of high-graded fixed coronary artery stenosis. Provocation with acetylcholine during catheterization induces coronary vasospasm. Based on these findings, Mr. Q is diagnosed with *vasospastic angina*.

Vasospastic angina (also referred to as *variant angina* or *Prinzmetal angina*) is chest pain caused by transient ischemia of the myocardium. Unlike classic angina pectoris, in which the mismatch between myocardial oxygen supply and demand is most often due to atherosclerotic coronary artery stenosis,

vasospastic angina is the result of coronary artery spasm (vasoconstriction) that creates a transient high-grade obstruction of blood flow through the artery. Vasospasm is thought to be secondary to hyperactivity of the vascular smooth muscle, though the phenomenon is not fully understood and is likely multifactorial. The most important risk factor for vasospastic angina is cigarette smoking. The character of the chest pain and associated symptoms during an episode of vasospastic angina is identical to that of classic angina pectoris, however vasospastic angina typically occurs at rest (most often between midnight and early morning) and does not usually occur with exercise. Episodes come on gradually and typically last for 5-15 minutes before self-resolving, although spasm can last longer and can even lead to ischemic tissue damage (i.e., myocardial infarction).

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Mr. Q's physician explains that the first step in the treatment of vasospastic angina is risk factor modification, counsels him regarding smoking cessation, and offers to provide additional resources to help him quit smoking. The physician also explains that there are medications that can treat vasospastic angina.

a) Which of the following classes of medications are used in the treatment of angina pectoris? Of these, which classes are effective for vasospastic angina?

i. α agonists
ii. α antagonists
iii. β agonists
iv. β antagonists
v. Calcium channel blockers
vi. ACE inhibitors
vii. Organic nitrates
viii. NSAIDs

β antagonists (iv), calcium channel blockers (v), and organic nitrates (vii) are used in the treatment of angina pectoris. Calcium channel blockers and organic nitrates are effective for treatment of vasospastic angina.

β antagonists, which are first-line agents for classic angina pectoris, are not effective for vasospastic angina. In fact, blockade of β_2 receptors on vascular smooth muscle in the coronary circulation can exacerbate vasospasm, making symptoms worse. The use of β antagonists in angina pectoris is detailed in the Angina Pectoris 1 module.

b) What are the major categories of calcium channel blockers (CCBs)? Give an example of each. How do they differ?

The major categories of CCBs are the *dihydropyridines* (*DHPs*) and the *non-DHPs*. The DHPs share the common suffix "***-dipine***;" examples include ***amlodipine***, nifedipine, felodipine, isradipine, nicardipine, and nisoldipine. Examples of non-DHPs include ***verapamil*** and diltiazem.

The DHPs and non-DHPs differ in their predominant effects. DHPs are more selective for vascular smooth muscle than for myocardium; they are potent vasodilators, and have little effect on inotropic state, heart rate, or AV conduction. In contrast, non-DHPs act on both vascular smooth muscle and myocardium; they are slightly less potent vasodilators than DHPs, and cause significant cardiac effects (decrease in inotropic state, heart rate, and AV conduction).

c) What is the mechanism of the CCBs in the treatment of angina pectoris, including vasospastic angina?

CCBs inhibit L-type Ca^{2+} channels (LTCCs) on vascular smooth muscle and cardiac cells, reducing Ca^{2+} influx into the cells.

In vascular smooth muscle, reduced intracellular [Ca^{2+}] leads to decreased activation of the myosin light chain kinase (MLCK), which in turn leads to decreased phosphorylation of myosin light chain (MLC), causing vasodilation. In classic angina pectoris, systemic vasodilation reduces mean arterial pressure and cardiac afterload, resulting in decreased myocardial oxygen demand and thereby reducing myocardial ischemia. In vasospastic angina, blockade of Ca^{2+} channels on the coronary arteries causes vasodilation and relieves the vasospasm.

In the heart, decreased calcium influx through the LTCCs leads to decreased intracellular [Ca^{2+}] (both as a direct effect and, more importantly, by reducing calcium-induced calcium release (CICR) from the SER, which in turn leads to (1) decreased binding of Ca^{2+} to troponin C (TnC), and ultimately decreased contractility; and (2) decreased phase 4 slope in the SA node, resulting in decreased heart rate. This decrease in contractility and heart rate both result in decreased myocardial oxygen demand, reducing myocardial ischemia. Note that these cardiac effects are mainly seen with the non-DHPs. The cardiac effects do not play a significant role in their efficacy in the treatment of vasospastic angina.

d) What are the primary adverse effects of the DHPs? The non-DHPs?

The primary adverse effects of the DHPs are the result of prominent systemic vasodilation. They include hypotension, headache, flushing, and peripheral edema.

The primary adverse effects of the non-DHPs are the result of prominent cardiac effects. They include sinus bradycardia (due to decreased SA node automaticity), AV block (due to decreased AV conduction velocity), and heart failure (due to decreased inotropic state). In addition, the non-DHPs (especially verapamil) can cause constipation due to interaction with calcium channels on GI smooth muscle and resulting decreased GI motility.

e) What are other indications for use of DHPs? Non-DHPs?

Both DHPs and non-DHPs are used in the treatment of hypertension (the DHPs are first-line agents). DHPs are also used in the treatment of pulmonary hypertension (limited efficacy). Non-DHPs are also used in the treatment of cardiac arrhythmias that can be terminated by slowing AV conduction.

f) Give an example of an organic nitrate. What is the mechanism of action of the organic nitrates in the treatment of angina pectoris, including vasospastic angina?

Examples of organic nitrates are ***nitroglycerin*** (a short-acting agent) and isosorbide dinitrate (ISDN; a long-acting agent).

The organic nitrates donate molecules of nitric oxide (NO), which diffuses into vascular smooth muscle cells and activates soluble guanylyl cyclase (sGC), which catalyzes the conversion of GTP to cGMP. This results in smooth muscle relaxation and vasodilation. The organic nitrates act most prominently on the venous system, resulting in increased compliance of the veins and decreased venous return to the heart. Decreased venous return results in decreased preload; the resulting decrease in ventricular radius decreases the wall stress (most precise definition of afterload), reducing myocardial oxygen demand. The organic nitrates also result in coronary artery vasodilation and systemic arterial vasodilation, which play a secondary role in the reduction of myocardial ischemia in classic angina pectoris. In vasospastic angina, however, the predominant mechanism of action is coronary artery vasodilation and relief of the vasospasm.

Nitroglycerin and ISDN differ in their onset and duration of action. Nitroglycerin (often given as a sublingual tablet) has a rapid onset of action, and is therefore used as needed during acute episodes of angina in order to relieve symptoms. In contrast, ISDN has a slower onset of action and a longer duration of action. ISDN is therefore used as a daily medication to prevent symptoms from occurring (as are the β antagonists and CCBs).

g) What is a major limitation to the dosing of the organic nitrates?

The body quickly develops *tolerance* to the organic nitrates, whereby the vascular effects are attenuated and the medications therefore lose efficacy in their ability to cause vasodilation. For this reason, patients must have a nitrate-free period of 12-14 hours every day.

References:
https://www.uptodate.com/contents/vasospastic-angina

https://www.uptodate.com/contents/calcium-channel-blockers-in-the-management-of-stable-angina-pectoris

https://www.uptodate.com/contents/nitrates-in-the-management-of-stable-angina-pectoris

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Myocardial infarction

Mr. L is a 62-year-old man who presents to the ED via ambulance. The paramedic relays the history obtained in the field – approximately 30 minutes ago at work, Mr. L had a sudden onset of 9/10 pressure-like pain in his chest radiating to his left shoulder and jaw, with associated dizziness, shortness of breath, and sweating. He has experienced similar but less severe pain previously with exertion, but nothing as severe or occurring at rest before. He has a history of hypertension, hyperlipidemia, and osteoarthritis. His prescribed medications include enalapril (ACE inhibitor; first-line antihypertensive agent) and lovastatin (cholesterol-lowering agent). He also takes ibuprofen frequently for his osteoarthritis.

In the ED, Mr. L's vital signs are remarkable for BP 150/95 and HR 115. He appears uncomfortable lying on the gurney, is sweating, and is clutching the left side of his chest (Levine's sign). The remainder of his physical exam, including complete cardiovascular exam, is unremarkable.
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The physician in the Emergency Department is worried that Mr. L may be having a *myocardial infarction* (*MI*).

An ECG is immediately obtained, which shows ST-segment elevation in the anterior leads (V1-V4), confirming the diagnosis of *ST-elevation MI* (*STEMI*).

MI is the result of ischemic injury to the myocardium, typically due to rupture of an atherosclerotic plaque with subsequent thrombosis and occlusion of the coronary artery. STEMI is characterized by *transmural* ischemic injury (involving the full thickness of the myocardium in the affected area). Risk factors for coronary artery disease and MI include obesity, hypertension, dyslipidemia, obesity, smoking, family history (especially of coronary disease at a young age), and lifestyle factors such as poor diet and low exercise. Patients classically present with pressure-like substernal chest pain that may radiate to the arm or jaw, and may be associated with diaphoresis, dyspnea, nausea, weakness, or anxiety. The onset of

the pain may be under any circumstances, and it is not relieved with rest. Myocardial ischemia can also cause ventricular arrhythmias, and patients may rarely present with cardiac arrest.
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In light of the ECG findings, the ED physician notifies the cardiac catheterization lab to prepare for *percutaneous coronary intervention* to visualize and relieve the occlusion and place a coronary artery stent.

While the catheterization lab is mobilizing for the procedure, the ED physician orders labs (including *cardiac troponins*, a marker of myocardial injury), and plans to administer one or more medications for the pharmacologic management of Mr. L's MI.

a) Which of the following medications or classes of medication are given for initial management of MI? More than one answer may be correct.

i. α agonist
ii. α antagonist
iii. β agonist
iv. β antagonist
v. Nitroglycerin
vi. Cardiac glycoside
vii. Aspirin

β antagonists (in the acute setting of MI, the agent of choice is intravenous ***metoprolol***), ***nitroglycerin*** (v), and ***aspirin*** (vii) are used in the acute management of MI.

b) What is the mechanism of action of β antagonists in the treatment of MI?

β receptor antagonists function by both decreasing myocardial oxygen demand (by decreasing inotropic state, heart rate, and blood pressure) and indirectly increasing myocardial oxygen supply (by decreasing heart rate). For specific details on the mechanisms by which β agonists produce these effects, see the Angina Pectoris 1 module.

c) What is the mechanism of action of nitroglycerin in the treatment of acute MI?

Nitroglycerin is an organic nitrate, a donor of nitric oxide (NO). NO diffuses into vascular smooth muscle cells, where it activates soluble guanylyl cyclase (sGC). sCG catalyzes the conversion of GTP to cGMP, which results in smooth muscle relaxation and vasodilation. Nitroglycerin predominantly acts on the venous system, and the resulting *venodilation* reduces venous return to the heart, thereby reducing preload; the resulting decrease in ventricular radius decreases the wall stress (most precise definition of afterload), reducing myocardial oxygen demand. To a lesser extent, nitroglycerin causes coronary artery vasodilation (increasing myocardial perfusion) and systemic arterial vasodilation (reducing afterload).

d) What are the primary adverse effects of nitroglycerin?

Primary adverse effects of nitroglycerin are the result of vasodilation and include headache, flushing, and hypotension/postural hypotension with reflex tachycardia.

e) Recent use of what class of medications is a contraindication to use of nitroglycerin? Why?

Recent use of a phosphodiesterase-5 (PDE5) inhibitor (e.g., ***sildenafil***) is a contraindication to administration of nitroglycerin. PDE5 inhibitors potentiate the effects of NO by preventing cGMP

degradation. If a PDE5 inhibitor has been recently used (e.g., within the last 24 hours), nitroglycerin can cause a dangerous drop in blood pressure.

f) What are other indications for the use of nitroglycerin?

Nitroglycerin is used for the treatment of angina pectoris, as it decreases myocardial oxygen demand and therefore improves oxygen supply/demand mismatch. It is also used in hypertensive emergencies and acute heart failure, as it can decrease blood pressure and cardiac afterload.

g) What is the mechanism of action of aspirin in the treatment of acute MI? Can other NSAIDs be used for this indication? Why or why not?

Aspirin acetylates cyclooxygenase (COX), leading to irreversible inhibition of the enzyme. COX-1 is the dominant isoform in platelets, where it catalyzes the first steps in the production of *thromboxane* A_2 (TXA_2). TXA_2 produced by platelets promotes vasoconstriction and platelet aggregation. Inhibition of COX-1 in platelets by aspirin inhibits platelet aggregation and thrombosis in the affected coronary artery.

Other NSAIDs (e.g., ibuprofen) *cannot* be used in the setting of acute MI. Non-aspirin NSAIDs actually have the opposite effect of aspirin and result in increased risk of cardiovascular thrombotic events due to predominant inhibition of PGI_2 (prostacyclin) synthesis by COX-2 in endothelial cells, which under normal circumstances promotes vasodilation and inhibits platelet aggregation. For this reason, non-aspirin NSAIDs have a black-box warning for the risk of cardiovascular thrombotic events. Recall that Mr. L takes frequent ibuprofen for his osteoarthritis, which likely increased his risk of myocardial infarction.
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Mr. L's catheterization reveals a complete occlusion of the left anterior descending artery, and thrombolysis and stent placement are successful. He does well in the post-procedural period and is expected to recover without significant impairment of myocardial function. The team now wants to determine the medications that Mr. L should be discharged home with.

h) Which of the following medications or classes of medications are continued long-term in patients following MI?

i. Nitroglycerin
ii. Aspirin
iii. β antagonist
iv. ACE inhibitor
v. AT_1 receptor blocker (ARB)

Aspirin (ii), β antagonists (iii), and ACE inhibitors (iv) or ARBs (v) are used following MI. Patients are typically maintained on low-dose aspirin and a β antagonist indefinitely. An ACE inhibitor or an ARB are often added, especially in patients with hypertension, heart failure, or reduced left ventricular ejection fraction.

In addition, patients are maintained long-term on a statin (cholesterol-lowering agent) and an additional antiplatelet agent (in addition to aspirin).

References:
https://www.uptodate.com/contents/overview-of-established-risk-factors-for-cardiovascular-disease

https://www.uptodate.com/contents/initial-evaluation-and-management-of-suspected-acute-coronary-syndrome-myocardial-infarction-unstable-angina-in-the-emergency-department

https://www.uptodate.com/contents/overview-of-the-acute-management-of-st-elevation-myocardial-infarction

https://www.uptodate.com/contents/overview-of-the-non-acute-management-of-st-elevation-myocardial-infarction

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Anaphylaxis; Hypotension

Ms. N is a 24-year-old female who is transported to the Emergency Department by ambulance. She was running in the park with a friend about 30 minutes ago when she was stung by a bee, to which she has a known allergy. Her friend witnessed the event and said they immediately sat down after the sting, and within minutes Ms. N started developing a pruritic (itchy) rash and feeling tingling of her lips and tongue. They called 911, and by the time EMS arrived she was also wheezing and complaining of difficulty breathing.

Ms. N's vital signs are as follows: T 37ºC (98.6ºF), BP 70/40, HR 110, RR 24, SpO2 98% on room air. A brief physical exam reveals a young woman in apparent distress. She is minimally responsive to verbal stimuli. There are scattered erythematous papules and plaques with raised borders on the skin of her trunk and extremities, consistent with urticaria (hives). Her lips and tongue appear swollen. She is tachypneic, using accessory muscles of respiration, and scattered expiratory wheezes are heard throughout the bilateral lung fields. She is tachycardic, with weak peripheral pulses and warm extremities.
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The ED physician diagnoses Ms. N with *anaphylaxis*.

Anaphylaxis is a multisystem disorder that most often occurs in response to exposure to an allergen. Common triggers include drugs, food allergens, and bites/stings. The pathophysiology of anaphylaxis involves binding of the allergen to *IgE antibodies* on the surface of *mast cells* and *basophils*, resulting in massive release of *histamine* and other chemical mediators into the circulation. This release of mediators has many systemic effects, including widespread vasodilation, edema, and bronchospasm. The presentation of anaphylaxis may include any combination of signs/symptoms affecting the following systems: cutaneous/mucosal (e.g., urticaria, flushing, itching, swelling of lips and/or tongue, periorbital edema), respiratory (e.g., nasal congestion, rhinorrhea, sensation of throat closing, stridor (due to upper airway swelling), cough, wheezing, shortness of breath), gastrointestinal (e.g., nausea, vomiting, cramping, diarrhea), and/or cardiovascular (e.g., tachycardia, dizziness, syncope, hypotension). Anaphylaxis is fatal in up to 2% of cases; death is most commonly due to respiratory failure or shock/cardiovascular collapse.
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The physician in the ED starts Ms. N on IV fluids and immediately administers a medication to treat her anaphylaxis.

a) What medication is used to treat anaphylaxis?

Epinephrine (***EPI***), an endogenous catecholamine, is used to treat anaphylaxis. EPI is administered as an intramuscular (IM) injection when used for this indication.

b) What is the mechanism of action of epinephrine in the treatment of anaphylaxis?

EPI binds to and stimulates α_1, α_2, β_1, and β_2 receptors. It causes α_1-mediated vasoconstriction, which reduces airway edema, supports blood pressure, and reduces bronchial secretions, and β_2-mediated bronchodilation. In addition, stimulation of β_2 receptors on mast cells and basophils prevents further release of chemical mediators.

c) EPI has different effects at physiologic levels than it does at pharmacologic levels. What is the difference, and what causes it?

The difference in response to epinephrine at physiologic (low-dose) and pharmacologic (high-dose) levels is due differences in its action on vascular smooth muscle. EPI stimulates both α_1 and β_2 receptors on vascular smooth muscle, which have opposing effects. EPI has a greater *potency* at β_2 receptors than at α_1 receptors, but α_1 receptors are present in greater numbers on vascular smooth muscle than are β_2 receptors. At physiologic (low) doses, the more potent action at β_2 receptors predominates, resulting in *vasodilation*. At pharmacologic (high) doses, the action at the more numerous α_1 receptors predominates (assume maximum occupancy of both types of receptor at high doses), resulting in *vasoconstriction*.

d) What are the primary adverse effects of EPI?

The primary adverse effects of EPI are increased heart rate and cardiac arrhythmias due to β_1-mediated cardiac stimulation.

e) What are other indications for EPI? What is the mechanism of action of EPI in these situations?

EPI is used in cardiac arrest, as it helps to support blood pressure by α_1-mediated vasoconstriction. EPI is also injected with local anesthetics such as lidocaine to prolong the action of the anesthetic by reducing blood flow to the area and consequent clearance of the anesthetic agent.

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Ms. N's wheezing improves, but her blood pressure remains low at 70/40. She is continued on IV fluids and given an additional dose of EPI. However, Ms. N's blood pressure still fails to normalize after maximal administration of EPI and fluid resuscitation.

f) What are additional agents acting on the autonomic nervous system that are used to increase blood pressure (called *vasopressors*)?

Norepinephrine (***NE***, an endogenous catecholamine) and ephedrine (an amphetamine-like indirect sympathomimetic) are both used in cases of severe hypotension. Note that while NE may be used in a situation like this to treat hypotension in anaphylaxis that is refractory to EPI, ephedrine is typically used for anesthesia-induced hypotension and would not likely be used in this situation.

g) What is the mechanism of action of NE? Why is NE not the treatment of choice for anaphylaxis?

NE stimulates α_1, α_2, and β_1 receptors, resulting in vasoconstriction and cardiac stimulation. Unlike EPI, NE has a very low potency at β_2 receptors. Although NE is a good agent for supporting blood pressure, it lacks the β_2-mediated bronchodilator effect of EPI and is therefore not the agent of choice for anaphylaxis.

h) What are the primary adverse effects of NE?

Like EPI, the primary adverse effects of NE are increased heart rate and cardiac arrhythmias due to β_1-mediated cardiac stimulation.

i) How do you expect Ms. N's heart rate to change in response to NE administration?

Even though tachycardia is a possible adverse effect of NE, it is more likely that her heart rate will *decrease* in response to NE administration. This is due to the *baroreceptor reflex* (*BRR*), whereby an increase in blood pressure results in a decrease in sympathetic tone and increase in parasympathetic tone to the cardiovascular system. At the SA node, this results in a decrease in heart rate.

References:
https://www.uptodate.com/contents/pathophysiology-of-anaphylaxis

https://www.uptodate.com/contents/anaphylaxis-acute-diagnosis

https://www.uptodate.com/contents/anaphylaxis-emergency-treatment

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Surgery

Ms. G is a 67-year-old female who is undergoing coronary artery bypass graft (CABG) surgery for severe three-vessel coronary artery disease.

The anesthesiologist explains that a combination of medications will be administered during the surgery. Included in these medications will be a *neuromuscular blocking agent*, a medication that causes relaxation of the skeletal muscles.

a) What receptors are targeted in the production of skeletal muscle relaxation during surgery? Where are these receptors found and how do they function?

Muscular nicotinic (N_M) receptors are targeted to produce SKM relaxation during surgery. N_M receptors are located at neuromuscular junctions (NMJs) on SKM in the somatic nervous system. N_M receptors are *ligand-gated ion channels*. When ACh released by presynaptic neurons binds to N_M receptors, the channels open to allow influx of Na^+ ions into the SKM cell, producing an *excitatory post-synaptic potential*. If the excitatory post-synaptic potential is large enough to bring the membrane potential to the threshold for activating the adjacent voltage-gated sodium channels, an *action potential* is triggered and the SKM cell subsequently contracts.

b) What are the two main categories of neuromuscular blocking agents? Give an example of each.

The two categories of neuromuscular blocking agent are *competitive agents* and *depolarizing agents*. The suffixes common to competitive agents are "***-curonium***" and "***-curium***;" ***vecuronium***, atracurium, and D-tubocurarine are examples. An example of a depolarizing agent is ***succinylcholine***.

c) What is the mechanism of action of the competitive neuromuscular blocking agents? What are the primary adverse effects?

Competitive neuromuscular blocking agents bind to the ACh binding sites on N_M receptors, but do not cause the ion channels to open and therefore produce no effect. Competitive neuromuscular blocking agents produce flaccid paralysis of the muscle.

The competitive agents (particularly D-tubocurarine) are not highly selective and also antagonize N_N receptors, producing significant ganglionic blockade. N_N antagonist adverse effects include hypotension (due to decreased sympathetic tone to vascular smooth muscle), as well as constipation, urinary retention, and xerostomia (due to decreased parasympathetic tone to the GI tract, urinary tract, and secretory glands, respectively). Additionally, the competitive agents can cause allergic reactions by causing histamine release from mast cells. Note that these effects are most pronounced in D-tubocurarine; vecuronium and atracurium are newer agents that produce much less ganglionic blockade and histamine release, and are therefore used more frequently than D-tubocurarine.

d) What is the mechanism of action of the depolarizing neuromuscular blocking agents? What are the primary adverse effects?

Depolarizing neuromuscular blocking agents also bind to the ACh binding sites on N_M receptors. Binding causes the ion channels to open and therefore depolarize the motor end plate; the resulting activation of the voltage-gated sodium channels can trigger muscle fasciculations. However, succinylcholine is resistant to hydrolysis by AChE and therefore remains at the NMJ and can continue to bind the N_M receptors, preventing repolarization of the motor end plate; the voltage-gated sodium channels therefore cannot recover from the inactivated state following their activation. Thus, the initial muscle fasciculations are quickly followed by flaccid paralysis.

The depolarizing agents can lead to hyperkalemia due to efflux of K^+ ions through open ion channels in muscle cell membranes. The risk of hyperkalemia with depolarizing neuromuscular blocking agents is elevated in patients with other risk factors for hyperkalemia, such as in those taking digoxin or K^+-sparing diuretics, or patients with tissue injuries or burns. Additionally, the depolarizing agents can cause malignant hyperthermia (characterized by hypercarbia, tachycardia, muscle rigidity, and later development of fever) in susceptible patients.

e) Can the paralysis produced by competitive and/or depolarizing neuromuscular blocking agents be reversed pharmacologically? If so, what agent is used and how does it function?

The paralysis produced by competitive neuromuscular blocking agents can be reversed by administration of an *anti-cholinesterase* (*anti-ChE*). Examples of anti-ChEs used for this purpose are ***pyridostigmine*** and neostigmine (common suffix "***-stigmine***"), and edrophonium. The stigmines carbamoylate the active site of AChE at the NMJ. Edrophonium interacts noncovalently with the active site of AChE. Inhibition of AChE prevents hydrolysis of ACh and allows ACh to reach higher concentrations at the NMJ to compete with the neuromuscular blocking agent for binding to N_M receptors.

Anti-ChEs cannot be used to reverse the effects of depolarizing neuromuscular blocking agent. However, succinylcholine has a short half-life (~5-10 minutes) as it is readily hydrolyzed by BuChE in the circulation, and its duration of action is therefore short-lived after administration is discontinued.

f) What are other indications for the use of anti-ChEs?

Anti-ChEs are also used in the treatment of myasthenia gravis (***pyridostigmine***, neostigmine), glaucoma (physostigmine, echothiophate), Alzheimer's disease (donepezil, galantamine, rivastigmine), and mAChR antagonist toxicity (physostigmine).

g) What are the primary adverse effects of the anti-ChEs?

The adverse effects of anti-ChEs are due to the increase in ACh at cholinergic NEJs (mAChR agonist adverse effects) and the increase in ACh at skeletal muscle NMJs (SKM adverse effects). mAChR agonist

adverse effects include vomiting, bronchoconstriction, increased bronchial secretions, diaphoresis, hypersalivation, lacrimation, urinary urgency, and visual disturbances. SKM adverse effects include muscle cramping, fasciculations, and weakness.

Note that the insecticides malathion, parathion, chlorpyrifos, diazinon, and trichlorfon, and the nerve agents soman and sarin are anti-ChEs. The toxic effects of these poisons are more extreme versions of the adverse effects of anti-ChE medications. The resulting respiratory failure (due to bronchoconstriction, increased bronchial secretions, and weakness or paralysis of the diaphragm) can be fatal.

References:
https://www.uptodate.com/contents/clinical-use-of-neuromuscular-blocking-agents-in-anesthesia

https://www.uptodate.com/contents/malignant-hyperthermia-clinical-diagnosis-and-management-of-acute-crisis

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AV block

Mr. T is a 70-year-old man who presents to the Emergency Department due to "fainting."

He was brought to the ED by his son, who witnessed the episode. His son explains that Mr. T has complained of generalized weakness and shortness of breath on exertion for the past week. He has additionally felt lightheaded on several occasions in the past week. This morning, he was seated when he felt lightheaded and then fainted. He regained consciousness within seconds and returned to his "normal self" immediately. Mr. T has a history of two myocardial infarctions at ages 58 and 67. His medications include metoprolol, enalapril (ACE inhibitor; first-line antihypertensive agent), aspirin, and simvastatin (cholesterol-lowering agent). In the ED, Mr. T's heart rate is 40 and his blood pressure is 95/60. He appears tired and can only answer simple questions, and his peripheral pulses are weak bilaterally.
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The physician in the ED obtains an ECG, which shows dissociation of atrial and ventricular impulses with a ventricular rate of 40, consistent with third-degree *AV block*.

AV block is characterized by delayed conduction of an atrial impulse to the ventricular conducting system through the AV node. Severity ranges from first-degree (conduction is slow through AV node, but all impulses are transmitted) to third-degree (no conduction through AV node, complete dissociation of atrial and ventricular impulses). Symptoms vary in severity depending on degree of conduction delay and degree of bradycardia; patients may be asymptomatic, or may present with fatigue, dyspnea, chest pain, syncope, or sudden cardiac death. There are many possible causes of AV block, including history of cardiac disease, recent cardiac surgery, and medications that impair AV conduction.

a) What in Mr. T's history may be contributing to the etiology of his condition?

Mr. T has a history of cardiovascular disease, including 2 myocardial infarctions. Myocardial infarction can cause damage to the AV node and conducting system that can lead to AV block. In addition, Mr. T is on metoprolol, a β_1 antagonist used in the treatment of hypertension and after myocardial infarction. β_1 antagonists slow conduction and can also cause or contribute to AV block.
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Given Mr. T's low blood pressure, weak pulses, and altered mental status, the ED team agrees they must act quickly to stabilize his condition.

b) Which of the following classes of medications are used in the acute treatment of AV block and bradycardia? More than one answer may be correct. Give an example of each.

i. mAChR agonists
ii. mAChR antagonists
iii. α agonists
iv. α antagonists
v. β agonists
vi. β antagonists

mAChR antagonists (ii) and β agonists (v) are used in the acute treatment of AV block and bradycardia. ***Atropine*** is an example of a mAChR antagonist and ***isoproterenol*** is a nonselective β agonist used for this indication.

Additionally note that unless the patient's third-degree AV block is ultimately alleviated by reducing the dose of metoprolol, he will require a pacemaker long-term.

c) What is the mechanism of atropine in the treatment of AV block and bradycardia?

Atropine is a competitive antagonist of mAChR. It competes with ACh for binding to the mAChR active site, resulting in decreased parasympathetic tone to various effector organs. In the heart, blockade of M_2 receptors in the SA and AV nodes results in increased heart rate and increased conduction velocity, respectively. (Note cardiac effects of atropine also include increased atrial contractility (M_2 receptors are present in the atria, but not the ventricles), which does not contribute to its effect in the treatment of AV block and bradycardia.)

Atropine is generally the first-line acute pharmacologic treatment of hemodynamically significant AV block.

d) What are the primary adverse effects of atropine?

The adverse effects of atropine can include dry mouth (xerostomia), urinary retention (especially in elderly men with BPH), constipation, attacks of angle-closure glaucoma in susceptible patients, confusion (especially in elderly patients or patients with underlying cognitive dysfunction), and drowsiness.

e) What is the mechanism of isoproterenol in the treatment of AV block and bradycardia?

Isoproterenol is a nonselective β agonist. It stimulates β_1 receptors in the SA and AV nodes, resulting in increased heart rate and increased conduction velocity, respectively. (Note that other effects of isoproterenol include β_1-mediated increase in atrial and ventricular inotropy and β_2-mediated vasodilation, which do not contribute to its efficacy in the treatment of AV block and bradycardia).

Isoproterenol is used in emergency situations only, typically when a patient fails to stabilize with atropine and external pacing of the heart.

f) What are the primary adverse effects of isoproterenol? What is the mechanism of these adverse effects?

Adverse effects of isoproterenol include tachycardia, arrhythmias, and angina pectoris. Tachycardia and arrhythmias are caused by β_1-mediated stimulation of the SA node and conducting system. Angina pectoris is due to increased myocardial oxygen demand due to β_1-mediated increase in heart rate and

contractility, especially in patients with underlying cardiovascular disease that limits ability to increase myocardial oxygen supply (see angina pectoris module for more detail).

References:
https://www.uptodate.com/contents/etiology-of-atrioventricular-block

https://www.uptodate.com/contents/third-degree-complete-atrioventricular-block

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Acute heart failure; Cardiogenic shock

Ms. F is a 67-year-old female who is currently hospitalized following a myocardial infarction. She lives in a rural town and initially presented with chest pain to a small hospital without the ability to perform percutaneous coronary intervention (PCI). She was treated there with nitroglycerin, aspirin, and metoprolol and transferred to a larger medical center. On arrival to the medical center, she endorsed chest pain lasting for 14 hours. Due to the long duration of her symptoms prior to arrival at the medical center, the decision was made not to perform PCI and she was instead treated with systemic fibrinolytic therapy and admitted to the hospital.

On hospital day 2, the nurse calls the team to Ms. F's room. Ms. F is complaining of new fatigue and shortness of breath, which is worse when she is lying down in bed. Her urine output has also fallen since yesterday. Her blood pressure is 88/60 and heart rate is 90. She appears somewhat confused and does not recall the date or why she is in the hospital. Her cardiac exam is remarkable for a new S3. Auscultation of the lungs reveals crackles at the bilateral bases. Her jugular venous pressure is elevated at 12 cm H_2O. Her extremities are cool and her capillary refill is prolonged. The team orders an echocardiogram, which shows decreased left ventricular function with decreased ejection fraction and elevated pulmonary artery pressure.
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Based on these findings, the team diagnoses Ms. F with *acute heart failure* (*HF*). In acute HF, the heart is unable to produce sufficient cardiac output to meet the requirements of the body. HF can be left-, right-, or bi-ventricular. The inability to maintain cardiac output results in backup of pressure proximally and produces the signs and symptoms characteristic of HF. In left ventricular HF, pressure backup in the pulmonary circulation results in *pulmonary edema*, which manifests as dyspnea on exertion, at rest, or while lying down (*orthopnea*). In right ventricular HF, pressure backup in the systemic circulation results most commonly in *peripheral edema*. MI is the most common cause of new onset acute HF in adults, due to myocardial dysfunction caused by ischemic injury. Other possible causes include *myocarditis* (inflammation of the myocardium) or *acute valvular failure* (such as severe mitral regurgitation).

Furthermore, Ms. F's presentation is concerning for *cardiogenic shock*, which occurs when the heart's inability to maintain cardiac output results in *end-organ damage*. Signs of cardiogenic shock include sustained hypotension with systolic BP <90 mmHg, confusion, signs of decreased extremity perfusion (e.g., cool extremities, decreased capillary refill), and signs of decreased kidney perfusion (e.g., decreased urine output, rising serum creatinine).
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The team treats Ms. F with a *diuretic* to help relieve her pulmonary edema. The team also wants to give a medication to help her heart pump more effectively.

a) What class of medication affecting the autonomic nervous system can be used for this purpose? Give an example.

β_1 agonists are used in the treatment of acute HF and cardiogenic shock. An example is ***dobutamine***.

b) What is the mechanism of dobutamine in the treatment of acute HF and cardiogenic shock?

Dobutamine stimulates β_1 adrenergic receptors in the heart, resulting primarily in an increase in inotropic state (contractility).

c) What are the adverse effects of β_1 agonists?

As β_1 receptors also mediate heart rate and the conducting system, β_1 agonists can cause tachycardia and arrhythmias.

d) Are there any medications that the team should avoid giving Ms. F in her current condition?

Yes, the team should avoid giving Ms. F β antagonists. Although β antagonist therapy is typically initiated within 24 hours of an MI, their use can further exacerbate HF and is therefore contraindicated in patients with acute HF.

References:
https://www.uptodate.com/contents/overview-of-the-acute-management-of-st-elevation-myocardial-infarction

https://www.uptodate.com/contents/approach-to-acute-decompensated-heart-failure-in-adults

https://www.uptodate.com/contents/treatment-of-acute-decompensated-heart-failure-in-acute-coronary-syndromes

https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-cardiogenic-shock-in-acute-myocardial-infarction

https://www.uptodate.com/contents/prognosis-and-treatment-of-cardiogenic-shock-complicating-acute-myocardial-infarction

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HFrEF

Mr. O is a 75-year-old male who presents to his primary care physician with a chief complaint of "leg swelling."

Mr. O has noticed progressive swelling of his feet and lower legs over the past 6 months. He has been feeling tired and had poor appetite, leading to a 10-pound weight loss over this time. He has had decreased exercise tolerance due to shortness of breath, and has to sleep on 3 pillows at night because he sometimes feels short of breath while lying down as well. Mr. O has a past history of hypertension, hypercholesterolemia, and 3 myocardial infarctions. He has not seen a doctor in several years and is not currently taking any medications. In the office, Mr. O's vital signs are significant for blood pressure of 140/95. On physical exam, his point of maximal impulse (PMI) is laterally displaced and an S_3 is heard on cardiac auscultation. The jugular venous pressure is estimated to be 15 cm H_2O. Faint crackles are heard

at the bilateral lung bases. His abdomen is nontender, moderately distended, and the liver edge is palpated 2 cm below the costal margin. There is pitting edema of the bilateral feet and lower legs.
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Mr. O's physician orders an ECG and an echocardiogram. The ECG shows Q waves suggestive of past myocardial infarction. The echocardiogram shows areas of abnormal ventricular wall motion and dilation of the left ventricle with a left ventricular ejection fraction of 35%.

Based on the history, physical exam, and echocardiogram findings, Mr. O's physician diagnoses him with *heart failure with reduced ejection fraction* (*HFrEF*).

Heart failure (*HF*) is, in general, the inability of the heart to provide adequate perfusion to the body at normal ventricular filling pressures. HF can present acutely (*acute HF*) or gradually (*chronic HF*), and can be due to dysfunction of ventricular pump function (*heart failure with reduced ejection fraction*, *HFrEF*; also called *systolic heart failure*) or dysfunction of ventricular filling (*heart failure with preserved ejection fraction*, *HFpEF*; also called *diastolic heart failure*). Here we will focus on chronic HFrEF.

There are many possible etiologies of HFrEF, including ischemic heart disease (*ischemic cardiomyopathy*), valvular disease, and hypertension. The symptoms of HFrEF include fatigue, poor appetite, symptoms of *pulmonary edema* (e.g., dyspnea on exertion, dyspnea while lying supine (*orthopnea*) or at night (*paroxysmal nocturnal dyspnea*)), and/or symptoms of systemic pressure backup (e.g., peripheral edema, abdominal distension/discomfort). Physical exam may reveal a displaced cardiac apex signifying an enlarged heart, S_3, murmur if there is valvular dysfunction, irregular cardiac rhythm, distended neck veins (elevated jugular venous pressure), crackles on lung auscultation, hepatomegaly, abdominal distension or ascites, and/or pitting peripheral edema. By definition, in HFrEF echocardiogram will show left ventricular ejection fraction of ≤40%.
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a) Which of the following classes of medications are used in the long-term treatment of HFrEF? More than one answer may be correct. Give an example of each.

i. α_1 agonists
ii. α_1 antagonists
iii. β agonists
iv. β antagonists
v. ACE inhibitors
vi. AT_1 receptor blockers
vii. Calcium channel blockers
viii. Aspirin

β antagonists (iii; e.g., ***metoprolol***, ***carvedilol***, bisoprolol), ACE inhibitors (v; e.g., ***captopril***), and ARBs (vi; e.g., ***losartan***) are used in the treatment of chronic HFrEF. Each of these classes of medications is associated with improved survival in patients with HFrEF.

Note that when selecting a β antagonist, only ***metoprolol***, ***carvedilol***, and bisoprolol have demonstrated efficacy in HFrEF, therefore one cannot take a "class effect" approach in selecting an agent. In contrast, one can take a "class effect" approach in the selection of an ACE inhibitor or ARB in the management of HFrEF.

b) What is the mechanism of the β antagonists in the treatment of HFrEF?

The mechanism of the β antagonists in the treatment of HFrEF is complex, and the improved survival in patients treated with β antagonists appears to be due to the blockade of several detrimental effects of excess catecholamines on the heart. Effects that are predictable from the effects of β_1 receptor blockade on the heart include decreased heart rate and decreased myocardial oxygen demand (by decreased heart rate and inotropic state). Other proposed effects include altered gene expression, restoration of myocardial β receptor responsiveness, suppression of harmful myocardial remodeling, reduction of circulating vasoconstrictors, and reduced risk of potentially fatal ventricular arrhythmias.

c) Some β antagonists have additional cardiovascular effects. What are these effects, and what is the mechanism by which they occur? Which β antagonist with additional cardiovascular effects is used in the treatment of HFrEF?

The most important additional cardiovascular effect of these medications is vasodilation. The mechanism of vasodilation produced by these agents is multifactorial, including increased nitric oxide (NO) production by vascular endothelial cells (see Vasoactive Mediators lecture), intrinsic β_2 agonist activity, α_1 antagonist activity, calcium channel blockade, activation of potassium channels, and antioxidant activity.

Carvedilol is a nonselective β antagonist with additional cardiovascular effects that is used in the treatment of HFrEF. Other examples of β antagonists with additional cardiovascular effects that are <u>not</u> used for HFrEF include labetalol (nonselective) and nebivolol (β_1 selective).

d) What is the mechanism of action of ACE inhibitors and ARBs in the treatment of HFrEF?

The mechanism of action of ACE inhibitors and ARBs in the treatment of HFrEF is not fully understood. They produce systemic vasodilation, resulting in reduced afterload. This reduces strain on the heart and thereby reduces myocardial oxygen demand. ACE inhibitors and ARBs reduce LV hypertrophy by reducing afterload and reduce deleterious cardiovascular remodeling through multiple mechanisms (e.g., reduced aldosterone production, inhibition of direct effects of Ang II on myocardium), thereby preventing further deterioration of myocardial function. There are numerous other likely mechanisms by which ACE inhibitors and ARBs improve survival in HFrEF, which are beyond the scope of this course.

e) What medication is used in HFrEF to increase cardiac contractility? How does this medication work?

Digoxin, a cardiac glycoside, is also used in the treatment of HF. Digoxin inhibits Na^+-K^+ ATPase in the myocardium, resulting in a decrease in the Na^+ gradient across the cell membrane. This leads to decreased activity of NCX, which is driven by the electrochemical gradient for Na^+. This subsequently results in increased intracellular [Ca^{2+}], maximizing actin-myosin crosslinking and increasing inotropic state. Digoxin improves the quality of life of patients with advanced HFrEF by reducing symptoms, however it does not improve survival. Digoxin also has a very narrow therapeutic index. For these reasons, digoxin is not commonly used and in the non-acute setting is only prescribed for patients with advanced HF and severe symptoms despite optimal therapy.

Digoxin also causes an increase in parasympathetic tone and decrease in sympathetic tone to the heart, which is counteractive to its activity in increasing contractility but accounts for its action in the treatment of cardiac arrhythmias and some of its adverse effects.

f) What are the primary adverse effects of digoxin?

The primary adverse effects of digoxin include AV block, ventricular arrhythmias, and adverse GI effects including nausea, vomiting, and anorexia.

g) Are there other classes of medications in addition to the β antagonists, ACE inhibitors, and ARBs that have been shown to improve survival in HFrEF?

Yes. Other medications that improve survival in HFrEF include the *aldosterone antagonists*, and the combination of *hydralazine* (an antihypertensive agent) with *organic nitrates* (e.g., isosorbide dinitrate). You will learn about the aldosterone antagonists in Renal System I. The use of hydralazine with organic nitrates is beyond the scope of this course.

References:
https://www.uptodate.com/contents/evaluation-of-the-patient-with-suspected-heart-failure

https://www.uptodate.com/contents/determining-the-etiology-and-severity-of-heart-failure-or-cardiomyopathy

https://www.uptodate.com/contents/pharmacologic-therapy-of-heart-failure-with-reduced-ejection-fraction

https://www.uptodate.com/contents/use-of-beta-blockers-in-heart-failure-with-reduced-ejection-fraction

https://www.uptodate.com/contents/use-of-angiotensin-converting-enzyme-inhibitors-in-heart-failure-with-reduced-ejection-fraction

https://www.uptodate.com/contents/use-of-angiotensin-ii-receptor-blocker-in-heart-failure-with-reduced-ejection-fraction

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Arrhythmias that can be terminated by slowing AV conduction

C is a previously healthy 16-year-old girl who presents to the Emergency Department with a chief complaint of "heart pounding."

She was sitting in class at school 1 hour ago when she suddenly felt her heart pounding and beating very fast. She additionally started to feel lightheaded, so was brought to the ED by her mother. She has had occasional episodes like this before; they have occurred both at rest and while playing sports, and all previous episodes have self-resolved within a few minutes. In the ED, C's heart rate is 210 and her blood pressure is 110/70. She appears tired and pale, but she is alert and answers questions appropriately. On auscultation, she is tachycardic with regular rhythm and no extra heart sounds. She has strong peripheral pulses and good capillary refill. The remainder of her physical exam is unremarkable.
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The physician obtains an ECG, which shows tachycardia (rate 210) with no P waves and narrow QRS complexes. These ECG findings are consistent with *supraventricular tachycardia* (*SVT*).

SVT is a broad category of tachyarrhythmias that originate at a level proximal to the ventricles. SVT includes AV reentrant tachycardia (AVRT), AV nodal reentrant tachycardia (AVNRT), atrial fibrillation, and others. In children, AVNRT accounts for the majority of SVT, followed by AVRT (the remainder of this module will focus on AVRT and AVNRT). In these tachyarrhythmias, some aberrancy in the

conduction system exists that allows cyclic reentry of electrical impulses into the AV node, resulting rapid repeated stimulation of the ventricles. The resulting tachycardia is typically at a rate of 180-240 bpm in children and adolescents, and may be slightly less in adults. Patients may occasionally be asymptomatic, but typically present with paroxysmal episodes of palpitations. They may also have lightheadedness, fatigue, chest discomfort, and less commonly syncope. Episodes come on abruptly and typically self-resolve in 10-15 minutes on average (although episodes may last only a couple of minutes or for hours).

When episodes do not self-resolve, or when patients are *hemodynamically unstable* (e.g., hypotension, weak peripheral pulses, confusion, etc.), the arrhythmia can be terminated by interventions that decrease conduction velocity through the AV node. Such interventions include *vagal maneuvers*, which increase parasympathetic tone to the heart to slow AV conduction, and certain medications.
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a) Which of the following medications or classes of medications can be used to treat arrhythmias that can be terminated by slowing AV conduction? More than one answer may be correct. Give an example of each.

i. α_1 agonists
ii. α_2 agonists
iii. α_1 antagonists
iv. β_1 agonists
v. β_2 agonists
vi. β antagonists
vii. mAChR agonists
viii. mAChR antagonists
ix. Non-DHP calcium channel blockers
x. Adenosine (endogenous nucleoside)
xi. Digoxin (cardiac glycoside)

β antagonists (vi; e.g., ***propranolol***, ***atenolol***), non-DHP calcium channel blockers (ix; e.g., ***verapamil***), ***adenosine*** (x), and ***digoxin*** (xi) can all be used in the treatment of arrhythmias that can be terminated by slowing AV conduction.

There are additional antiarrhythmic agents that are also used for this indication; these medications will be introduced in Cardiovascular System II.

b) What is the first-line pharmacologic therapy for the acute termination of these arrhythmias? What is the mechanism of action?

Adenosine is the first-line therapy for arrhythmias such as AVRT and AVNRT. Adenosine is an endogenous nucleoside that is stimulates adenosine receptors in the heart, resulting in a decrease in AV conduction velocity. Stimulation of A1 receptors also causes a decrease in sinus rate, which does not contribute to its effect in the treatment of these arrhythmias.

c) What is the mechanism of action of verapamil in the treatment of these arrhythmias?

Verapamil is a non-dihydropyridine (non-DHP) calcium channel blocker (CCB). Verapamil binds to and inhibits L-type Ca^{2+} channels on cardiac myocytes, causing a decrease in the *slow inward Ca^{2+} current* ($i_{Ca\text{-}L}$). In slow fibers (i.e., SA and AV nodes), $i_{Ca\text{-}L}$ is the current responsible for Phase 0 of the slow response action potential; by decreasing $i_{Ca\text{-}L}$, verapamil slows the Phase 0 slope/amplitude and consequently decreases conduction velocity through the AV node. For more detail, see the Cardiac Electrophysiology lecture.

d) Are there other indications for use of verapamil?

Yes. Verapamil is also used in the treatment of angina pectoris and hypertension. You will learn more about this medication and other calcium channel blockers in the Cardiovascular Pharmacology lecture.

e) What is the mechanism of action of β antagonists in the treatment of these arrhythmias?

β antagonists block β_1 receptors in the AV node, resulting in a decrease in $i_{Ca\text{-}L}$ and subsequent decrease in AV conduction velocity as above.

f) What is the mechanism of action of digoxin in the treatment of these arrhythmias?

Digoxin increases parasympathetic and decreases sympathetic tone to the heart via a CNS effect. In the AV node, this results in a decrease in AV conduction velocity. This also results in a decrease in sinus rate, which does not contribute to its effect in the treatment of these arrhythmias. Note that by its effects on autonomic tone, digoxin would be predicted to have a negative inotropic effect on the heart; however it actually results in a net increase in inotropy due to effects ion channels on cardiac myocytes (for more detail, see the Ventricular Function lecture (slides about *digitalis*), Cardiovascular Pharmacology lecture, and HFrEF module).

References:

https://www.uptodate.com/contents/overview-of-the-acute-management-of-tachyarrhythmias

https://www.uptodate.com/contents/narrow-qrs-complex-tachycardias-clinical-manifestations-diagnosis-and-evaluation

https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-supraventricular-tachycardia-in-children

https://www.uptodate.com/contents/management-of-supraventricular-tachycardia-in-children

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Pulmonary hypertension

Ms. M is a previously healthy 30-year-old female who presents to her primary care physician with a chief complaint of "shortness of breath."

She has had a gradual progression of shortness of breath over the past year. It initially occurred only with strenuous activity such as running and she attributed it to deconditioning, but she now feels short of breath with walking and is unable to run. She has no associated cough or wheezing, and she does not have shortness of breath at rest or while lying down. She also has been increasingly tired during this time. Over the last month she has noticed that her feet seem to be slightly swollen. In the office, Ms. M's vital signs are within normal limits. Her respiratory exam is normal. A right ventricular heave is noted on palpation of the precordium. On cardiac auscultation, the intensity of P2 is increased. She has jugular venous distension, with the jugular venous pressure wave visible 8 cm above the sternal angle (normal ≤4 cm). Her peripheral pulses are strong bilaterally, and there is trace pitting edema of the bilateral lower extremities. The remainder of her physical exam is unremarkable.

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Ms. M's physician orders an echocardiogram, which shows *elevated pulmonary artery pressure*, *right ventricular hypertrophy*, and normal left heart function. She then undergoes right heart catheterization, which confirms the diagnosis of *pulmonary hypertension*.

Pulmonary hypertension is a disease characterized by a mean pulmonary artery pressure ≥25 mmHg (normal 8-20 mmHg). There are many different etiologies of pulmonary hypertension, including primary disease of the pulmonary arterioles, left heart disease, chronic lung disease, and others. Patients initially present with fatigue and shortness of breath. The right ventricle may hypertrophy as a result of pumping against an increased pulmonary artery pressure. Furthermore, if the right heart is unable to maintain adequate cardiac output against the elevated pulmonary artery pressure, right heart failure develops. Patients with right ventricular hypertrophy and right heart failure may experience additional symptoms such as angina, syncope, and peripheral edema. Pulmonary hypertension is a progressive disease, and at advanced stages management becomes increasingly difficult and may require lung transplantation. Early diagnosis and initiation of treatment is therefore important to prevent progression of the disease.
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Ms. M's physician recommends pharmacologic treatment of her pulmonary hypertension.

a) Which of the following are pharmacologic targets in the treatment of pulmonary hypertension?

i. Natriuretic peptides
ii. Endothelins (ETs)
iii. Kallikrein-kinin system (KKS)
iv. Eicosanoids
v. Renin-angiotensin system (RAS)
vi. Calcium channels
vii. Nitric oxide (NO) production

Medications used in the treatment of pulmonary hypertension target the endothelins (ii), eicosanoids (iv), calcium channels (vi), and nitric oxide production (vii).

b) What class of drugs targeting the endothelins (ETs) is used in the treatment of pulmonary hypertension? What is the suffix common to these medications? Give an example.

ET receptor antagonists (ERAs) are used in the treatment of pulmonary hypertension. The suffix common to these medications is "***-entan***." Examples include nonselective ERAs ***bosentan*** and macitentan, and ET_A-selective ambrisentan.

c) What is the mechanism of action of bosentan in the treatment of pulmonary hypertension? How does the mechanism of an ET_A-selective agent differ from that of bosentan?

Bosentan nonselectively blocks ET receptors. Recall that ET_A and ET_B receptors have opposite effects. Under normal circumstances, ET_A-mediated vasoconstriction predominates over ET_B-mediated vasodilation. Therefore, blocking both ET_A and ET_B receptors results in vasodilation. Vasodilation of the pulmonary vasculature results in decreased pulmonary vascular resistance and subsequent decrease in mean pulmonary artery pressure.

ET_A-selective agents such as ambrisentan block ET_A-mediated vasoconstriction, but still allow stimulation of ET_B receptors, resulting in vasodilation. However, ambrisentan does not appear to be more efficacious than nonselective ERAs.

d) What are the primary adverse effects of bosentan?

Bosentan can cause headache, nasopharyngitis, flushing (due to vasodilation), and peripheral edema. Importantly, bosentan can cause significant hepatotoxicity and therefore liver function must be monitored with periodic labs. Additionally, the ERAs are teratogenic; they are contraindicated in pregnancy and patients should be counseled about contraceptive options and the risks of becoming pregnant while on these medications.

e) What two classes of drugs targeting nitric oxide (NO) production are used in the treatment of pulmonary hypertension? Give an example of each.

PDE5 inhibitors and sCG activators are used in the treatment of pulmonary hypertension. Examples of PDE5 inhibitors include ***sildenafil***, tadalafil, vardenafil, and avanafil (common suffix "***-afil***"). An example of an sCG activator is riociguat.

f) What is the mechanism of action of sildenafil in the treatment of pulmonary hypertension?

Sildenafil inhibits PDE5, an enzyme present in vascular smooth muscle cells that normally breaks down cGMP and therefore inhibits NO-mediated vasodilation. By inhibiting PDE5, sildenafil potentiates the effects of NO, resulting in vasodilation. Vasodilation in the pulmonary vasculature results in decreased pulmonary vascular resistance and subsequently decreases mean pulmonary artery pressure.

g) What is the mechanism of action of the sCG activators in the treatment of pulmonary hypertension?

Soluble guanylyl cyclase (sCG) is an enzyme present in vascular smooth muscle cells that, when bound by NO, converts GTP to cGMP, ultimately resulting in smooth muscle relaxation and vasodilation. sCG activators stabilize the binding of endogenous NO to sCG, allowing for increased enzyme activity and therefore increased vasodilation. Note that riociguat can also activate sGC even in the absence of NO, which is advantage over the *-afils* which require the presence of NO.

h) What class of medications targeting calcium channels is used in the treatment of pulmonary hypertension? What is the suffix common to these medications? Give an example.

The dihydropyridines (DHPs), a class of calcium channel blockers, are used in the treatment of pulmonary hypertension. The suffix common to these medications is "***-dipine***." Examples include ***amlodipine***, nifedipine, felodipine, isradipine, nicardipine, and nisoldipine.

i) What is the mechanism of action of amlodipine in the treatment of pulmonary hypertension?

Amlodipine inhibits L-type Ca^{2+} channels (LTCCs), resulting in vasodilation and subsequent decrease in pulmonary vascular resistance and mean pulmonary artery pressure.
(Note that DHPs are used off-label for the treatment of pulmonary hypertension, but have limited efficacy.)

j) Which eicosanoid is targeted in the treatment of pulmonary hypertension? What root is common to the eicosanoids and their synthetic derivatives?

PGI_2 (prostacyclin; one of the *vasodilator prostaglandins*) is targeted in the treatment of pulmonary hypertension. Strategies include the use of synthetic versions or derivatives of PGI_2, or IP (PGI_2) receptor agonists. The common root to the eicosanoids and their synthetic derivatives is "***prost***." Examples used in pulmonary hypertension include epoprostenol (synthetic PGI_2), iloprost (synthetic PGI_2 analog), and treprostinil (synthetic PGI_2 analog). An example of an IP receptor agonist is selexipag.

References:
https://www.uptodate.com/contents/the-epidemiology-and-pathogenesis-of-pulmonary-arterial-hypertension-group-1

https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-pulmonary-hypertension-in-adults

https://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-in-adults

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Erectile dysfunction

Mr. U is a 67-year-old male who presents to his primary care physician for his annual physical exam.

Mr. U reports feeling well since his last visit. However, on review of systems he endorses that he has been having difficulty maintaining an erection, and this has been increasingly frustrating for him as he has been unable to have intercourse with his partner. This problem has become more notable in the last few months. He reports his libido is normal, he is not experiencing any conflict in his relationship with his partner, and he is interested in sexual relations. He is not experiencing morning erections. His physician reviews his history. Mr. U has a history of hypertension, hypercholesterolemia, stable angina pectoris, and peripheral vascular disease. His medications include captopril, simvastatin (cholesterol-lowering agent), and verapamil. He has smoked 1.5 packs of cigarettes daily for 40 years. In the office, Mr. U's vital signs are within normal limits. His physical exam is remarkable for symmetrically diminished peripheral pulses and cool extremities. The remainder of his physical exam, including genitourinary exam, is normal.
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Male sexual dysfunction is a broad category of disease encompassing *erectile dysfunction* (*ED*), decreased libido, and ejaculatory disorders. ED is defined as the inability to acquire and maintain an erection. There are many causes of ED, including problems with sexual stimulation (psychosocial factors, e.g., depression, relationship strain), problems with neural stimulation (e.g., autonomic neuropathy, stroke), problems with blood flow to the penis (e.g., peripheral vascular disease), and various drugs (e.g., antidepressants). Because there are so many possible factors contributing to sexual dysfunction, obtaining a detailed history is crucial to determining the etiology of a patient's condition and the appropriate management strategy.
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Given his history of coronary artery disease (angina), peripheral vascular disease, and several risk factors for cardiovascular disease (hypertension, hypercholesterolemia, smoking history), Mr. U's physician suspects Mr. U is experiencing vascular ED. Mr. U asks if there is a medication that could help treat this condition.

a) What class of medications is commonly used in the treatment of ED? What is the suffix common to these drugs? Give an example.

Phosphodiesterase-5 (*PDE5*) *inhibitors* are commonly used in the treatment of ED. The suffix common to the PDE5 inhibitors is "***-afil***." Examples include ***sildenafil***, tadalafil, vardenafil, and avanafil.

b) What is the mechanism of action of the PDE5 inhibitors in the treatment of ED?

Vasodilation in the corpora cavernosa of the penis is imperative to the ability to acquire and maintain and erection. The enzyme PDE in vascular smooth muscle catalyzes the degradation of cGMP, terminating the

vasodilating effect of nitric oxide (NO). There are multiple PDE isoforms, and PDE5 is the predominant form present in the corpus cavernosum. PDE5 inhibitors reduce cGMP degradation, potentiating the effects of NO and resulting in vasodilation.

c) What are the primary adverse effects of the PDE5 inhibitors?

The primary adverse effects of the PDE5 inhibitors are headache and flushing (due to systemic vasodilation), dyspepsia, muscle pain (myalgia), vision loss, changes in blue-green color discrimination, and hearing loss. Additionally, the use of PDE5 inhibitors is contraindicated in patients taking organic nitrates, as the combination of these medications can cause a severe and dangerous drop in blood pressure.

d) What are other indications for the use of PDE5 inhibitors?

Sildenafil and tadalafil are also used in the treatment of pulmonary hypertension. Additionally, tadalafil is used in the treatment of benign prostatic hyperplasia (BPH).

References:
https://www.uptodate.com/contents/overview-of-male-sexual-dysfunction

https://www.uptodate.com/contents/evaluation-of-male-sexual-dysfunction

https://www.uptodate.com/contents/sexual-activity-in-patients-with-cardiovascular-disease

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Osteoarthritis

Mr. K is a 65-year-old male who presents to his primary care physician with a chief complaint of "knee pain."

He has had progressively worsening bilateral knee pain for the last several years. The pain is dull and aching, worsens with activity, and is relieved with rest. Recently, the pain has limited how far he can walk in his neighborhood. His knees feels stiff when he wakes up in the morning, then loosen up as he moves around. He sometimes feels like his knees will buckle while he is walking, but he has not fallen. He has no history of past knee injuries. Mr. K's past medical history is significant for obesity (BMI 32) and hospitalization two years ago with an acute GI bleed secondary to a duodenal ulcer. On physical exam, both knees appear mildly swollen but there is no warmth or discoloration. There is tenderness to palpation along the joint line of both knees. Range of motion is moderately limited symmetrically, and there is palpable crepitus on movement of the joints. The remainder of his physical exam is unremarkable.
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Mr. K's physician tells him that his history and physical exam are consistent with a diagnosis of *osteoarthritis* (*OA*).

OA, the most common form of arthritis, is a joint disease characterized by the gradual onset of joint pain, joint stiffness, and limitation of range of motion. The pathogenesis of OA involves a combination of degeneration of the articular cartilage, changes to underlying bone, and inflammation of the joint space. OA most commonly affects the knees, hips, joints in the hands and feet (interphalangeal joints, first carpometacarpal joint, first metatarsophalangeal joint), and articular facets of the cervical and lumbar spine. Important risk factors include age, history of joint injury or surgery, and obesity. The pain in OA

worsens with activity, typically increases throughout the day, and is relieved by rest. Joint stiffness is worst in the morning on waking and typically resolves within 30 minutes. Patients also may complain of the feeling of joint instability and buckling. On physical exam, patients may have joint line tenderness, bony swelling of the joint, limited joint range of motion, and/or crepitus.
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a) What common class of medications is used in the symptomatic treatment of OA? There are two categories of drugs within this class (nonselective and selective); give an example of each and the suffix common to the selective agents.

The non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat the symptoms of OA. Examples of nonselective NSAIDs (also called *traditional NSAIDs* (*tNSAIDs*)) include ***aspirin***, ***ibuprofen***, naproxen, diclofenac, indomethacin, ketoprofen, and ***acetaminophen***. An example of a selective COX-2 inhibitor is ***celecoxib*** (common suffix "***-coxib***").

b) What is the mechanism of action of the tNSAIDs?

tNSAIDs nonselectively inhibit the enzyme cyclooxygenase (COX), which catalyzes the first steps in the generation of prostanoids. tNSAIDs inhibit both COX isoforms (COX-1 and COX-2). Expression of COX-2 is induced at sites of injury and inflammation. COX-2 is also constitutively expressed in the brain, and fever is associated with increased production of PGE_2. tNSAIDs inhibit the production of prostanoids involved in these processes, resulting in anti-inflammatory, antipyretic, and analgesic effects.

c) What are the primary adverse effects of the tNSAIDs (not including acetaminophen)? What is the mechanism of these adverse effects?

Many of the primary adverse effects of the tNSAIDs are due to the inhibition of prostanoid production in various tissues:

- Inhibition of COX-1 in the gastric mucosa causes reduction in the cytoprotective prostaglandins PGE_2 and PGI_2, which can lead to abdominal pain, peptic or intestinal ulcers, and/or GI bleeding. Misoprostol, a synthetic analog of PGE_1, can in theory be given to prevent ulcer formation in patients taking chronic NSAIDs (however, in practice patients do better with the addition of an H_2 histamine antagonist rather than misoprostol).
- Inhibition of production of the vasodilator PGs (PGE_2 and PGI_2) by COX-2 in the kidney can result in a decrease in renal blood flow and glomerular filtration rate. This effect is especially prominent in patients with decreased baseline renal function (e.g., renal artery stenosis) or impaired renal function, and can lead to acute kidney injury.
- Inhibition of prostaglandin production in the uterine smooth muscle can delay labor. (This effect can be used off-label (indomethacin) to stop uterine contractions in preterm labor to prevent premature delivery.)
- Inhibition of production of the vasodilator PGs (PGE_2 and PGI_2) in the fetus can cause premature closure of the *ductus arteriosus*, an important fetal vascular structure. For this reason, tNSAIDs should be used with caution during the third trimester of pregnancy. (Conversely, the NSAID indomethacin is used in premature infants with hemodynamically significant *patent ductus arteriosus* to promote closure.)
- Inhibition of PGE_2 and PGI_2 production in the lungs, as well as increased production of leukotrienes (secondary to inhibition of PGE_2 synthesis – PGE_2 is an inhibitor of 5-LOX), can cause bronchoconstriction and exacerbation of asthma. This is called *aspirin-induced respiratory disease* (*AERD*), but can occur with any of the tNSAIDs.

- *All tNSAIDs except aspirin:* Inhibition of PGI_2 production by COX-2 in endothelial cells results in increased platelet activation and increases the risk of cardiovascular thrombotic events such as myocardial infarction and ischemic stroke.
- Inhibition of TXA_2 production by COX-1 in platelets reduces platelet activation and can lead to prolonged bleeding, increasing the risk of bleeding complications such as GI bleeds and hemorrhagic stroke. This can be seen with all NSAIDs, however it is most problematic with *aspirin* due to irreversible inhibition of COX-1.

Additionally, tNSAIDs can cause allergic reactions, including anaphylaxis.

d) How is acetaminophen different from the other tNSAIDs? What is the primary adverse effect of acetaminophen?

The mechanism of action of acetaminophen is not fully understood. Like the other tNSAIDs, acetaminophen inhibits COX-1 and COX-2, however there are likely other mechanisms by which acetaminophen exerts its analgesic effect. Additionally, unlike the other tNSAIDs, acetaminophen does not exhibit significant anti-inflammatory effects. It is hypothesized that the reason for acetaminophen's minimal anti-inflammatory action is that the drug is a poor inhibitor of COX in the high-peroxide environment in areas of inflammation.

The primary adverse effect of acetaminophen is hepatotoxicity, which can lead to acute liver failure requiring liver transplant. Notably, acetaminophen overdose is the most common cause of acute liver failure in the United States.

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After reviewing his past medical history, Mr. K's physician decides to prescribe the selective COX-2 inhibitor celecoxib for his knee pain.

e) Why is celecoxib preferred to other NSAIDs in this situation?

Mr. K has a history of a duodenal ulcer complicated by a GI bleed. COX-1 is constitutively expressed in the GI tract, where it plays an important role in cytoprotection through the production of PGE_2 and PGI_2. These PGs reduce gastric acid secretion and increase bicarbonate and mucus secretion, protecting the GI mucosa and preventing ulcer formation. Selective COX-2 inhibitors such as celecoxib are as effective as nonselective NSAIDs in their anti-inflammatory, analgesic, and antipyretic effects, but carry a lower risk of adverse GI effects because COX-1 is minimally affected. (Note that there is still a risk of GI adverse effects, and these agents should therefore be used with caution in patients like Mr. K.)

f) What are the primary adverse effects of selective COX-2 inhibitors?

The primary adverse effects of celecoxib are similar to those of the tNSAIDs, and are the result of COX-2 inhibition in various tissues. They include adverse GI effects such as abdominal pain, ulcers, and bleeding (lower risk than with tNSAIDs); decreased renal blood flow and glomerular filtration rate in patients with decreased baseline renal function (e.g., renal artery stenosis) or impaired renal function; increased risk of cardiovascular thrombotic events; and allergic reactions, including anaphylaxis.

g) What are other examples of indications for use of NSAIDs?

Most tNSAIDs (e.g., aspirin, ibuprofen) are used in the symptomatic management of a wide variety of conditions, including mild-to-severe pain, fever, osteoarthritis, rheumatoid arthritis, dysmenorrhea (pain during menstruation), and migraine. Daily low-dose aspirin is also used for cardioprotection in patients at risk of cardiovascular disease.

Acetaminophen does not exhibit significant anti-inflammatory effects, so is not as effective as other tNSAIDs in the treatment of conditions with inflammation. Acetaminophen is primarily used in the management of mild-to-severe pain, fever, and osteoarthritis.

Selective COX-2 inhibitors (e.g., celecoxib) are used primarily in the management of moderate-to-severe pain, osteoarthritis, and rheumatoid arthritis.

References:
https://www.uptodate.com/contents/pathogenesis-of-osteoarthritis

https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-osteoarthritis

https://www.uptodate.com/contents/nsaids-therapeutic-use-and-variability-of-response-in-adults

https://www.uptodate.com/contents/nsaids-pharmacology-and-mechanism-of-action

https://www.ncbi.nlm.nih.gov/pubmed/11566461

https://www.uptodate.com/contents/nonselective-nsaids-overview-of-adverse-effects

Appendix 2: Renal System 1 (RS1) Pharmacology Cases

Hypertension 1

Mr. R is a 63-year-old man who presents to a new primary care physician to establish care.

Mr. R reports that he has not seen a doctor in the past 10 years. He sometimes measures his blood pressure at the grocery store, and it has been "on the high side – maybe 150s or 160s." He denies ever being diagnosed with hypertension before, and only noticed an increase in his blood pressure readings in the last few years. In the office, Mr. R's blood pressure is 150/100. His physical exam, including complete cardiovascular exam, is normal.

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Mr. R's physician wishes to obtain routine screening labs, and would like Mr. R to begin taking a medication for his blood pressure. The physician chooses to prescribe an agent that acts by targeting the *renin-angiotensin-aldosterone system* (*RAAS*).

a) There are five classes of medication that target the RAAS. What are they, and on what step(s) of the pathway does each act?

Inhibitors of renin secretion, direct renin inhibitors (DRIs), ACE inhibitors (ACEIs), AT_1 receptor blockers (ARBs), and aldosterone antagonists all target the RAAS.

β antagonists (and, less importantly, α_2 agonists) prevent renin secretion by juxtaglomerular cells of the kidney. Recall that the sympathetic nervous system (via stimulation of β_1 receptors) is one of four regulators of renin secretion. The other regulators are renal baroreceptors, macula densa, and hormones (e.g., Ang II, ANP).

DRIs inhibit renin, which catalyzes the conversion of angiotensinogen to angiotensin I (Ang I). This is the rate-limiting step of the RAAS pathway. Recall that Ang I is not an active peptide.

ACEIs inhibit the enzyme angiotensin-converting enzyme (ACE), which catalyzes the conversion of Ang I to the active Ang II.

ARBs block the AT_1 receptors on tissues such as blood vessels, nephrons, and adrenal cortex.

Aldosterone antagonists block the mineralocorticoid receptor in the epithelial cells of the connecting tubule (CNT) and collecting duct (CD) of the nephron, as well as in various other tissues.

b) Of the above classes of medication, which one(s) are first-line agents for the treatment of HTN? Give an example of each and, if applicable, the suffix common to the class.

ACEIs (suffix "***-pril***," e.g., ***enalapril***) and ARBs (suffix "***-sartan***," e.g., ***losartan***) are used in the first-line treatment of HTN.

c) What is the mechanism of ACEIs and ARBs in the treatment of hypertension?

ACEIs inhibit ACE, resulting in decreased levels of Ang II. ARBs block the AT_1 receptor, thereby preventing receptor activation by Ang II. Both medications therefore act by reducing the action of Ang II, resulting in vasodilation (by inhibition of both AT_1-mediated and sympathetic vasoconstriction) and reduction in sodium and fluid retention by the kidney.

d) What are the primary differences between ACEIs and ARBs? Is there a preference for the use of an ACEI vs. an ARB in Mr. R?

There are two primary differences between ACEIs and ARBs:

(1) ACEIs inhibit ACE, the enzyme that catalyzes the conversion of Ang I to Ang II. However, ACE also participates in other reactions, including the metabolism of kinins. Inhibition of ACE therefore leads to accumulation of kinins, leading to various effects. Kinins stimulate nitric oxide (NO)-mediated vasodilation and exhibit cardioprotective effects, both of which may contribute to the beneficial effects of ACEIs. In addition, accumulation of bradykinin can result in cough and/or angioedema that are not seen with ARB use.

(2) While ACEIs decrease the amount of circulating Ang II, ARBs inhibit Ang II action by blocking AT_1 receptors. They do not inhibit AT_2 receptors, which cause NO-mediated vasodilation and cardioprotective effects. However, recall that AT_2 receptors are primarily expressed in fetal tissue and are not widespread in adult tissue (however they are expressed at higher levels in patients with cardiovascular disease), and the effects of increased AT_2 stimulation in ARB use has not been proven beneficial.

There is no preference for one class over the other in this patient, as ACEIs and ARBs have demonstrated similar efficacy in the treatment of HTN and similarly low rates of serious adverse effects.

e) In addition to HTN, what are other indications for the use of ACEIs and ARBs?

ACEIs and ARBs are also used in the treatment of heart failure with reduced ejection fraction (HFrEF), myocardial infarction (MI), and chronic kidney disease (CKD) with proteinuria. Because there are presently more data supporting the efficacy of ACEIs in HFrEF and MI, an ACEI would be the agent of choice unless the patient cannot tolerate an ACEI (e.g., history of angioedema with ACEI).

f) Which of the following classes of medication are also used in the treatment of HTN? Which is a first-line agent?

i) Carbonic anhydrase inhibitors (CAIs)
ii) Loop diuretics (LDs)
iii) Thiazide diuretics (TZs)
iv) K^+-sparing diuretics
v) Osmotic diuretics
vi) Aquaretics
vii) Antidiuretics

Loop diuretics (ii), thiazide diuretics (iii), and K^+-sparing diuretics (iv) are used in the treatment of HTN. TZs are first-line antihypertensive agents. The use of these agents for the treatment of hypertension is covered in detail in the "Hypertension 2" module. (Note that loop diuretics are only used in the treatment of hypertension associated with volume overload.)

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Mr. R's physician prescribes the ARB losartan, which Mr. R begins taking as directed.

He returns for a follow-up appointment two weeks later, at which time he reports feeling well but that his blood pressure measured at home has not improved. In the office, his blood pressure is 155/100.

The physician reviews the results of Mr. R's screening labs with him. Notably, his creatinine at the first visit was 1.2, and a repeat creatinine today is 2.5.

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Mr. R's physician advises him to stop taking the losartan, and schedules a renal artery Doppler ultrasound, which shows bilateral *renal artery stenosis*. The physician calls Mr. R to inform him of his diagnosis of *renovascular hypertension*.

Renovascular hypertension is form of secondary hypertension (hypertension caused by some other problem). It accounts for a very small fraction (<1%) of patients with mildly elevated blood pressure, but is a more significant cause of severe or malignant hypertension. Renovascular disease can have a number of etiologies, one of which is atherosclerotic cardiovascular disease. Risk factors are therefore similar to other atherosclerotic disease, including age, smoking history, hypercholesterolemia, family history of cardiovascular disease, and other manifestations of atherosclerotic disease (e.g., angina pectoris, peripheral vascular disease). HTN due to renal artery stenosis is caused by increased activation of the RAAS – the stenosis causes a decrease in renal perfusion pressure, renal baroreceptors consequently trigger increased renin secretion, and increased Ang II results in systemic HTN.

g) Why can renal insufficiency occur in patients with renal artery stenosis with use of ACEIs and ARBs?

When a patient with renal artery stenosis is treated with an ACEI or ARB, two major mechanisms occur that contribute to an acute decompensation of renal function.

(1) Inhibition of Ang II action results in a decrease in systemic mean arterial pressure. When there is a significant stenosis of the renal artery, the drop in mean arterial pressure causes a significant decrease in the glomerular capillary hydraulic pressure and GFR.

(2) Under normal circumstances, an acute decrease in GFR results in a lower solute load sensed by the macula densa, renin secretion increases, and the Ang II-mediated increase in efferent > afferent renal arteriolar resistance leads to an increase in glomerular capillary hydraulic pressure and maintenance of GFR. When this regulatory mechanism is inhibited by ACEIs and ARBs, the kidney is unable to compensate for the decreased pressure, and the GFR falls.

Additionally, in renal artery stenosis the kidney RAAS is an important mechanism for maintaining GFR – due to the stenosis, glomerular capillary hydraulic pressure will be lower than normal, so the ability of the RAAS to increase efferent > afferent arteriolar resistance is extremely important. Inhibition of the RAAS by an ACEI or ARB in a patient with renal artery stenosis would therefore result in an acute decrease in GFR even if the systemic mean arterial pressure did not fall.

References:

https://www.uptodate.com/contents/renin-angiotensin-system-inhibition-in-the-treatment-of-hypertension

https://www.uptodate.com/contents/mechanism-of-action-of-diuretics

https://www.uptodate.com/contents/use-of-thiazide-diuretics-in-patients-with-primary-essential-hypertension

https://www.uptodate.com/contents/evaluation-of-secondary-hypertension

https://www.uptodate.com/contents/major-side-effects-of-angiotensin-converting-enzyme-inhibitors-and-angiotensin-ii-receptor-blockers

https://www.uptodate.com/contents/renal-effects-of-ace-inhibitors-in-hypertension

https://jasn.asnjournals.org/content/jnephrol/1/6/845.full.pdf

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CKD with proteinuria

Ms. L is a 56-year-old woman with a history of stage 3 chronic kidney disease (CKD) secondary to hypertension and type 2 diabetes who presents to her primary care physician for a follow-up appointment.

Ms. L reports feeling well since her last appointment and has no complaints today. Her most recent eGFR is 50 mL/min/1.73 m^2. She takes chlorthalidone for hypertension and metformin for diabetes.

Ms. L's complete physical exam today is unremarkable. Labs were obtained before her appointment, significant for eGFR 45 mL/min/1.73 m^2, and urine albumin:creatinine ratio 100 mg/g (moderately increased; normal <30).
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Chronic kidney disease (CKD) is a common condition, defined as kidney damage and/or impairment in kidney function that is present for at least three months. There are many causes of CKD; the most common etiologies in adults in the United States are diabetes mellitus (types 1 and 2) and hypertension. Staging of CKD is based on the GFR and presence/degree of proteinuria. Manifestations vary with the stage of disease and with disease etiology; patients are typically asymptomatic in early stages, and develop symptoms with disease progression. Signs and symptoms may include fatigue, nausea, vomiting, edema, hypertension, decreased urine output, anemia, and electrolyte derangements (e.g., hyperphosphatemia, hypocalcemia), among others. As the disease progresses, patients may develop end-stage renal disease (ESRD), requiring hemodialysis or renal transplant.
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Ms. L's physician explains that Ms. L has elevated protein in her urine, a sign of worsening kidney disease. She would like to prescribe a new medication in light of Ms. L's new proteinuria.

a) What class(es) of medication are used in the treatment of CKD with proteinuria? What is the mechanism of action for this indication?

Angiotensin converting enzyme inhibitors (ACEIs; e.g., ***enalapril***) and AT_1 receptor blockers (ARBs; e.g., ***losartan***) are used in the treatment of CKD with proteinuria. These agents inhibit the RAAS, which both reduces proteinuria and slows the progression of kidney damage.

By inhibiting the action of Ang II, ACEIs and ARBs cause a reduction in the glomerular capillary hydraulic pressure and decreased filtration fraction, reducing protein excretion into the tubular fluid. Studies suggest that Ang II antagonism also causes changes to the glomerular filtration barrier to improve selective permeability against proteins, independent of the reduction in glomerular capillary hydraulic pressure. Additionally, Ang II impairs reabsorption of protein from the tubular fluid in the proximal tubule; RAAS inhibition therefore improves protein reabsorption and reduces protein excretion in the urine.

In addition to improving proteinuria, ACEIs and ARBs are protective against progression of CKD. Their use prevents damage to glomeruli by reduction in glomerular capillary hydraulic pressure, and slows fibrosis of renal parenchyma. This renoprotective benefit of ACEIs and ARBs has been demonstrated in CKD with proteinuria regardless of etiology; however, no benefit has been demonstrated in CKD without proteinuria.

b) Ms. L is also taking chlorthalidone, a thiazide diuretic. What precautions should be taken regarding the addition of an ACEI or ARB?

Caution should be taken when prescribing an ACEI or ARB in a patient taking a diuretic due to the risk of precipitating renal insufficiency (i.e., the "double whammy"), particularly in patients with poor renal perfusion (e.g., renovascular disease), dehydration, elderly patients, or others at risk of renal insufficiency. In such patients with low renal perfusion pressure, the RAAS is particularly important to the maintenance of GFR, as it causes an increase in the glomerular capillary hydraulic pressure via Ang II-mediated increase in efferent > afferent arteriolar resistance. Diuretics cause a decrease in the effective circulating volume (ECV) and mean arterial pressure, further decreasing the renal perfusion pressure. Addition of an ACEI or ARB in these patients inhibits the RAAS-dependent maintenance of GFR, and renal function can acutely decline.

Similarly, the "triple whammy" (the combination of an ACEI or ARB with a diuretic and an NSAID) should be avoided in at-risk patients, as NSAIDs decrease the glomerular capillary perfusion pressure by inhibiting the synthesis of vasodilator prostaglandins, which dilate the afferent arteriole.

Ms. L is otherwise in good health and we have no reason to suspect poor renal perfusion, therefore prescription of an ACEI or ARB in addition to her chlorthalidone is not contraindicated.
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Ms. L's physician prescribes enalapril, an ACEI. Before her next follow-up appointment, she wishes to obtain labs to monitor electrolytes, creatinine, and proteinuria.

c) What electrolyte derangement is possible with use of an ACEI or ARB? Why does this occur?

Hyperkalemia (elevated serum potassium concentration) is a possible adverse effect of ACEIs and ARBs. This effect is typically most significant in patients with underlying renal insufficiency, diabetes, or with concurrent use of other medications that can cause hyperkalemia.

The RAAS affects serum K^+ concentration via the action of aldosterone. Under normal conditions, aldosterone mediates secretion of K^+ from the blood into the urine. Aldosterone binds to its receptors in the principal cells of the connecting tubule (CNT) and collecting duct (CD), leading to increased expression of several membrane proteins. Increased expression of Na^+-K^+ ATPase, ROMK, and BK channels results directly in increased K^+ secretion into the tubular lumen. Additionally, increased expression of ENaC results in increased Na^+ reabsorption in the CNT and CD, generating a greater negative potential between the tubular lumen and the principal cells, and driving further K^+ secretion into the tubular lumen via ROMK and BK channels.

ACEIs and ARBs inhibit the action of Ang II, causing a decrease in aldosterone secretion by the adrenal cortex. Decreased circulating aldosterone can result in hyperkalemia by decreasing K^+ excretion by the kidneys by the above mechanisms.

d) What are the other primary adverse effects of ACEIs and ARBs?

In addition to hyperkalemia, adverse effects of both ACEIs and ARBs include hypotension (especially in patients with elevated serum renin levels at baseline) and decreased kidney function in patients with poor renal perfusion. ACEIs can also cause cough and, rarely, angioedema due to elevated levels of bradykinin. Both ACEIs and ARBs are teratogenic, and are therefore contraindicated in pregnancy.

e) What must be considered regarding the use of chlorthalidone in CKD?

All diuretics, including thiazide diuretics, become less effective as GFR declines. Diuretics must be secreted into the tubular lumen by organic acid transporters in the proximal tubule, such that they can bind to transporters on the apical surface of tubular epithelial cells and exert their effects. In CKD (especially with GFR <30 mL/min/1.73 m^2), increased levels of organic acids in the serum compete for secretion by organic acid transporters into the tubular lumen, resulting in decreased delivery of drug to the site of action and decreased efficacy.

In addition, volume retention often plays an important role in hypertension associated with CKD. Thiazide diuretics are less powerful at modulating volume than loop diuretics, therefore in a patient with CKD in whom volume overload is a contributing factor, a loop diuretic would be the preferred option.

References:
https://www.uptodate.com/contents/definition-and-staging-of-chronic-kidney-disease-in-adults

https://www.uptodate.com/contents/epidemiology-of-chronic-kidney-disease

https://www.uptodate.com/contents/diagnostic-approach-to-the-patient-with-newly-identified-chronic-kidney-disease

https://www.uptodate.com/contents/secondary-factors-and-progression-of-chronic-kidney-disease

https://www.uptodate.com/contents/antihypertensive-therapy-and-progression-of-nondiabetic-chronic-kidney-disease-in-adults

https://www.uptodate.com/contents/major-side-effects-of-angiotensin-converting-enzyme-inhibitors-and-angiotensin-ii-receptor-blockers

https://www.uptodate.com/contents/thiazides-versus-loop-diuretics-in-the-treatment-of-hypertension

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Acute mountain sickness

Ms. W is a 25-year-old female who presents to her primary care physician for a travel consult. She is planning a trip soon to climb Mount Kilimanjaro, a volcano in Tanzania with an elevation of 19,000 ft. She has never climbed at such elevations before, but heard from a friend who recently summited Denali (elevation 20,000 ft) that at high elevations you can start to develop symptoms such as headaches, lightheadedness, and confusion, and is wondering if there is a medication that she can bring with her to prevent these high altitude problems.

Ms. W's physician explains that the symptoms she is describing are due to *acute mountain sickness*, and that there is a prophylactic medication she can take.
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Acute mountain sickness (AMS) is a constellation of symptoms that occur when a person who is not acclimatized to high elevations ascends to high elevation at a rapid rate (typically at elevations greater than 6500 ft and at a rate greater than 2000 ft elevation gain per day). Any individual who is ascending is susceptible to developing AMS regardless of factors such as age or physical fitness; however, obesity, intense physical exertion at altitude, and living at lower elevations increase risk. Symptoms typically manifest 6-12 hours after reaching altitude, and may include headache, lightheadedness, nausea, vomiting, fatigue, and sleep disturbances. If very severe, AMS can progress to *high altitude cerebral*

edema (*HACE*), which manifests as ataxia (gait instability) and progressive decline in mental status. The pathophysiology of AMS is not fully understood, but is believed to arise from consequences of hypoxemia at high altitude, such as increased vascular permeability. Recall that chemoreceptors sense the fall in P_{O2} and trigger an increase minute ventilation. However, hyperventilation results in respiratory alkalosis, and the fall in P_{CO2} attenuates the increase in minute ventilation (chemoreceptors respond more strongly to P_{CO2} than P_{O2}). The body is therefore limited in its ability to correct the hypoxemia by hyperventilation, and the symptoms of AMS develop.

a) What medication is used in the prophylactic treatment of AMS? To what class of medications does this drug belong?

The diuretic ***acetazolamide***, a carbonic anhydrase inhibitor (CAI), is used for AMS prophylaxis.

b) What is the mechanism of action of CAIs in the kidney? How does this help prevent AMS?

CAIs inhibit carbonic anhydrase (CA) located in the cytosol and brush border of tubular epithelial cells of the proximal tubule. Under normal conditions, CA catalyzes the conversion of $CO_2 + H_2O \Leftrightarrow H_2CO_3$; H_2CO_3 then spontaneously dissociates to $H^+ + HCO_3^-$. (In epithelial cells, the forward direction is important; in the lumen of the proximal tubule, the reverse direction is important.) H^+ is secreted into the tubular fluid via the Na^+/H^+ exchanger (NHE), driving the reabsorption on Na^+ from the tubular fluid. CA inhibition results in decreased H^+ secretion and therefore decreased Na^+ reabsorption. In addition, H^+ secretion is necessary for reabsorption of HCO_3^- in the proximal tubule. Decreasing HCO_3^- reabsorption in the early proximal tubule attenuates the increase in tubular fluid Cl^- concentration that normally occurs by the mid-proximal tubule, thereby decreasing the driving force for paracellular Cl^- reabsorption in the mid-to-late proximal tubule. The resulting decrease in paracellular Cl^- reabsorption, in turn, attenuates the development of a small lumen-positive transepithelial potential difference in the mid-to-late proximal tubule, which in turn decreases the paracellular reabsorption of Na^+ in the mid-to-late proximal tubule, further contributing to the natriuresis.

By inhibiting HCO_3^- reabsorption, CAIs produce a metabolic acidosis. Among other mechanisms, it is believed that this metabolic acidosis counters the respiratory alkalosis resulting from hyperventilation, allowing further chemoreceptor-mediated increase in minute ventilation and improvement in hypoxemia.

c) Which of the following are also indications for the use of CAIs? How does it function in the treatment of these problems?

i) Hypertension
ii) Idiopathic intracranial hypertension
iii) Glaucoma
iv) Nephrolithiasis
v) Cerebral edema

CAIs are used in the treatment of idiopathic intracranial hypertension (ii) and glaucoma (iii).

Idiopathic intracranial hypertension is a disease characterized by elevated intracranial pressure with no identifiable cause (such as an intracranial mass). Treatment is targeted at reducing the rate of production of cerebrospinal fluid (CSF) in order to lower intracranial pressure. Carbonic anhydrase is an important enzyme involved in the production of CSF. Inhibition of carbonic anhydrase by CAIs therefore acts to slow CSF production and relieve the elevated intracranial pressure.

Glaucoma is a disease characterized by elevated intraocular pressure, leading to neuropathy of the optic nerve. Treatment is targeted at reducing the rate of production of aqueous humor or enhancing the rate of

drainage of aqueous humor from the eye in order to lower intraocular pressure. Carbonic anhydrase is involved in the production of aqueous humor, therefore inhibition by CAIs reduces the rate of aqueous humor production.

d) What are the primary adverse effects of CAIs?

The primary adverse effects of CAIs include metabolic acidosis, hypokalemia, and nephrolithiasis (calcium phosphate-containing renal stones).

e) What are the mechanisms of hypokalemia and nephrolithiasis with CAI use?

Hypokalemia: CAIs inhibit Na^+ reabsorption in the proximal tubule, resulting in increased Na^+ delivery to the connecting tubule and collecting duct. This drives increased Na^+ reabsorption via ENaC, increasing the lumen-negative transepithelial potential difference and thereby creating a more favorable electrochemical gradient of K^+ secretion via the ROMK and BK potassium channels. This is the same mechanism by which loop diuretics and thiazide diuretics produce hypokalemia.

Nephrolithiasis: Inhibition of HCO_3^- in the proximal tubule results in a more alkaline tubular fluid. Calcium phosphate has decreased solubility at high pH, and can precipitate to form stones in the alkaline condition resulting from CAI use.

References:
https://www.uptodate.com/contents/acute-mountain-sickness-and-high-altitude-cerebral-edema

https://www.physiology.org/doi/full/10.1152/japplphysiol.01572.2005?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed

https://www.uptodate.com/contents/idiopathic-intracranial-hypertension-pseudotumor-cerebri-prognosis-and-treatment

https://www.uptodate.com/contents/open-angle-glaucoma-treatment

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Hypertension 2

Ms. H is a 36-year-old female who presents to her primary care physician for follow-up of primary hypertension.

Ms. H has had mildly elevated blood pressures (~130s/80s) at home for the last several years, and was diagnosed with primary hypertension by her physician one year ago. She has tried lifestyle modifications such as low-salt diet and exercise, but has not experienced significant reduction in her blood pressure. In fact, for the last several months her home readings have averaged in the low 140s/90s. She feels that the lifestyle changes have not been working for her and it is now a good time to discuss medical management.
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Primary (or *essential*) *hypertension* (*HTN*) is defined as elevated blood pressure (≥130/80) that is not the result of another disease process. The pathogenesis of primary HTN is poorly understood, and is believed to be the result of various genetic and environmental factors. Risk factors for primary hypertension include age, obesity, family history, heavy alcohol consumption, high-salt diet, sedentary lifestyle, and

African American ethnicity. Hypertension is a risk factor for a variety of other conditions, including left ventricular hypertrophy (LVH), heart failure, stroke (ischemic vs. hemorrhagic), coronary artery disease (e.g., myocardial infarction), and chronic kidney disease. HTN is typically asymptomatic, therefore screening by blood pressure monitoring during routine office visits is important to establish a diagnosis and initiate treatment. Treatment of primary HTN involves lifestyle modification (e.g., low-salt diet, exercise, weight loss, limiting alcohol intake) in all patients, and possibly pharmacotherapy.
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Ms. H's physician agrees that this is an appropriate time to start an antihypertensive medication.

a) Which of the following classes of medications affecting the renal system are used in the treatment of HTN? Give an example of each. Which are first-line agents?

i) Carbonic anhydrase inhibitors (CAIs)
ii) Loop diuretics (LDs)
iii) Thiazide diuretics (TZs)
iv) K^+-sparing diuretics
v) Osmotic diuretics
vi) Aquaretics
vii) Antidiuretics
viii) ACE inhibitors (ACEIs)
ix) AT_1 receptor blockers (ARBs)

Loop diuretics (ii; e.g., ***furosemide***, ***bumetanide***), thiazide diuretics (iii; e.g., ***hydrochlorothiazide***, ***chlorthalidone***), K^+-sparing diuretics (iv; e.g., ***amiloride***, ***triamterene***, ***spironolactone***), ACEIs (viii; e.g., ***enalapril***), and ARBs (ix; e.g., ***losartan***) are used in the treatment of HTN. TZs, ACEIs, and ARBs are first-line agents.

Note that loop diuretics are only effective in the treatment of primary hypertension if there is associated volume overload.

b) Ms. H mentions that she and her husband are considering having a child. Are any of the aforementioned medications contraindicated in pregnancy?

ACEIs and ARBs are contraindicated in pregnancy because they are associated with significant fetal renal abnormalities. Additionally, there is concern regarding the use of aldosterone antagonists (e.g., spironolactone) during pregnancy due to possible interference with androgen-dependent developmental processes, especially in male fetuses; these medications have never been proven safe in pregnancy.

c) What is the mechanism of action of the diuretics (LDs, TZs, and K^+-sparing diuretics) in the treatment of HTN?

Each of these classes of medications induce natriuresis (excretion of Na^+ & counterion) through inhibition of specific ion transporters on the apical surface of tubular epithelium: LDs inhibit the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) in the thick ascending limb, TZs inhibit the Na^+-Cl^- cotransporter (NCC) in the distal convoluted tubule, and K^+-sparing diuretics inhibit the epithelial Na^+ channel (ENaC) in the connecting tubule and collecting duct (direct inhibition by amiloride, triamterene; indirect inhibition via mineralocorticoid receptor antagonism by spironolactone, eplerenone). This natriuresis results in a greater solute concentration in the tubular fluid; consequently, less water is reabsorbed, and the effective circulating volume (ECV) decreases. The decrease in ECV results in a decrease in cardiac output and, consequently, mean arterial pressure (especially initially). Other poorly understood mechanisms likely contribute as well, especially once steady-state is reached (recall that the total decrease in ECV is limited due to diuretic braking), such as the decrease in SVR observed with the use of TZs.

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Ms. H's physician prescribes chlorthalidone, a TZ.

d) What are other indications for use of TZs?

TZs are also used in the treatment of edema (although they are much less efficacious than the loop diuretics), nephrolithiasis with Ca^{2+}-containing (calcium phosphate, calcium oxalate) stones due to idiopathic hypercalciuria, and nephrogenic diabetes insipidus. The mechanism for use in nephrogenic diabetes insipidus is covered in the "Diabetes Insipidus" module.

e) What effect do TZs have on each of the following serum values? Why?

i) Sodium
ii) Potassium
iii) Calcium
iv) Magnesium
v) Uric acid
vi) pH

i) Sodium: Hyponatremia. TZs result in loss of Na^+ and water via natriuresis and diuresis, respectively. The decrease in effective circulating volume (ECV) triggers the thirst center in the brain, signaling to the patient to drink more water. Replacement of the lost water, but not the lost Na^+, results in hyponatremia.

ii) Potassium: Hypokalemia. TZs inhibit Na^+ reabsorption in the distal convoluted tubule, resulting in increased Na^+ delivery to the connecting tubule and collecting duct. This drives increased Na^+ reabsorption via ENaC, increasing the lumen-negative transepithelial potential difference and thereby creating a more favorable electrochemical gradient of K^+ secretion via the ROMK and BK potassium channels. This is the same mechanism by which CAIs and LDs produce hypokalemia.

iii) Calcium: Hypercalcemia. There are two mechanisms by which TZs produce hypercalcemia. The volume depletion created by diuresis causes an increase in Na^+ reabsorption in the proximal tubule, increasing the electrochemical gradient for Ca^{2+} reabsorption via passive paracellular transport.. [See Regulation of Calcium, Magnesium, and Phosphate Excretion lecture for detail on calcium handling in the DCT.] This effect is the mechanism by which TZs can be used to treat nephrolithiasis, as decreased [Ca^{2+}] in the tubular fluid reduces the formation of Ca^{2+}-containing renal stones.

iv) Magnesium: Hypomagnesemia. TZs cause decreased transcellular reabsorption of Mg^{2+} in the distal convoluted tubule by causing downregulation of the apical Mg^{2+} transporter TRPM6. There is also evidence that the hypokalemia associated with TZ use may inhibit Mg^{2+} uptake in the distal nephron.

v) Uric acid: Hyperuricemia. TZs produce hyperuricemia via direct and indirect mechanisms. Urate is reabsorbed in the proximal tubule by several apical transporters including OAT4, which exchanges urate in the tubular fluid for organic anions in the proximal tubular epithelial cells. TZs function as organic anions and are secreted by OAT4, driving the reabsorption of urate. TZs similarly compete with urate for secretion into the tubular fluid by other transporters. In addition, urate reabsorption in the proximal tubule trends with reabsorption of Na^+. In response to the hypovolemia resulting from TZ use, increased sympathetic output and Ang II mediate an increase in Na^+/H^+ exchanger expression in the proximal tubule, increasing Na^+ reabsorption and in turn driving increased urate reabsorption. These are the same mechanisms by which LDs lead to hyperuricemia.

vi) pH: Metabolic alkalosis. TZs inhibit Na^+ reabsorption in the distal convoluted tubule, resulting in increased Na^+ delivery to the connecting tubule and collecting duct. This drives increased Na^+

reabsorption via ENaC, increasing the electrochemical gradient for H^+ secretion (and generation of new HCO_3^-) by Type A intercalated cells. This is the same mechanism by which LDs produce metabolic alkalosis.

f) Which of the following are additional adverse effects of TZs?

i) Postural hypotension
ii) Hyperlipidemia
iii) Gynecomastia (growth of breast tissue)
iv) Ototoxicity
v) Hyperglycemia

Postural hypotension (i) secondary to hypovolemia, hyperlipidemia (ii), and hyperglycemia (v) are also adverse effects of TZs.

Gynecomastia (iii) is a possible adverse effect of aldosterone antagonists such as spironolactone. Ototoxicity (iv) is a possible adverse effect of LDs.

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One year later, Ms. H has been taking chlorthalidone as directed and her blood pressure has improved somewhat but is still not at goal. Her physician would like to add amiloride, a K^+-sparing diuretic.

g) What are the indications for use of K^+-sparing diuretics?

In addition to HTN, K^+-sparing diuretics are used in the treatment of edema and hyperaldosteronism (primary or secondary). In addition, the aldosterone antagonists (spironolactone, eplerenone) are used in heart failure with reduced ejection fraction (HFrEF) and following myocardial infarction in patients with low ejection fraction and heart failure or diabetes.

h) What effect do K^+-sparing diuretics have on each of the following serum values? Why?

i) Sodium
ii) Potassium
iii) Calcium
iv) Magnesium
v) Uric acid
vi) pH

i) Sodium: No significant change.

ii) Potassium: Hyperkalemia. Under normal conditions, Na^+ reabsorption via ENaC in the connecting tubule and collecting duct creates a lumen-negative transepithelial potential, thereby increasing the electrochemical gradient for K^+ secretion into the tubular fluid via the ROMK and BK potassium channels. Inhibition of ENaC diminishes this electrochemical gradient and decreases K^+ secretion. Hyperkalemia with the use of K^+-sparing diuretics is primary seen in patients with other risk factors for hyperkalemia, such as those with renal insufficiency or taking other medications that predispose to hyperkalemia.

iii) Calcium: No significant change.

iv) Magnesium: No significant change.

v) Uric acid: No significant change.

vi) pH: Metabolic acidosis. Under normal conditions, Na^+ reabsorption via ENaC in the connecting tubule and collecting duct creates an electrochemical gradient that drives H^+ secretion (and generation of new HCO_3^-) by Type A intercalated cells. Inhibition of ENaC diminishes this electrochemical gradient and decreases H^+ secretion. (Note that metabolic acidosis produced by K^+-sparing diuretics is not generally problematic.)

i) What are the other primary adverse effects of K^+-sparing diuretics?

Spironolactone can produce endocrine side effects due to various interactions with testosterone and cross-reactivity with androgen receptors (aldosterone and androgens are steroid hormones that are similar in structure). These side effects can include gynecomastia (breast tissue growth in males) and sexual dysfunction. (Eplerenone, which has greater specificity for the mineralocorticoid receptor, is not associated with endocrine side effects.) Note that the ENaC blockers (amiloride, triamterene) do not produce these endocrine side effects.

j) Why are K^+-sparing diuretics often used in combination with TZs or LDs?

The addition of a K^+-sparing diuretic to a TZ or LD increases natriuretic efficacy by inhibiting Na^+ reabsorption in the connecting tubule and collecting duct (recall that Na^+ reabsorption in these segments increases in a load-dependent manner with TZ and LD use). Addition of a K^+-sparing diuretic also attenuates the hypokalemia and metabolic alkalosis that can result from TZ and LD use. In practice, this is more commonly used to ameliorate the hypokalemia associated with LD use, as the potassium loss associated with TZ use is less severe and can usually be managed with oral potassium supplementation.

K^+-sparing diuretics are used as monotherapy most often in the case of HTN due to primary or secondary hyperaldosteronism. Because HTN in these cases is driven entirely or in part by elevated serum aldosterone, blockade of the mineralocorticoid receptor (by spironolactone, eplerenone) or inhibition of the downstream effects of aldosterone (by amiloride, triamterene) are very effective pharmacologic strategies to normalize the blood pressure.

References:

https://www.uptodate.com/contents/overview-of-hypertension-in-adults

https://www.uptodate.com/contents/mechanism-of-action-of-diuretics

https://www.uptodate.com/contents/use-of-thiazide-diuretics-in-patients-with-primary-essential-hypertension

https://www.uptodate.com/contents/management-of-hypertension-in-pregnant-and-postpartum-women

https://www.uptodate.com/contents/diuretics-and-calcium-balance

https://www.uptodate.com/contents/effect-of-diuretics-on-magnesium-handling-by-the-kidney

https://www.uptodate.com/contents/diuretic-induced-hyperuricemia-and-gout

https://www.uptodate.com/contents/epidemiology-pathophysiology-and-causes-of-gynecomastia

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Edema: HFrEF

Mr. T is a 68-year-old man with a history of heart failure with reduced ejection fraction (HFrEF) secondary to ischemic heart disease who presents to the emergency department with a chief complaint of "difficulty breathing."

Mr. T has been prescribed medications for his heart failure, but ran out about 2 weeks ago. Starting about five days ago, Mr. T developed shortness of breath while lying down (*orthopnea*) that progressed to the point of needing to use three pillows to sleep comfortably. He has noticed progressive shortness of breath with walking in the last several days, and today he has felt slightly short of breath at rest as well. He has felt increasingly tired and has had little appetite during this time period, and he has noticed swelling of both legs over the last several days that started in his ankles and has progressed to the level of his knees.

Mr. T's vital signs in the ED are as follows: T 37.0ºC (98.6ºF), BP 130/80, HR 84, RR 19, SpO2 92% on room air. On physical exam, he appears uncomfortable and speaks in short sentences. His point of maximal impact is laterally displaced. On cardiac auscultation, an S_3 is present and a grade 3/6 holosystolic murmur is heard at the apex with radiation to the axilla. Estimated jugular venous pressure is 14 cm H_2O. There are crackles auscultated bilaterally at the lung bases. There is pitting edema of the feet and lower legs bilaterally to the knees.

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Mr. T's physician in the emergency department orders an ECG, chest x-ray, echocardiogram, and labs.

The ECG is significant for Q waves in the lateral leads (I, aVL, V5, V6), consistent with a past myocardial infarction. The chest x-ray is significant for an enlarged cardiac silhouette and moderate pulmonary edema. The echocardiogram shows dilation of the left atrium and ventricle, moderate mitral regurgitation, and left ventricular ejection fraction of 30% (normal 50-70%).

Labs are significant for markedly elevated serum brain natriuretic peptide (BNP; indicating stretching of the ventricles).

Based on the history, physical exam, and test results, Mr. T's physician diagnoses him with *acute decompensated heart failure* and he is admitted to the hospital.

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Heart failure is the inability of the heart to provide adequate perfusion to the body at normal ventricular filling pressures. In heart failure with reduced ejection fraction (HFrEF), this is due to inability of the heart to pump adequately in systole, and by definition echocardiogram will show left ventricular ejection fraction of ≤40%. There are many possible etiologies of HFrEF, including ischemic heart disease, valvular disease, and hypertension. Patients with chronic HFrEF may experience periods of worsening symptoms (*decompensation*), during which they may complain of increased fatigue, dyspnea/orthopnea (due to pulmonary edema), soft tissue edema, and weight gain – this is called *acute decompensated heart failure* (ADHF, commonly referred to as *heart failure exacerbation*), and may be precipitated by factors such as worsening heart function, dietary changes (e.g., large sodium load leading to fluid retention), or medication nonadherence. The symptoms in ADHF are largely due to fluid overload and the resulting edema in various tissues.

a) What classes of medication are used in the treatment of edematous states such as acute decompensated heart failure? Give an example of each.

Loop diuretics (LDs; e.g., ***furosemide***, ***bumetanide***), thiazide diuretics (TZs; e.g., ***hydrochlorothiazide***, ***chlorthalidone***), and K^+-sparing diuretics (e.g., ***amiloride***, ***triamterene***, ***spironolactone***) are used in the treatment of edematous states such as heart failure and hepatic cirrhosis.

b) What is the mechanism of action these medications in the treatment of edematous states? Which class is most efficacious for this indication and why?

LDs, TZs, and K^+-sparing diuretics all treat edematous states by producing a diuresis, and therefore facilitating the removal of excess fluid from the body. The diuresis produced by each of these medications is secondary to natriuresis, the excretion of Na^+ in the urine. LDs inhibit the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) in the thick ascending limb, TZs inhibit the Na^+-Cl^- cotransporter (NCC) in the distal convoluted tubule, and K^+-sparing diuretics inhibit the epithelial Na^+ channel (ENaC) in the connecting tubule and collecting duct. Natriuresis results in a greater solute concentration in the tubular fluid, and consequently less water is reabsorbed.

LDs are the most efficacious for acute management of edematous states because they produce the greatest degree of natriuresis – up to a 25% initial decrease in Na^+ reabsorption. LDs (termed "high ceiling" diuretics for this reason) can therefore facilitate the rapid diuresis of large quantities of fluid. TZs and K^+-sparing diuretics are much less efficacious than LDs in the treatment of edema.
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The hospital team begins Mr. T on furosemide. They plan to closely monitor his urine output to quantify the diuresis, and monitor changes in his physical exam (lower extremity edema, cardiopulmonary exam) for response to therapy.

c) What are other indications for the use of LDs?

LDs are also indicated for the treatment of HTN (if associated with volume overload), acute hypercalcemia, and idiopathic intracranial HTN.

d) What effect do LDs have on each of the following serum values? Why?

i) Sodium
ii) Potassium
iii) Calcium
iv) Magnesium
v) Uric acid
vi) pH

i) Sodium: Hyponatremia. LDs result in loss of Na^+ and water via natriuresis and diuresis, respectively. The decrease in effective circulating volume (ECV) triggers the thirst center in the brain, signaling to the patient to drink more water. Replacement of the lost water, but not the lost Na^+, results in hyponatremia. Note that the hyponatremia resulting from LD use is less significant than that resulting from TZ use because LDs abolish the renal medullary gradient, so the kidney is unable to concentrate the urine and retain excess water in response to the decrease in ECV.

ii) Potassium: Hypokalemia. LDs inhibit Na^+ reabsorption in the thick ascending loop, resulting in increased Na^+ delivery to the connecting tubule and collecting duct. This drives increased Na^+ reabsorption via ENaC, increasing the electrochemical gradient for K^+ and resulting in increased K^+ secretion via ROMK. This is the same mechanism by which CAIs and TZs produce hypokalemia.

iii) Calcium: Hypocalcemia; iv) Magnesium: Hypomagnesemia. Under normal conditions, NKCC in the thick ascending loop transports Na^+, K^+, and Cl^- from the tubular fluid into tubular epithelial cells; much of the reabsorbed K^+ then leaks back into the tubular fluid via ROMK and Cl^- is transported out of the cells into the blood, creating a lumen-positive transepithelial potential, which in turn drives the paracellular reabsorption of cations, including Ca^{2+} and Mg^{2+}. By inhibiting NKCC, LDs diminish this

electrochemical gradient and decrease Ca^{2+} and Mg^{2+} reabsorption. [See Regulation of Calcium, Magnesium, and Phosphate Excretion lecture for detail on calcium and magnesium handling in the thick AL.] This effect is the mechanism by which LDs can be used to treat acute hypercalcemia.

v) Uric acid: Hyperuricemia. LDs produce hyperuricemia via direct and indirect mechanisms. Urate is reabsorbed in the proximal tubule by several apical transporters including OAT4, which exchanges urate in the tubular fluid for organic anions in the proximal tubular epithelial cells. LDs function as organic anions and are secreted by OAT4, driving the reabsorption of urate. LDs similarly compete with urate for secretion into the tubular fluid by other transporters. In addition, urate reabsorption in the proximal tubule trends with reabsorption of Na^+. In response to the hypovolemia resulting from LD use, increased sympathetic output and Ang II mediate an increase in Na^+/H^+ exchanger expression in the proximal tubule, increasing Na^+ reabsorption and in turn driving increased urate reabsorption. These are the same mechanisms by which TZs lead to hyperuricemia. Notably, this production of hyperuricemia can lead to the precipitation of gout.

vi) pH: Metabolic alkalosis. LDs inhibit Na^+ reabsorption in the thick ascending limb, resulting in increased Na^+ delivery to the connecting tubule and collecting duct. This drives increased Na^+ reabsorption via ENaC, increasing the electrochemical gradient for H^+ secretion (and generation of new HCO_3^-) by Type A intercalated cells. This is the same mechanism by which TZs produce metabolic alkalosis.

e) Which of the following are other adverse effects of LDs?

i) Postural hypotension
ii) Hyperlipidemia
iii) Gynecomastia (growth of breast tissue)
iv) Ototoxicity
v) Hyperglycemia

Postural hypotension (i) secondary to hypovolemia, hyperlipidemia (ii), ototoxicity (iv), and hyperglycemia (v) are also adverse effects of LDs. Note that the hyperlipidemia and hyperglycemia with LDs is typically less severe than that resulting from TZ use.

Gynecomastia (iii) is a possible adverse effect of aldosterone antagonists such as spironolactone.

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Mr. T has an excellent response to treatment with furosemide; over 48 hours his shortness of breath, jugular venous distension, and leg edema gradually improve. As the team is preparing to discharge Mr. T from the hospital, they discuss what medications he should be taking at home.

f) Which of the following classes of medications are associated with improved survival in patients with HFrEF? Why?

i) ACE inhibitors (ACEIs)
ii) AT_1 receptor blockers (ARBs)
iii) Osmotic diuretics
iv) Antidiuretics
v) Aldosterone antagonists
vi) α antagonists
vii) β antagonists
viii) Cardiac glycosides (e.g., digoxin)

ACEIs (i), ARBs (ii), aldosterone antagonists (v), and β antagonists (vii) are associated with improved survival in patients with HFrEF.

ACEIs (e.g., ***enalapril***) and ARBs (e.g., ***losartan***) are associated with reduced symptoms, decreased rate of hospitalization, and improved survival in HFrEF. ACEIs and ARBs cause vasodilation, reducing preload and afterload on the heart. In addition, they combat deleterious cardiac hypertrophy and remodeling in heart failure caused by locally produced Ang II. Other mechanisms also likely contribute to the beneficial effects of these medications, such as reduction in sympathetic tone and cardioprotection by increased kinins (ACEIs only). (More outcomes data are available for ACEIs than ARBs in the treatment of HFrEF and after myocardial infarction, therefore ACEIs are used unless the patient cannot tolerate ACEI therapy.) These are the same mechanisms by which ACEIs and ARBs benefit patients following myocardial infarction.

Aldosterone antagonists (e.g., ***spironolactone***, eplerenone) are also associated with reduced symptoms and improved survival in HFrEF. Aldosterone antagonists cause diuresis and blood pressure reduction, resulting in decreased preload and afterload on the heart. Additionally, in HFrEF there is upregulation of local production of aldosterone, which is implicated in the detrimental cardiac remodeling and development of arrhythmias; blockade of mineralocorticoid receptors combats these effects. Finally, there is evidence that aldosterone antagonists prevent harmful arrhythmias by preventing hypokalemia. These are the same mechanisms by which aldosterone antagonists benefit patients following myocardial infarction.

The β antagonists carvedilol, metoprolol, and bisoprolol are associated with improved outcomes in HFrEF. The improved survival in patients treated with β antagonists appears to be due to the blockade of several detrimental effects of excess catecholamines on the heart. Recall from Cardiovascular System 1, predictable effects of β_1 receptor blockade on the heart include decreased heart rate and decreased myocardial oxygen demand (by decreased heart rate and inotropic state). Other proposed effects include altered gene expression, restoration of myocardial β receptor responsiveness, suppression of harmful myocardial remodeling, reduction of circulating vasoconstrictors, and reduced risk of potentially fatal ventricular arrhythmias.

References:

https://www.uptodate.com/contents/approach-to-acute-decompensated-heart-failure-in-adults

https://www.uptodate.com/contents/treatment-of-acute-decompensated-heart-failure-components-of-therapy

https://www.uptodate.com/contents/pharmacologic-therapy-of-heart-failure-with-reduced-ejection-fraction

https://www.uptodate.com/contents/use-of-diuretics-in-patients-with-heart-failure

https://www.uptodate.com/contents/mechanism-of-action-of-diuretics

https://www.uptodate.com/contents/diuretics-and-calcium-balance

https://www.uptodate.com/contents/effect-of-diuretics-on-magnesium-handling-by-the-kidney

https://www.uptodate.com/contents/diuretic-induced-hyperuricemia-and-gout

https://www.uptodate.com/contents/use-of-angiotensin-converting-enzyme-inhibitors-in-heart-failure-with-reduced-ejection-fraction

https://www.uptodate.com/contents/use-of-mineralocorticoid-receptor-antagonists-in-heart-failure-with-reduced-ejection-fraction

https://www.uptodate.com/contents/use-of-beta-blockers-in-heart-failure-with-reduced-ejection-fraction

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Cerebral edema

Mr. A is a 72-year-old man who arrives to the emergency department via ambulance after being found down in his home.

Mr. A is accompanied by paramedics and his wife, who provide the history. Mr. A was in his usual state of health until 10:00 am this morning, when his wife found him minimally responsive on the floor of the kitchen. His wife called 911, and an ambulance arrived to transport him to the hospital. In the field, Mr. A was minimally responsive to verbal stimulus and responsive to pain. His vital signs were stable during transport to the hospital.

Mr. A has a past medical history of hypertension, hypercholesterolemia, myocardial infarction, and heart failure with reduced ejection fraction (HFrEF). His medications include enalapril, metoprolol (a beta blocker), lovastatin (a cholesterol-lowering agent), and a baby aspirin.

Mr. A's vital signs in the ED are as follows: T 37.4ºC (99.3ºF), BP 170/95, HR 55, RR 8, SpO2 97% on room air. He opens his eyes briefly to verbal stimulus but cannot answer questions or follow complex commands. His pupils are equal, round, and reactive to light. He responds to pain stimulus on the left side but not the right. He appears to have facial droop on the right side, and is hyporeflexic in the right upper and lower extremities. There are no signs of injury resulting from the fall.
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A stroke code is initiated. A CT scan of the brain is performed, which shows evidence of ischemic stroke in the territory of the left middle cerebral artery. There is evidence of cerebral edema secondary to the stroke, with left-to-right midline shift (indicating swelling within the left hemisphere of the brain). Tissue plasminogen activator (tPA; a thrombolytic given to promote blood clot breakdown and restore blood flow) is given and Mr. A is transferred to the neurologic ICU for further management. The team discusses the evidence of cerebral edema on CT, and how to address it.
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Intracranial pressure (ICP) is very tightly regulated under normal conditions. The three major intracranial components include brain parenchyma, cerebrospinal fluid, and blood; because the skull is a fixed volume, a small increase in the volume of any given component can lead to a large increase in the ICP. There are many possible etiologies of increased ICP; one important etiology is *cerebral edema*. Cerebral edema is *intracellular* edema, and is caused by conditions such as ischemic insult to the brain parenchyma (i.e., ischemic stroke) or traumatic brain injury. Increased ICP can have devastating consequences, including damage to structures in the brain, coma, and death. It is therefore important to promptly identify increased ICP, determine the underlying cause, and initiate treatment to lower the pressure. You will learn much more about ICP and the consequences of elevated ICP during the Mind, Brain, and Behavior courses.

a) What medication affecting the renal system is used in the treatment of cerebral edema? To what class of medications does it belong?

Mannitol, an osmotic diuretic, is used in the treatment of cerebral edema.

b) What is the mechanism of action of mannitol in the treatment of cerebral edema?

Mannitol is a sugar alcohol that is unable to enter cells. It is given by intravenous infusion, and, since it is unable to enter cells, it increases the osmolality of the extracellular fluid and draws water out of cells. This fluid shift decreases the volume occupied by brain tissue, relieving the increased intracranial pressure.

c) What are other indications for the use of mannitol?

Mannitol is used in the treatment of other conditions requiring shift of fluid from the intracellular to the extracellular compartment, such as in acute angle-closure glaucoma (draw fluid from posterior chamber to decrease pressure in the eye), as well as to rapidly induce large natriuresis and diuresis, such as to promote the urinary excretion of toxic substances after an ingestion.

d) What is the mechanism of action of mannitol in the induction of natriuresis and diuresis?

Mannitol is freely filtered by the glomerulus into the tubular fluid, and is not able to be reabsorbed. It acts as an osmotic agent, raising the total solute concentration of the tubular fluid. Since passive water reabsorption is driven by the osmotic gradient, the increased solute concentration in the tubular fluid decreases total water reabsorption, causing diuresis. In addition, the decreased water reabsorption decreases the Na^+ concentration of the tubular fluid, diminishing the gradient for Na^+ reabsorption and therefore causing natriuresis; mannitol can result in up to a 20% decrease in Na^+ reabsorption.
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The hospital team administers an IV bolus of mannitol. They continue to closely monitor Mr. A in the neurological ICU. 2 hours later, Mr. A's nurse informs the team that his oxygen saturation has dropped to 88%, and is not improving with increased supplemental oxygen flow. The team believes this may be an adverse effect of the mannitol and goes to Mr. A's room to examine him.

e) What adverse effect of mannitol is likely affecting Mr. A?

The primary adverse effect of mannitol is the development of pulmonary edema in patients with decreased left ventricular function; recall that Mr. A has a history of HFrEF.

f) What is the mechanism of the development of pulmonary edema with mannitol use?

Although mannitol leads to diuresis and volume depletion, there is an initial expansion of the intravascular volume as water shifts from the intracellular to the extracellular compartment. In patients with preexisting left ventricular dysfunction, this volume expansion can overwhelm the ability of the left ventricle to maintain adequate cardiac output. Backup of pressure in the pulmonary circulation then results in pulmonary edema as fluid shifts out of the vasculature and into pulmonary interstitial and alveolar space, causing respiratory distress.

References:
https://www.uptodate.com/contents/mechanism-of-action-of-diuretics

https://www.uptodate.com/contents/evaluation-and-management-of-elevated-intracranial-pressure-in-adults

https://www.uptodate.com/contents/complications-of-mannitol-therapy

https://www.uptodate.com/contents/pathophysiology-of-cardiogenic-pulmonary-edema

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Hyponatremia (SIADH)

Ms. V is a 41-year-old woman who is currently admitted to the ICU after suffering multiple trauma in a motor vehicle accident.

In the accident, Ms. V suffered splenic laceration and open right tibia/fibula fracture. It is now post-operative day 1 following exploratory laparotomy for repair of the splenic laceration and open reduction and internal fixation of the fracture. She remained stable overnight and is awake this morning. She is complaining of pain in her abdomen and right lower extremity, which is reasonably well controlled on her current dose of morphine. Her vital signs are within normal limits (including the absence of orthostatic hypotension) and physical exam is remarkable only for appropriate tenderness to palpation near her incisions.
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The team reviews the labs obtained this morning, and notes an interval decrease in the serum sodium from 143 mEq/L on admission to 130 mEq/L (normal 135-145 mEq/L). All other lab values are within normal limits. The team calculates the serum osmolality to be 270 mOsm/kg (normal 285-295 mOsm/kg). They also obtain a urine osmolality, which is 150 mOsm/kg. (In situations of low serum osmolality, urine osmolality <100 mOsm/kg in indicates normal suppression of ADH.)

The team discusses Ms. V's labs – in summary, she has hypoosmolar hyponatremia, and her urine osmolality is not appropriately decreased as would be expected. These findings are consistent with *syndrome of inappropriate antidiuretic hormone secretion* (*SIADH*).
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SIADH is a condition of dysregulation of ADH secretion, resulting in excess water retention by the kidney. This causes an expansion of total body water, resulting in hyponatremia. In addition, the initial increase in ECV causes compensatory natriuresis and (to a lesser degree) diuresis, which further contributes to hyponatremia and returns the volume status to normal. For this reason, patients with SIADH typically have *euvolemic* hyponatremia. There are many different conditions that may cause SIADH, including various intracranial processes (e.g., head trauma, stroke, intracerebral hemorrhage), ADH-secreting tumors (most commonly small cell lung carcinoma), surgery/pain, pulmonary disease, and various medications. Identification and treatment of hyponatremia is critical, as it can lead to a spectrum of neurologic disturbance including seizures, coma, and even death.

Management of SIADH involves a tiered approach. Identification and management of the underlying condition, if possible, is imperative. Most cases of SIADH can be managed with fluid restriction, with goal free water intake of <800 mL/day. Only in severe cases of SIADH, where the sodium level is extremely low and/or the patient is symptomatic, are medications indicated.

a) What class of medications is used in the treatment of SIADH? Give an example.

Aquaretics are used in the treatment of SIADH. Examples of aquaretics are ***conivaptan***, ***tolvaptan***, ***demeclocycline***, and lithium.

b) What are the mechanisms of action of conivaptan, tolvaptan, and demeclocycline? How do these medications help in the treatment of SIADH?

Conivaptan and tolvaptan are V_2 receptor antagonists. They bind to V_2 receptors on the basolateral surface of the principal cells of the connecting tubule and collecting duct, preventing stimulation by ADH. This results in decreased ADH-mediated aquaporin-2 expression and decreased reabsorption of water in these segments.

Demeclocycline causes decreased sensitivity of the cells of the connecting tubule and collecting duct to stimulation by ADH, also resulting in decreased aquaporin-2 expression and decreased reabsorption of water.

In SIADH, elevated circulating levels of ADH results in increased stimulation of V_2 receptors and increased water reabsorption by the kidney. By inhibiting the response of the kidney to the elevated levels of ADH, the aquaretics prevent the excessive water reabsorption and hyponatremia caused by SIADH.

c) What are other indications for use of aquaretics? How do they work in these situations?

Conivaptan and tolvaptan are also used in the treatment of hypervolemic hyponatremia caused by disease processes such as advanced heart failure, liver cirrhosis, or nephrotic syndrome. In each of these diseases, cardiopulmonary and arterial baroreceptors perceive decreased pressure and volume, triggering the release of increased ADH from the posterior pituitary and resulting in water retention and hypervolemia. However, despite water retention and expansion of the extracellular fluid (ECF) volume, the effective circulating volume (ECV) does not increase and the process continues (i.e., there is dissociation between ECF and ECV). Increase in total body water resulting from water retention dilutes the total body sodium, resulting in hyponatremia.

Blockade of V_2 receptor in the connecting tubule and collecting duct by conivaptan and tolvaptan prevent further ADH-mediated water retention, causing diuresis and allowing normalization of sodium levels.

d) What are the primary adverse effects of the aquaretics?

All aquaretics can cause hypernatremia (due to excretion of free water in excess of sodium excretion) and dehydration.

Demeclocycline can also produce GI side effects (nausea, vomiting) and photosensitivity.

Lithium can cause various neuropsychiatric adverse effects and weight gain. Note that lithium is unlikely to be used as an aquaretic, but it is important to understand the aquaretics effects of lithium when used in the treatment of other conditions (e.g., bipolar disorder).

References:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC100882/

https://www.uptodate.com/contents/diagnostic-evaluation-of-adults-with-hyponatremia

https://www.uptodate.com/contents/pathophysiology-and-etiology-of-the-syndrome-of-inappropriate-antidiuretic-hormone-secretion-siadh

https://www.uptodate.com/contents/treatment-of-hyponatremia-syndrome-of-inappropriate-antidiuretic-hormone-secretion-siadh-and-reset-osmostat

https://www.uptodate.com/contents/mechanism-of-action-of-diuretics

https://www.uptodate.com/contents/hyponatremia-in-patients-with-heart-failure

https://www.uptodate.com/contents/hyponatremia-in-patients-with-cirrhosis

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Diabetes insipidus

Mr. N is a 29-year-old man who presents to his primary care physician with a chief complaint of "increased urination at night."

Over the past two months, Mr. N has been waking up during the night to urinate. He now awakens two to three times nightly, which has caused him to be tired during the day and less productive at work. He has limited the amount of water he drinks in the evening and does not have any fluid after 9 pm, however this has not led to any improvement in his symptoms. He notes that he has to urinate more frequently during the day as well, and has had increased thirst during this time period, especially upon awakening in the morning after not drinking overnight.

Mr. N has a history of bipolar disorder diagnosed at age 19 and for which he takes lithium daily. He is otherwise in good health. His physical exam is normal.

Mr. N's physician begins by ordering a basic metabolic panel, urinalysis, and urine osmolality.
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The results of Mr. N's initial labs return. The basic metabolic panel is within normal limits. Urinalysis is remarkable only for specific gravity of 1.007 (normal 1.010-1.030). The urine osmolality is 200 mOsm/kg (normal 300-900 mOsm/kg).

Mr. N's physician orders a water deprivation test, which is meant to determine if the body is able to appropriately concentrate the urine in response to dehydration. He drinks no water overnight, and labs drawn in the morning show: serum sodium 148 mEq/L (normal 135-145 mEq/L), serum osmolality 300 mOsm/kg (normal 275-295 mOsm/kg), urine osmolality 220 mOsm/kg (normal 300-900 mOsm/kg).

Based on these results, Mr. N's physician concludes that he did not appropriately concentrate his urine in response to water restriction, indicative of *diabetes insipidus* (*DI*).
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DI is a condition of inappropriate excretion of large volumes of dilute urine ("water diuresis") due to disruption of the ADH-mediated mechanism of urine concentration in the connecting tubule and collecting duct. There are two main categories of DI – central and nephrogenic. Central DI is due to insufficient ADH secretion by the posterior pituitary gland. It is most often idiopathic (possibly due to autoimmune destruction of ADH-producing cells in the hypothalamus), or can be due to conditions such as head trauma or surgical damage. Nephrogenic DI is due to decreased responsiveness of the kidney to ADH. Nephrogenic DI can be due to genetic defects in the V_2 receptor or aquaporin-2, which would present in infancy or early childhood. Acquired nephrogenic DI in adulthood is most commonly caused by lithium use or hypercalcemia. Patients with DI present with polyuria (increased urination), nocturia (urination at night), and polydipsia (increased thirst, in response to elevation of serums sodium and osmolality). The goal of treatment of DI is to decrease urine output.
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Mr. N's physician suspects he has nephrogenic DI secondary to chronic lithium use, and wants to confirm by performing a test that discriminates between central and nephrogenic DI. To test this, the physician

administers a single dose of a medication that is used to treat central DI and monitors the response by remeasuring the urine osmolality after administration.

a) What medication is used in the treatment of central DI? To which class of medications does it belong?

Desmopressin, an antidiuretic, is used in the treatment of central DI.

b) What is the mechanism of action of desmopressin in the treatment of DI? How can desmopressin be used in the diagnosis of central vs. nephrogenic DI?

In central DI, the release of ADH from the pituitary gland is decreased, while the renal tubules remain sensitive to ADH. Desmopressin binds to and stimulates V_2 receptors on principal cells in the connecting tubule and collecting duct, resulting in increased expression of aquaporin-2 on the apical cell membrane and thus increasing the permeability of these segments to water. Water can then be reabsorbed in the connecting tubule and collecting duct to equilibrate the tubular fluid with the medullary concentration gradient and produce concentrated urine.

Desmopressin is used diagnostically to distinguish between central and nephrogenic DI because individuals with central DI will respond appropriately to a single dose of desmopressin to produce concentrated urine. In contrast, in nephrogenic DI the kidney is not responsive to desmopressin, and there will not be an increase in urine osmolality after a single dose of desmopressin.

c) What are other indications for the use of desmopressin?

Other indications for the use of desmopressin include nocturnal enuresis (bedwetting) and nocturia. In each of these situations, desmopressin causes the production of higher concentration (and therefore lower volume) urine to help patients go longer intervals without having to urinate.

d) What are the primary adverse effects of desmopressin?

The primary adverse effect of desmopressin is hyponatremia, which can occur as a result of increased water retention.
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The physician administers desmopressin. 2 hours later, the urine osmolality is 270 mOsm/kg (initial value was 220 mOsm/kg). Mr. N's physician concludes that this is indicative of nephrogenic DI (if the kidneys were unaffected, we would expect desmopressin to result in urine concentrated to >300 mOsm/kg).

Chronic lithium use is a common cause of acquired nephrogenic DI. The first step in treatment of nephrogenic DI is to treat any identifiable underlying disorder or discontinue any offending agents. After speaking with Mr. N's psychiatrist, the decision is made to discontinue Mr. N's lithium and transition to valproate for maintenance therapy of his bipolar disorder.

At his next follow-up appointment he reports no improvement in his symptoms and is still waking up multiple times nightly to urinate. The physician explains that, while the condition often improves after discontinuation of lithium, the tubular damage caused by the lithium may be irreversible. Mr. N asks if there are other options to help his condition.

e) What class of medication is used in the treatment of nephrogenic DI?

Thiazide diuretics (TZs; e.g., ***hydrochlorothiazide***, ***chlorthalidone***) are used in the treatment of nephrogenic DI.

f) What is the mechanism of action of TZs in the treatment of nephrogenic DI?

TZs cause natriuresis and diuresis, resulting in a decrease in effective circulating volume (ECV). In response to the decreased ECV, there is an increase in Na^+ and water reabsorption in the proximal tubule, resulting in decreased water delivery to the ADH-sensitive connecting tubule and collecting duct and therefore decreased urine volume independent of ADH.

References:

https://www.uptodate.com/contents/evaluation-of-patients-with-polyuria

https://www.uptodate.com/contents/clinical-manifestations-and-causes-of-central-diabetes-insipidus

https://www.uptodate.com/contents/clinical-manifestations-and-causes-of-nephrogenic-diabetes-insipidus

https://www.uptodate.com/contents/treatment-of-central-diabetes-insipidus

https://www.uptodate.com/contents/treatment-of-nephrogenic-diabetes-insipidus