Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Washington Pharmacy Advisory Committee Meeting

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Agenda Topics

- Overview of Disease State
- Indications
- Dosage & Formulations
- Guideline Updates

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Analgesics: Opioid Agonists – Long Acting

Opioid, Long-Acting – Disease State Description

- While definitions vary, chronic pain is generally defined as pain lasting > 3 months or past the time required for normal tissue healing
  - It has various etiologies, including injury, inflammation, and underlying medical conditions
- Approximately 11.2% of adults report daily pain, which is greatly misunderstood
  - Historically, data have suggested that pain may be undertreated, but newer estimates imply that opioid treatment for pain may be overutilized
  - An estimated 20% of patients presenting to outpatient providers with noncancer pain or pain-related diagnoses, whether acute or chronic, receive an opioid prescription
- In 2018, 15% of the US population received ≥ 1 opioid prescription
  - Annually from 2012, there has been a continued decreased in opioid prescribing. Likewise, the yearly rate for high-dose opioid prescriptions has decreased by 66.1% from 2006 to 2018
  - Unfortunately, approximately 67,367 people have died from overdoses related to opioid pain medications in the United States (US) in 2018
  - Opioid related overdose deaths were higher among males (20.4%) in comparison to females (9.4%)
  - Despite this, persistent pain that is uncontrolled may have clinical, psychological, and social consequences; thus, it is critical to weigh the risks and benefits of opioid use and reevaluate patients routinely for appropriate dose, duration, and treatment choice, including both pharmacologic and non-pharmacologic modalities

CDC, 2019

Opioid, Long-Acting – Guidelines

- **Department of Health and Human Services, 2019**
  - In October 2019, the HHS published a new guideline for clinicians on dosage reduction or discontinuation of long-term opioid analgesics
  - This guidance discusses the risks of opioid taper and advises that opioids should not be quickly tapered or discontinued abruptly due to the potential for opioid withdrawal which can result in acute withdrawal symptoms, pain exacerbation, psychological distress, and suicidal ideation in patients who are physiologically dependent
  - Except for life-threatening circumstances (e.g., impending overdose), it is not recommended to abruptly reduce an opioid dose or discontinue an opioid
  - Guidance details situations when it may be appropriate to taper to a reduced dosage (e.g., pain improvement, patient request, no clinically meaningful improvement in pain or function with opioids, increasing doses without improvements in pain, signs of opioid misuse, side effects impacting function or quality of life, risks for an impending overdose/serious event, concurrent medications or comorbidities increasing the risk for adverse events, extended treatment period without clear benefits versus harms)
  - Other key recommendations include: referring patients with serious mental illness, high suicide risk, or suicidal ideation to a behavioral health provider prior to taper; assessing patients for opioid use disorder if they show signs of opioid misuse and offering medication-assisted treatment if appropriate; advising patients of risks for overdose if they abruptly return to their higher dose; tapering by 5% to 20% every 4 weeks is common, but longer tapering schedules may be required; and considering transition to buprenorphine for patients on high doses and unable to taper

Opioid, Long-Acting – Guidelines

- **National Comprehensive Cancer Network (NCCN), 2019**
  - NCCN published guidelines on the treatment of cancer pain in adults in 2019 specific to pain scale ratings
  - On a scale of 0 to 10, the pain scale is rating of 1 to 3 is mild pain, 4 to 7 is moderate pain, and ≥ 8 is severe pain
    - The recommendation in opioid-naïve patients with mild pain (1 to 3) is non-opioid and adjuvant therapies unless contraindications due to adverse effects or drug interactions are present
    - For moderate pain (4 to 7), NCCN recommends adding a short-acting opioid as needed. NCCN defines opioid tolerant patients by the FDA definition: patients receiving at least 25 mcg/h fentanyl patch, at least 60 mg of morphine daily, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer
  - The NCCN recommendation for opioid-tolerant patients is the same as opioid-naïve patients, except that they specify titrating short-acting opioid dose by 30% to 50% daily
  - Recommendations for both opioid-naïve and opioid-tolerant patients include opioid rotation if limiting adverse effects are noted and opioid reassessment of efficacy and adverse effects in 1 to 4 weeks
  - Long-acting opioids are recommended if 3 to 4 daily doses of short-acting opioid are consistently needed
  - If pain is persistent, NCCN recommends that the opioid should be scheduled with rescue dose as needed
  - Consideration for treatment in the hospital or hospice setting for patient-specific goals is recommended for any severe pain (≥ 8)
  - NCCN recommends against the use of meperidine (due to central nervous system [CNS] toxicity) and mixed agonist-antagonists (limited usefulness) for cancer pain
  - Also, they recommend to consider supplementing with doses of short-acting opioid when using methadone as a long-acting opioid. NCCN also provides extensive guidance on dosing, adverse effect management, and pain assessment

Opioid, Long-Acting – Guidelines

- **American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP), 2020**
  - Published a new clinical practice guideline on the managing acute pain associated from non–low back, musculoskeletal injuries in adults who are outpatient
  - Recommendations are provided for nonpharmacologic and pharmacologic treatment modalities
  - Clinicians are recommended to treat patients with topical NSAIDs with or without menthol gel as first-line therapy to decrease or relieve symptoms and to improve physical functioning and the patient's treatment satisfaction
  - It is suggested that clinicians treat patients with oral NSAIDs (to reduce/relieve symptoms and to improve physical function) or with oral acetaminophen to reduce pain
  - Additionally, it is suggested that clinicians treat patients with specific acupressure for reduction of pain and improvement of physical functioning or with transcutaneous electrical nerve stimulation to reduce pain
  - Lastly, it is suggested against clinicians treating patients with opioids, including tramadol

Opioid, Long-Acting – Guidelines

- **FDA, 2019**
  - FDA announced changes to the Transmucosal Immediate-Release Fentanyl (TIRF) REMS program
  - Changes include requiring prescribers to document a patient's opioid tolerance concurrently with each prescription of a TIRF medicine for outpatient use
  - Requiring inpatient pharmacies to develop internal policy and procedures to verify opioid tolerance in hospitalized patients requiring TIRF medicines
  - TIRF meds for outpatient use must have evidence or other documentation of safe use conditions, including concurrent documentation of opioid tolerance; and requiring the development of a new patient registry to monitor for serious adverse events including overdose (both fatal and non-fatal)

- **CDC, 2019**
  - CDC clarified that their guidelines on opioid prescribing are not intended to deny opioid therapy for pain management for any patients with chronic pain, particularly in pts with sickle cell disease, undergoing cancer treatment, and cancer survivors with chronic pain
  - It aims to ensure that clinicians and patients consider all safe and effective treatment options

Opioid, Long-Acting – Guidelines

- **DEA Communication, April 2020**
  - **DEA published their 2020 edition of Drugs of Abuse Resource Guide – updated since 2017**
  - **Includes information on a drug's origin, street names, mode of abuse, its effects, and legal status in the US**
  - **Now includes information on vaping, as well as updated info on fentanyl, marijuana, and stimulant drugs**

- **FDA Communication, September 2020**
  - **The FDA has issued warning letters to 17 website owners for the illegal sales of unapproved and misbranded opioids; this includes those sold without a prescription and products without adequate directions for use**

- **New Generic- hydrocodone extended-release, January 2020**
  - First generic for Zohydro ER approved by the FDA from Alvogen
  - Alvogen has launched its generic formulation
  - In addition, Macoven launched an authorized generic

Opioid, Long-Acting – Guidelines

- **FDA Communication, July 2020**
  - The FDA has released a drug safety communication and a MedWatch for opioid pain relievers and opioid use disorder (OUD) agents recommending HCP discuss/consider naloxone use with all patients at the time of prescribing
  - FDA is requiring manufacturers for all opioid pain relievers and OUD treatments (e.g., buprenorphine, methadone and naltrexone) add recommendations on naloxone to the product labeling for Healthcare Practitioners to consider/discuss prescribing naloxone
  - When these meds are prescribed or renewed, the FDA is recommending the potential need for a naloxone Rx be evaluated
  - Corresponding updates will also be made to the Med Guides. In addition, for patients that are not receiving a Rx for an opioid analgesic or OUD treatment, consideration should be given to prescribing naloxone for them if they are at a higher risk of opioid overdose (e.g., current/prior diagnosis of OUD or prior opioid overdose)
  - The FDA also recommends HCP consider prescribing naloxone when a patient has household members (e.g., children, close contacts) who may be at risk for accidental ingestion or opioid overdose

- **Discontinuations**
  - **morphine sulfate/naltrexone (Embeda), October 2019**
    - Pfizer will discontinue manufacture and distribution of all strengths of Embeda capsules
    - Stop sale date was 11/15/2019 and anticipated unavailability timeframe is early 2020
  - **fentanyl extended-release film (Duragesic), April 2020**
    - FDA has reported Janssen's Duragesic will be permanently discontinued as a business decision (Only brand-name will be discontinued)
    - FDA is recommending product remain on formularies until July 31, 2021, when the last batch expires

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Antiemetics/Antivertigo Agents:

- 5-HT3 Receptor Antagonists
- Substance P/Neurokinin 1 (NK1) Receptor Antagonists
- Substance P/Neurokinin 1 Receptor Antagonist Combinations

Disease State Description - Antiemetic/Antivertigo Agents

- Chemotherapy-induced vomiting (emesis) and nausea can significantly impact a patient's quality of life, leading to poor compliance with future chemotherapy or radiation treatments
- In addition, nausea and vomiting can lead to several adverse events, such as nutrient depletion, metabolic imbalances, erosion of self-care, anorexia, diminished performance and mental status, wound dehiscence, tears in the esophagus, and cessation of potentially useful or curative cancer treatment
- Approximately 70% to 80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting, whereas 10% to 44% experience anticipatory nausea and/or vomiting
- Furthermore, more than 90% of patients using highly emetogenic chemotherapeutic agents will experience acute emesis; however, only approximately 30% of these patients will experience a vomiting episode if they receive an antiemetic prior to their highly emetogenic chemotherapeutic treatment

National Comprehensive Cancer Network, 2017

Disease State Description - Antiemetic/Antivertigo Agents

- Motion sickness
  - Result of a conflict between the various senses in regard to motion
  - The overall incidence of dizziness, vertigo, and imbalance is 5% to 10%
  - There are multiple causes of vertigo, such as head trauma, cerebellar lesions, vestibular disease, or migraine
  - Symptoms include nausea, vomiting, pallor, sweating, and often a sense of impending doom
  - There are both non-pharmacologic and pharmacologic interventions for the prevention or management of motion sickness
    - None are ideal, and the medications typically cause drowsiness or similar adverse effects
    - Symptomatic treatment of motion sickness generally includes the use of antihistamines, benzodiazepines, or antiemetics
    - Vestibular rehabilitation in select patients may be used with a goal of treating the underlying cause

- Nausea and vomiting of pregnancy ("morning sickness")
  - Can occur at any time of day and can affect pregnant women with varying symptoms from nausea to severe vomiting
  - Lifestyle changes for women with nausea and vomiting of pregnancy include rest, avoiding nauseating stimuli, eating small, frequent low fat meals that are low in spices

Centers for Disease Control and Prevention, 2010

The Medical Letter, 2013

Treatment Guidelines- NCCN, 2020

- The choice of antiemetic should be based on emetic risk of the chemotherapy, prior experience with antiemetics, and patient factors. It should be initiated prior to the start of chemotherapy to provide maximal protection against chemotherapy-induced emesis
  - The antiemetic therapy should be continued for the same timeframe as the duration of the emetic activity of the chemotherapeutic agent being used

- The guidelines identify emesis prevention treatment options for high, moderate, low, and minimal emetic risk intravenous (IV) chemotherapy, oral chemotherapy, and radiation therapy, as well as breakthrough treatment for chemotherapy-induced N/V

- To prevent acute and delayed emesis, in patient receiving IV HEC
  - 3- or 4-drug combination of an NK1 receptor antagonist (duration and dosing is dependent on formulation), a 5-HT3 receptor antagonist (day 1), and dexamethasone (days 1 through 4), with or without olanzapine (days 1 through 4) or
  - 3-drug regimen of olanzapine, palonosetron, and dexamethasone may also be used

Treatment Guidelines- NCCN, 2020

- Prevent acute and delayed emesis in patient receiving IV MEC
  - 5-HT_3 antagonist and dexamethasone as a 3 day regimen
  - NK_1 antagonist should be added for select patients with additional risk factors or previous treatment failures with a steroid and 5-HT_3 antagonist alone (ranging from 1 to 3 days based on the treatment regimen selected)
  - NCCN does not specify one 5-HT_3 antagonist or NK_1 antagonist over another (or route/formulation)
  - Equivalent alternatives to this include 3-day olanzapine-containing regimens (olanzapine, palonosetron, and dexamethasone)

- For IV low emetogenic risk chemotherapy
  - Dexamethasone, metoclopramide (Reglan), prochlorperazine (Compazine, Compro), or an oral 5-HT_3 antagonist may be used and repeated daily for multiday doses of chemotherapy
  - There is no routine prophylaxis for patients who receive minimal emetic risk IV chemotherapy

- For breakthrough treatment of chemotherapy-induced N/V
  - The general principle is to add 1 agent from a different class, as needed, to the existing regimen (e.g., antipsychotic, benzodiazepine, cannabinoid, dopamine receptor antagonist, phenothiazine, 5-HT_3 antagonist, scopolamine patch, or corticosteroid)

- For radiation-induced N/V associated with upper abdomen/localized sites or total body irradiation
  - Oral granisetron or ondansetron with or without oral dexamethasone as pretreatment for each day of therapy

Updated Information

- **amisulpride (Barhemsys)**
  - **In February 2020, FDA approved a new medication indicated in adults for 1) prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class and 2) treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis**
  - **Indications:**
    - **Prevention of postoperative nausea and vomiting (PONV), either alone or in combination with an antiemetic of a different class**
    - **Treatment of PONV in patients who have received antiemetic prophylaxis with an agent of a different class or have not received prophylaxis**
  - **Limitations**
    - **Lactation: A lactating woman may pump and discard breast milk for 48 hours after Barhemsys administration**
    - **QT Prolongation: Occurs in a dose- and concentration-dependent manner. Avoid use in patients with congenital long QT syndrome and in patients taking droperidol. ECG monitoring is recommended in patients with pre-existing arrhythmias/cardiac conduction disorders; electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia); congestive heart failure; and in patients taking other medicinal products (e.g., ondansetron) or with other medical conditions known to prolong the QT interval**
  - **Dosing:**
    - **Prevention of PONV, either alone or in combination with another antiemetic: 5 mg as a single intravenous dose infused over 1 to 2 minutes at the time of induction of anesthesia**
    - **Treatment of PONV: 10 mg as a single intravenous dose infused over 1 to 2 minutes in the event of nausea and/or vomiting after a surgical procedure**
  - **Formulations:**
    - **Injection: 5 mg/2 mL (2.5 mg/mL) or 10 mg/4 mL (2.5 mg/mL) in a single-dose vial**

Updated Information

- **metoclopramide (Gimoti)**
  - **In June 2020, FDA approved a new formulation of metoclopramide in the form of a nasal spray**
  - **Indications:**
    - **The relief of symptoms in adults with acute and recurrent diabetic gastroparesis**
  - **Limitations**
    - **Not recommend for use in:**
      - **Pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates**
      - **Moderate or severe hepatic impairment (Child-Pugh B or C), moderate or severe renal impairment (creatinine clearance less than 60 mL/minute), and patients concurrently using strong CYP2D6 inhibitors due to the risk of increased drug exposure and adverse reactions**
    - **Depression and suicidal ideation/suicide: Avoid use**
    - **BBW:**
      - **Tardive dyskinesia (TD), other extrapyramidal symptoms (EPS), and neuroleptic malignant syndrome (NMS): Avoid concomitant use of other drugs known to cause TD/EPS/NMS and avoid use in patients with Parkinson's disease. If symptoms occur, discontinue and seek immediate medical attention**
  - **Dosing:**
    - **Adults < 65 years of age: Recommended dosage is 1 spray (15 mg) in one nostril, 30 minutes before each meal and at bedtime (maximum of 4 sprays daily) for 2 to 8 weeks, depending on symptomatic response**
    - **Adults ≥ 65 years of age: Not recommended in geriatric patients as initial therapy**
  - **Formulations:**
    - **Nasal Spray: 15 mg metoclopramide in each 70 microliter spray**

Updated Information

- **fosnetupitant/palonosetron (Akynzeo)**
  - **In August 2020, approval of a new dosage form of the injection which is a solution in a single dose 20 mL vial for IV infusion (235 mg fosnetupitant/0.25 mg palonosetron). Previously, only available as a capsule (300 mg netupitant/0.5 mg palonosetron) and a lyophilized powder in a single-dose vial for reconstitution (235 mg fosnetupitant/0.25 mg palonosetron)**
  - **Indications:**
    - Indicated in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy
    - Akynzeo is a combination of palonosetron, a serotonin-3 (5-HT3) receptor antagonist, and netupitant or fosnetupitant, substance P/neurokinin-1 (NK-1) receptor antagonists: palonosetron prevents nausea and vomiting during the acute phase and netupitant/fosnetupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy
  - **Limitations**
    - Pregnancy: May cause fetal harm
    - Hepatic Impairment: Avoid use in patients with severe hepatic impairment
    - Renal Impairment: Avoid use in patients with severe renal impairment or endstage renal disease
  - **Dosing:**
    - The recommended dosage is one Akynzeo vial diluted and administered as 30-minute infusion starting approximately 30 minutes prior to the start of chemotherapy
  - **Formulations:**
    - Capsules: 300 mg netupitant/0.5 mg palonosetron
    - Injection: 235 mg fosnetupitant/0.25 mg palonosetron as a lyophilized powder in single-dose vial for reconstitution
    - **Injection: 235 mg fosnetupitant/0.25 mg palonosetron solution in single dose 20 mL vial**

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Antihypertensives:
- Direct Renin Inhibitor Combinations
- Direct Renin Inhibitors
- Neprilysin Inhibitor (ARNI) Angiotensin II Receptor Antagonist Combinations

Disease State Description

Hypertension

- Approximately 108 million (45%) adults in the United States have high blood pressure along with 1 of 3 American adults having prehypertension
- The highest prevalence is among African American men and women
  - Approximately 54% of African American men and women have high blood pressure, compared to about 46% of white men and women and 39% of non-Hispanic Asians and 36% of Hispanics
- It is estimated that hypertension is controlled in only 54% of patients with the condition

Center for Disease Control, 2020

Updated Information

- **sacubitril/valsartan (Entresto)**
  - **October 2019: FDA approved a new indication for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patient ≥ 1 yo**
  - **Indications**
    - To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction
      - Is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB
    - **For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older**
  - **Warnings and Precautions**
    - Observe for signs and symptoms of angioedema and hypotension
    - Monitor renal function and potassium in susceptible patients
    - Pregnancy Category X
  - **Dosage**
    - Dosage is stratified by indication and weight-based
  - **Availability**
    - Film-coated tablets: 24/26 mg; 49/51 mg; 97/103 mg

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Antivirals:
Hepatitis C Agents

Disease State Description – Hepatitis C Agents

- Hepatitis C virus (HCV) infection is the most common chronic blood-borne infection in the United States (US)
- In approximately 15% to 25% of patients who become infected with hepatitis C, the virus is eliminated during the acute phase of the infection by T cell-mediated antiviral mechanisms; however, in the other 75% to 85% of patients, the HCV persists for decades
- An estimated 23,000 to 46,000 children in the US have HCV
  - New HCV infections in children are primarily the result of perinatal transmission
- Approximately 2.7 million people in the US are chronically infected, although it is estimated that nearly 75% of these people may be unaware of their infection due to the insidious progression of the disease
  - HCV accounts for 40% of chronic liver disease in the US
  - In patients with chronic HCV infection followed for 20 years, disease progression to cirrhosis occurs in about 20% to 25%
- Transmission of HCV occurs primarily through percutaneous exposure to infected blood
- The most important risk for HCV infection is injection-drug use, which accounts for at least 60% of acute HCV infections in the US
  - Other modes of transmission include mother-to-infant, receiving a blood or organ donation prior to 1992, occupational exposures, chronic hemodialysis, and contaminated devices shared for non-injection drug use, such as intranasal illicit drug use
  - Sexual transmission also occurs but generally seems to be inefficient except among human immunodeficiency virus (HIV)-infected men who have unprotected sex with men
  - Other risk factors include incarceration and receiving a tattoo in an unregulated setting. It is estimated that 29% of incarcerated persons in the North America are anti-HCV positive

CDC, 2020

Guidelines – Hepatitis C Agents

- United States Preventive Services Task Force (USPSTF), 2020
  - In 2020, the United States Preventive Services Task Force (USPSTF) expanded the population for a 1-time screening to asymptomatic adults 18 to 79 years of age
  - Similarly, joint guidelines from the American Association for Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) recommend a 1-time, routine, opt-out HCV testing for anyone 18 years and older

- Centers for Disease Control and Prevention, 2020
  - The CDC recommends that in areas where the HCV infection rate is ≥ 0.1%, all adults be screened at least once for hepatitis C virus (HCV) infection
  - All pregnant women be screened during each pregnancy

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Any Genotype

Treatment Experience	Treatment	Duration (weeks)	Rating
Any Genotype - Simplified Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪glecaprevir/pibrentasvir ▪sofosbuvir/velpatasvir Patients **with compensated** cirrhosis: ▪glecaprevir/pibrentasvir ▪sofosbuvir/velpatasvir (all genotypes except GT 3 without Y93H present)	 8 12 8 12	
Any Genotype			
Treatment-Experienced (previous sofosbuvir/ velpatasvir/ voxilaprevir treatment failure)	Patients **with or without** compensated cirrhosis: ▪glecaprevir/pibrentasvir + sofosbuvir + weight-based-RBV ▪sofosbuvir/velpatasvir/voxilaprevir + weight-based RBV	 16 24	 Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous glecaprevir/ pibrentasvir treatment failure)	Patients **with or without** compensated cirrhosis: ▪glecaprevir/pibrentasvir + sofosbuvir + weight-based RBV ▪sofosbuvir/velpatasvir/voxilaprevir ▪sofosbuvir/velpatasvir/voxilaprevir + weight-based RBV (patients with compensated cirrhosis)	 16 12 12	 Class IIa, Level B Class IIa, Level B Class IIa, Level C

Updated Information

- **sofosbuvir/velpatasvir (Epclusa)**
  - **March 2020: FDA approved Epclusa for the treatment of HCV genotypes 1, 2, 3, 4, 5, and 6 in pediatric patients ≥ 6 years of age or weighing ≥ 17 kg; previously, it was only indicated in adults. FDA also approved a new 200/50 mg tablet strength; previously, only a 400/100mg fixed-dose tablet was approved**
  - **July 2020: Include use in treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis or with compensated cirrhosis**
  - **Indications:**
    - The treatment of adult and **pediatric patients 6 years of age and older or weighing at least 17 kg** with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection (1):
      - Without cirrhosis or with compensated cirrhosis
      - With decompensated cirrhosis for use in combination with ribavirin
  - **Limitations**
    - BBW: Hepatitis B reactivation has been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death
  - **Dosing:**
    - Recommended dosage in adults: One tablet (400 mg of sofosbuvir and 100 mg of velpatasvir) taken orally once daily with or without food
    - Recommended dosage in pediatric patients 6 years and older: Recommended dosage in pediatric patients ≥ 6 years of or weighing at least 17 kg is based on weight. Refer to PI or TCR for specific dosing guidelines
  - **Formulations:**
    - Tablets: 400 mg of sofosbuvir and 100 mg of velpatasvir; **200 mg of sofosbuvir and 50 mg of velpatasvir**

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Endocrine and Metabolic Agents: Androgens - Testosterone

Disease State Description - Androgenic Agents, Topical

- Male hypogonadism is caused by insufficient production of testosterone and characterized by low serum concentrations and may present as testosterone deficiency, infertility, or both
- Approximately 20% of men ages 60 to 69 years old and 30% of men ages 70 to 79 years old have serum testosterone levels below the normal range
- After 30 years of age, testosterone levels in men decrease at rates up to 2% annually
- Symptoms at presentation will primarily depend on the patient's age at the time of disease onset and can include
  - Impotence
  - Decreased libido
  - Fatigue
  - Loss of energy
  - Mood Depression
  - Regression of secondary sex characteristics
- Potential risks due to male hypogonadism include:
  - Osteoporosis, sexual dysfunction, depression, and cardiovascular disease

Urologic Clinics, 2002

Guidelines - Androgenic Agents, Topical

- American College of Physicians (ACP), 2020
  - Published a clinical guideline on testosterone treatment for adult men with age-related low testosterone
  - This guideline has been endorsed by the American Academy of Family Physicians (AAFP) and suggest a discussion between clinicians and patients regarding if testosterone therapy should be started for men with age-related low T with sexual dysfunction who want to improve sexual function
  - Patient's preferences as well as benefits and risks of therapy should be considered
  - It is suggested symptoms be reassessed within 12 months and periodically, and testosterone therapy be discontinued in patients with no improvement in sexual function
  - As clinical efficacy and safety are comparable for transdermal and intramuscular (IM) testosterone treatment, but costs are lower for IM formulations, these formulations are suggested for improving sexual function when starting testosterone therapy
  - It is suggested not to start testosterone therapy for improvement of energy, vitality, physical function, or cognition in men with age-related low T

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Endocrine and Metabolic Agents:
Bone Density Regulators- Sclerostin Inhibitors

Disease State Description - Bone Resorption Inhibitors

- Osteoporosis is characterized by the deterioration of bone tissue and low bone mass
- Approximately 10 million Americans have the diagnosis of osteoporosis, and an additional 43 million have low bone mass, placing them at increased risk for this disease
  - As many as 1 in 2 women and 1 in 5 men are at risk for an osteoporosis-related fracture during their lifetime
  - Approximately 1 in 4 men in the U.S. over the age of 50 will have an osteoporosis-related fracture in his remaining lifetime
  - Osteoporosis is common in all racial groups but is most common in Caucasians
- There are 3 categories of osteoporosis:
  - Postmenopausal
    - Postmenopausal osteoporosis affects mainly trabecular bone in the decade after menopause as estrogen deficiency increases bone resorption more than bone formation
  - Age-related
    - Age-related osteoporosis results from increased bone resorption that begins shortly after peak bone mass is obtained. Cortical and trabecular bone are both affected.
  - Secondary osteoporosis
    - Caused by medications (glucocorticoids, excess thyroid replacement, some antiepileptic drugs, and long-term heparin use) or diseases (hyperthyroidism, type 1 diabetes)

National Osteoporosis Foundation, 2015

Guidelines - Bone Resorption Inhibitors

- Endocrine Society, 2020
  - In 2020, the ES updated their 2019 guidance on the management of osteoporosis in postmenopausal women to include Evenity (romosozumab)
  - Romosozumab was concluded to be a potential treatment option for select postmenopausal women at very high risk of osteoporotic fracture, however patients should be carefully selected due to the serious cardiovascular (CV) events observed in a clinical trial with an active comparator
  - To reduce the risk for vertebral, hip, and nonvertebral fractures, treatment with monthly romosozumab (210 mg) is recommended for up to 1 year in postmenopausal women with osteoporosis at very high risk for fracture, including those with low bone density T-scores (<-2.5) and fractures or with multiple vertebral fractures; however, women at high risk of stroke or CV disease (e.g., past myocardial infarction [MI] or stroke) should not receive romosozumab until further evaluation of the CV risk from this agent
  - After completing a course of romosozumab, it is recommended that patients receive treatment with antiresorptive therapies to maintain improvements in bone density and reductions in fracture risk

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Migraine Agents:
- Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists
- Selective Serotonin Agonists (5-HT1)

Disease State Description - Antimigraine Agents

- **Migraine Headache**
  - Accounts for 10% to 20% of all headaches in adults and affects over 39 million men, women, and children in the United States (U.S.)
  - Headache is one of the most common complaints by patients when presenting to a physician
    - 64% of physician-diagnosed patients who experience migraines and 41% of undiagnosed migraine sufferers reported severe impairment or the need for bed rest due to their migraine symptoms
    - In addition, 18% of women, 6% of men, and 10% of children experience migraine, an epidemiologic profile that has remained stable over many years
  - Approximately 85% of patients with migraine headaches suffer less than 3 to 4 attacks per month
    - The median frequency of migraine attacks among migraine sufferers is 1.5 per month
  - Migraine headache must be differentiated from tension-type headache
    - Key criteria for the diagnosis of migraine headache includes an episodic headache lasting from 4 to 72 hours with at least 2 of the following symptoms: unilateral pain, throbbing, aggravated by routine physical activity, pain of moderate to severe intensity
    - During the headache at least 1 of the following are present: nausea and/or vomiting, or photophobia and phonophobia

Migraine Research Foundation, 2018

- **Cluster Headache (CH)**
  - A severe, primary headache disorder characterized by extreme pain on one side of the head and autonomic symptoms (e.g., nasal congestion, lacrimation)
  - CH periods can persist for weeks to months with daily or more frequent attacks of 15 to 180 minutes in duration
  - The estimated lifetime prevalence of CH is more than one in 1,000. CH can be either episodic or chronic in nature with episodic CH being the predominant form
  - Individuals with episodic CH experience periods of attack followed by periods of remission, whereas individuals with chronic CH have minimal to no periods of remission between headache attacks

American Headache Society, 2016

Disease State Description - Antimigraine Agents

- American Headache Society (AHS), 2019
  - Published its position statement on integrating new migraine treatments into clinical practice
  - There were no changes in recommended usage or place in therapy for agents in this class from previous guidelines
  - Included recommendations regarding use non-triptan, injectable agents, including Botox and monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) (Ajovy, Emgality or the CGRP receptor Aimovig) for migraine prevention in patients who experience episodic (CGRP agents only) or chronic (both classes) migraine

- American Academy of Neurology (AAN) & American Headache Society (AHS), 2019
  - In their 2012 practice guidelines (reaffirmed 2015), pharmacologic treatment for episodic migraine prevention in adults, the AAN and the AHS advise that antiepileptic drugs (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, timolol) are established as effective in migraine prevention, with the exception of frovatriptan which is established for short-term menstrually associated migraine (MAM) prevention
  - Naratriptan, zolmitriptan, antidepressants (amitriptyline, venlafaxine), and beta-blockers (atenolol, nadolol) are probably effective in migraine prevention; but no triptan is approved for the prevention of migraines
  - **In 2019, AAN and AHS updated the guidelines for acute treatment of migraine in children and adolescents**
  - **They endorse the use of sumatriptan/naproxen and almotriptan oral tablets, rizatriptan ODT, and nasal zolmitriptan in adolescents to reduce headache pain**
  - **Triptans have more supportive evidence in adolescents than in children, where NSAIDs and acetaminophen are recommended options**

Analgesics – Antimigraine Agents

- **lasmiditan (Reyvow)**
  - **October 2019: FDA approved Reyvow, a serotonin (5-HT) 1F receptor agonist indicated for the acute treatment of migraine with or without aura in adults**
  - **Indication**
    - The acute treatment of migraine with or without aura in adults
    - Limitations of Use: Not indicated for the preventive treatment of migraine
  - **Warnings**
    - Driving Impairment: Advise patients not to drive or operate machinery until at least 8 hours after taking each dose of Reyvow. Patients who cannot follow this advice should not take Reyvow. Patients may not be able to assess their own driving competence and the degree of impairment caused by Reyvow
    - Central Nervous System (CNS) Depression: May cause CNS depression and should be used with caution if used in combination with alcohol or other CNS depressants
    - Serotonin Syndrome: Reactions consistent with serotonin syndrome were reported in patients treated with Reyvow. Discontinue if symptoms of serotonin syndrome occur
  - **Dosage**
    - The recommended dose is 50 mg, 100 mg, or 200 mg taken orally, as needed
    - No more than one dose should be taken in 24 hours
  - **Availability**
    - Tablets: 50 mg, 100 mg

Analgesics – Antimigraine Agents

- **erenumab-aooe (Aimovig)**
  - **October 2019: FDA approved a 140 mg/mL prefilled syringe and autoinjector (70 mg/mL already approved)**
  - **Indication**
    - For the preventive treatment of migraine in adults
  - **Warnings**
    - Hypersensitivity Reactions: Reactions have included angioedema, urticaria, facial flushing, and rash. If a hypersensitivity reaction occurs, consider discontinuing treatment and initiate appropriate therapy
    - Constipation with Serious Complications: Serious complications of constipation may occur
    - Hypertension: New-onset or worsening of pre-existing hypertension may occur
  - **Dosage**
    - Recommended dosage is 70 mg once monthly; some patients may benefit from a dosage of 140 mg once monthly
  - **Availability**
    - Injection: 70 mg/mL solution in a single-dose prefilled SureClick® autoinjector
    - **Injection: 140 mg/mL in a single-dose prefilled SureClick® autoinjector**
    - Injection: 70 mg/mL solution in a single-dose prefilled syringe
    - **Injection: 140 mg/mL solution in a single-dose prefilled syringe**

Analgesics – Antimigraine Agents

- **galcanezumab-gnlm (Emgality)**
  - **January 2020: FDA approved an expanded indication for the treatment of episodic cluster headache. It was already approved for the preventive treatment of migraine**
  - **Indication**
    - Preventive treatment of migraine
    - **Treatment of episodic cluster headache**
  - **Warnings**
    - Hypersensitivity Reactions: If hypersensitivity occurs, consider discontinuing and institute appropriate therapy
  - **Dosage**
    - Migraine recommended dosage: 240 mg loading dose (administered as two consecutive injections of 120 mg each), followed by monthly doses of 120 mg
    - Episodic cluster headache recommended dosage: 300 mg (administered as three consecutive injections of 100 mg each) at the onset of the cluster period, and then monthly until the end of the cluster period
  - **Availability**
    - Injection: 120 mg/mL solution in a single-dose prefilled pen
    - Injection: 120 mg/mL solution in a single-dose prefilled syringe
    - Injection: 100 mg/mL solution in a single-dose prefilled syringe

Analgesics – Antimigraine Agents

- **fremanezumab-vfrm (Ajovy)**
  - **January 2020: FDA approved a new formulation of Ajovy, a 225 mg/1.5 mL autoinjector. It was already approved in this strength as a prefilled syringe, and both are approved for the preventive treatment of migraine in adults and can be self-administered (SC) following training**
  - **Indication**
    - The preventive treatment of migraine in adult
  - **Warnings**
    - Hypersensitivity Reactions: If hypersensitivity occurs, consider discontinuing and institute appropriate therapy
  - **Dosage**
    - Two subcutaneous dosing options of Ajovy are available to administer the recommended dosage:
      - 225 mg monthly, or
      - 675 mg every 3 months (quarterly)
    - The 675 mg quarterly dosage is administered as three consecutive injections of 225 mg each
  - **Availability**
    - **Injection: 225 mg/1.5 mL solution in a single-dose prefilled autoinjector**
    - Injection: 225 mg/1.5 mL solution in a single-dose prefilled syringe

Analgesics – Antimigraine Agents

- **ubrogepant (Ubrelvy)**
  - **January 2020: FDA approved Ubrelvy, a calcitonin gene-related peptide receptor (CGRP) antagonist indicated for the acute treatment of migraine with or without aura in adults; it is not indicated for the preventive treatment of migraine**
  - **Indication**
    - **The acute treatment of migraine with or without aura in adults**
    - **Limitations of Use: Not indicated for the preventive treatment of migraine**
  - **Warnings**
    - **Pregnancy: Based on animal data, may cause fetal harm**
    - **Avoid use in patients with end-stage renal disease**
  - **Dosage**
    - **The recommended dose is 50 mg or 100 mg taken orally, as needed. If needed, a second dose may be administered at least 2 hours after the initial dose**
    - **The maximum dose in a 24-hour period is 200 mg**
    - **Severe Hepatic or Severe Renal Impairment: Recommended dose is 50 mg; if needed, a second 50 mg dose may be taken at least 2 hours after the initial dose**
  - **Availability**
    - **Tablets: 50 mg and 100 mg**

Analgesics – Antimigraine Agents

- **rimegepant (Nurtec ODT)**
  - **February 2020: FDA approved Nurtec ODT, indicated for the acute treatment of migraine with or without aura in adults; it is not indicated for the preventive treatment of migraine**
  - **Indication**
    - **The acute treatment of migraine with or without aura in adults**
    - **Limitations of Use: Not indicated for the preventive treatment of migraine**
  - **Warnings**
    - **Hypersensitivity Reactions: If a serious hypersensitivity reaction occurs, discontinue treatment and initiate appropriate therapy. Severe hypersensitivity reactions have included dyspnea and rash, and can occur days after administration**
    - **Hepatic Impairment: Avoid use in patients with severe hepatic impairment**
  - **Dosage**
    - **The recommended dose is 75 mg taken orally, as needed**
    - **The maximum dose in a 24-hour period is 75 mg**
    - **The safety of treating more than 15 migraines in a 30-day period has not been established**
  - **Availability**
    - **Nurtec ODT orally disintegrating tablets: 75 mg**

Analgesics – Antimigraine Agents

- **eptinezumab-jjmr (Vyepti)**
  - **February 2020: FDA approved Vyepti, indicated for the preventive treatment of migraine in adults**
  - **Indication**
    - **For the preventive treatment of migraine in adults**
  - **Warnings**
    - **Hypersensitivity Reactions: Reactions have included angioedema, urticaria, facial flushing, and rash. If a hypersensitivity reaction occurs, consider discontinuing treatment and initiate appropriate therapy**
  - **Dosage**
    - **Recommended dosage is 100 mg as an intravenous infusion over approximately 30 minutes every 3 months; some patients may benefit from a dosage of 300 mg**
  - **Availability**
    - **Injection: 100 mg/mL solution in a single-dose vial**

Central Nervous System – Antimigraine Agents

- **Discontinuation**
  - **sumatriptan (Imitrex), April 2020**
    - **The FDA has reported GSK has made a business decision to discontinue manufacturing Imitrex 6 mg SDV**
    - **Distribution of the product is expected to conclude in August 2020**
    - **Only brand-name product will be discontinued**
  - **ergotamine tartrate/caffeine (Cafergot), July 2020**
    - **Sandoz reported to FDA discontinuation of Cafergot manufacturing**

Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Pulmonary Hypertension Agents:

- Endothelin Receptor Antagonists
- Prostacyclin Receptor Agonists
- Prostaglandin Vasodilators
- SGC Stimulator
- Phosphodiesterase Inhibitors (PDEI)

Disease State Description - Pulmonary Arterial Hypertension

- The prevalence varies substantially depending on the type, etiology, and underlying condition; estimated to be ~15 per million people
- Pulmonary hypertension (PH) is characterized by an increase in pulmonary arterial pressure and secondary right ventricular failure. This is defined as a resting mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg
- Symptoms include dyspnea, dizziness, syncope, fatigue, edema (peripheral), angina, palpitations, and other symptoms, all of which are exacerbated by exertion
- PH does not have a cure and, if left untreated, PH is a life-threatening disease with poor prognosis
- Management of PH should be limited to specialized centers where clinicians are experienced in the evaluation and treatment of patients with PH
- Although the number of approved therapies for PAH has grown in the past years, the prognosis is still poor, with approximately 50% mortality within the first 5 years after diagnosis

World Health Organization, 2013

Disease State Description - Pulmonary Arterial Hypertension

- There are many causes of PAH including idiopathic or underlying disease and hereditary causes
  - Cellular changes in the walls of pulmonary arteries, and it appears that mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene plays a key role in the pathogenesis of heritable PAH
  - Other etiologies in PAH include drugs and toxins, collagen vascular resistance, human immunodeficiency virus (HIV), portal hypertension, chronic thromboembolism, and congenital heart disease
- The World Health Organization (WHO) classifies PH patients into 5 groups based on etiology
  - Group I now refers to pulmonary arterial hypertension (PAH)
  - Group II refers to PH due to left heart disease
  - Group III refers to PH due to lung disease
  - Group IV refers to PH due to blood clots in the lungs
  - Group V refers to refers to PH due to blood and other rare disorders
- In 2013, clinical classifications were updated to provide the same PH classifications for adult and pediatric patients. In addition, the individual categorization of the persistent PH of neonates (PPHN) was included

American College of Cardiology, 2013

Updated Information

- **treprostinil (Orenitram)**
  - **October 2019: FDA approved an expanded indication for a delay disease progression in the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1); previously, it was only approved for improve exercise capacity**
  - **Indications:**
    - **To delay disease progression and to improve exercise capacity**
    - **The studies that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%)**
  - **Warnings/Precautions:**
    - Contraindicated in severe hepatic impairment (Child Pugh Class C)
    - Do not abruptly discontinue dosing
    - In patients with diverticulosis, tablets can become lodged in a diverticulum
  - **Dosage:**
    - Starting dose: 0.125 mg TID or 0.25 mg BID
    - Titrate by 0.125 mg TID or by 0.25 mg or 0.5 mg BID, not more frequently than every 3 to 4 days as tolerated
  - **Formulations:**
    - Extended-Release Tablets: 0.125 mg, 0.25 mg, 1 mg, 2.5 mg and 5 mg

Updated Information

- **Risk Evaluation and Mitigation Strategies (REMS) Update**
  - **riociguat (Adempas)**
    - **February 2020:**
      - **REMS update to make changes to the prescriber and patient enrollment forms for consistency and clarity**
  - **macitentan (Opsumit)**
    - **April 2020:**
      - **FDA established a single shared system (SSS) REMS Opsumit and corresponding generics, called the Macitentan REMS Program**
      - **The new SSS REMS will replace the original REMS once the first generic for macitentan is approved**

Appendices

Treatment Guidelines- ASCO, 2017

- Radiation therapy
  - Patients with select low-emetogenic risk radiation therapy should be offered dexamethasone with other alternatives considered for rescue therapy based on prior treatment and location of radiation
  - Patients with moderately emetogenic radiation therapy should receive a 5-HT3 receptor antagonist with or without dexamethasone prior to each fraction for the first 5 fractions
  - Patients with highly emetogenic radiation therapy should receive a 5-HT_3 receptor antagonist and dexamethasone before each fraction and on the day after each fraction, even if radiation therapy is not planned for that day

- Pediatrics patients
  - Receiving MEC, ASCO recommends treatment with a 5-HT_3 receptor antagonist and dexamethasone
  - Receiving HEC, ASCO recommends treatment with a 5-HT_3 receptor antagonist, aprepitant (if eligible), and dexamethasone, noting that higher weight-based dosing may be necessary
    - Pediatric patients receiving HEC who are unable to receive dexamethasone should receive palonosetron and aprepitant

Treatment Guidelines- ASCO, 2017

- ASCO antiemetic guidelines recommend the choice of antiemetic treatment should be based on the radiotherapy and chemotherapy agent with the greatest degree of emetic risk
  - Optimal treatment should be used with initial chemotherapy to limit anticipatory nausea and vomiting
- Chemotherapy
  - Patients with minimal emesis risk should not be routinely offered antiemetic prophylaxis
  - For patients receiving low-emetic-risk chemotherapy, ASCO recommends adults should be offered a single dose of a 5-HT_3 antagonist or a single 8-mg dose of dexamethasone prior to treatment
  - For patients receiving moderately emetogenic chemotherapy (MEC), ASCO recommends treatment with a 2-drug combination of a 5-HT_3 antagonist and dexamethasone (day 1)
  - For patients who receive highly emetogenic chemotherapy (HEC), ASCO recommends a 4-drug combination of an NK1 receptor antagonist (duration based on formulation), a 5-HT3 receptor antagonist (day 1), dexamethasone (days 1 through 4), and olanzapine (days 1 through 4)
- Patients with breakthrough nausea and vomiting despite optimal prophylaxis, including olanzapine, may be offered an additional drug from another class for subsequent treatments (those who did not receive olanzapine should be offered olanzapine first)
- For multiday chemotherapy, after assessing emetic risk of the agents prescribed, patients should receive an agent of highest therapeutic index daily during chemotherapy and for 2 days thereafter

Treatment Guidelines- ASA, 2013

- The American Society of Anesthesiologists has published recommendations on the prevention of post-operative nausea and vomiting (PONV) within their guidelines on postanesthetic care
- They recommend routine assessment and monitoring for N/V
- For prophylaxis and treatment of N/V, they evaluated the following classes of medication and rated them based on the quality of evidence (range of A to C, from randomized controlled trials to informal opinion and determination of beneficial [B] or equivocal [E]):
    - Antihistamines (Category A3-B evidence)
    - 5-HT_3 receptor antagonists (Category A1-B evidence as a class)
    - Tranquilizers/neuroleptics (e.g., droperidol [Category A1-B evidence]
    - Haloperidol [Category A2-B evidence]
    - Hydroxyzine [Category A3-B evidence]
    - Perphenazine [Category A3-B evidence]
    - Prochlorperazine [Category A1-E evidence]
  - For prophylaxis of PONV using multiple agents, they determined that multiple agents may be used when needed (Category A2-B evidence)
  - They further note that pharmacologic treatment of N/V is recommended as it improves patient satisfaction and comfort and reduces time to discharge

Treatment Guidelines- ACOG, 2018

- Prompt treatment of N/V of pregnancy is important to prevent hyperemesis gravidarum
- First-line treatment of N/V of pregnancy consists of nonpharmacological options (e.g., assessing supplementation change options, ginger capsules, acupressure)
- For persistent symptoms, pharmacologic treatment with vitamin B6 (pyridoxine) or vitamin B6 plus doxylamine, including co-formulated products such as Diclegis or Bonjesta, are recommended
  - If symptoms continue to persist, other medications can be considered for off-label use, including dimenhydrinate, diphenhydramine, prochlorperazine, and promethazine
  - Should symptoms continue to persist, treatment options are based on hydration status and include the previously mentioned off-label options as well as the additional options of chlorpromazine, methylprednisolone, metoclopramide, ondansetron, and trimethobenzamide
- No single method has demonstrated superiority over another and that treatment options within each step are presented alphabetically rather than in any preference order
- Diclegis, a fixed-dose combination of the antihistamine doxylamine 10 mg plus pyridoxine 10 mg, is the first FDA-approved, pregnancy category A delayed-release combination medication for the treatment of N/V of pregnancy

Treatment Guidelines- AHA, 2018

- AHA updated the Scientific Statement on resistant hypertension (RH)
  - Defines RH as above-goal elevated blood pressure (BP) despite concurrent use of 3 antihypertensive drug classes at maximally tolerated doses or BP that requires ≥ 4 medications to achieve a target level
    - Hypertension is typically treated with a diuretic, a long-acting calcium channel blocker, and a renin-angiotensin system blocker (ACEI or ARB)
  - Similar to the 2017 ACC/AHA BP target of ≤ 130/80 mm Hg in patients on antihypertensive therapy
  - Diagnosis of RH should be made based on a 24-hour ambulatory BP measured after medication adherence has been confirmed
  - Recommended treatment for confirmed RH includes optimization of lifestyle interventions, use of a long-acting thiazide-like diuretic (e.g., chlorthalidone, indapamide), and addition of a mineralocorticoid receptor antagonist (e.g., spironolactone, eplerenone)
    - If BP remains above target levels, addition of agents with different mechanisms, and possibly referral to a hypertension specialist, are advised
    - RH assessment should consider lifestyle, drug-drug interactions, secondary hypertension, and presence of end organ damage

Treatment Guidelines

- American College of Cardiology (ACC) and American Heart Association (AHA), 2017
  - For the management of HF, routine combined use of an ACE inhibitor or angiotensin receptor blockers with a beta-blocker is recommended in all patients with reduced ejection fraction heart failure (HF*r*EF), unless contraindicated
  - Drugs with an indication for HF include many ACE inhibitors and some beta-blockers
  - ARBs that are indicated for HF when a patient is intolerant to an ACE inhibitor include candesartan (Atacand) and valsartan (Diovan)
  - In addition, for patients with HF*r*EF:
    - Diuretics are recommended if fluid retention is present
    - Aldosterone antagonists (spironolactone [Aldactone] and eplerenone [Inspra]) are recommended in patients who also have adequate renal function
    - Digoxin can be beneficial to decrease hospitalizations due to HF
    - The combination of hydralazine and isosorbide dinitrate is recommended in African Americans with HF*r*EF who are persistently symptomatic with the use of an ACE inhibitor and a beta-blocker
  - The ACC/AHA also recommends the use of ARBs in patients unable to tolerate an ACE inhibitor and in patients with HF following a non-ST-elevated myocardial infarction (NSTEMI) or ST-elevated myocardial infarction (STEMI)

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Any Genotype

Treatment Experience	Treatment	Duration (weeks)	Rating
Any Genotype - Simplified Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪glecaprevir/pibrentasvir ▪sofosbuvir/velpatasvir Patients **with compensated** cirrhosis: ▪glecaprevir/pibrentasvir ▪sofosbuvir/velpatasvir (all genotypes except GT 3 without Y93H present)	 8 12 8 12	
Any Genotype			
Treatment-Experienced (previous sofosbuvir/ velpatasvir/ voxilaprevir treatment failure)	Patients **with or without** compensated cirrhosis: ▪glecaprevir/pibrentasvir + sofosbuvir + weight-based-RBV ▪sofosbuvir/velpatasvir/voxilaprevir + weight-based RBV	 16 24	 Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous glecaprevir/ pibrentasvir treatment failure)	Patients **with or without** compensated cirrhosis: ▪glecaprevir/pibrentasvir + sofosbuvir + weight-based RBV ▪sofosbuvir/velpatasvir/voxilaprevir ▪sofosbuvir/velpatasvir/voxilaprevir + weight-based RBV (patients with compensated cirrhosis)	 16 12 12	 Class IIa, Level B Class IIa, Level B Class IIa, Level C

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 1

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1a – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ elbasvir/grazoprevir (without baseline NS5A RAVs)	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir (non-African American, HIV-uninfected, and HCV RNA level is < 6 million IU/mL)	8	Class I, Level B
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	Patients **with compensated** cirrhosis:		
	▪ elbasvir/grazoprevir (without baseline NS5A RAVs)	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level B
Treatment-Experienced (previous failure of PEG-IFN /RBV)	Patients **without** cirrhosis:		
	▪ elbasvir/grazoprevir (without baseline NS5A RAVs)	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	Patients **with compensated** cirrhosis:		
	▪ elbasvir/grazoprevir (without baseline NS5A RAVs)	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	12	Class I, Level B
Genotype 1a – Alternative Treatments			
Treatment-Experienced (previous failure of PEG-IFN /RBV)	Patients **with compensated** cirrhosis:		
	▪ ledipasvir/sofosbuvir + weight-based RBV	12	Class I, Level A

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 1 (Continued)

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1b – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir (non-African American, HIV-uninfected, and HCV RNA level is < 6 million IU/mL)	8	Class I, Level B
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	Patients **with compensated** cirrhosis:		
	▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level B
Treatment-Experienced (previous failure of PEG-IFN /RBV)	Patients **without** cirrhosis:		
	▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	Patients **with compensated** cirrhosis:		
	▪ elbasvir/grazoprevir	12	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	12	Class I, Level B
Genotype 1b – Alternative Treatments			
Treatment-Experienced (previous failure of PEG-IFN /RBV)	Patients **with compensated** cirrhosis:		
	▪ ledipasvir/sofosbuvir + weight-based RBV	12	Class I, Level A

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 1 (Continued)

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1 (regardless of subtype, unless noted) – Recommended Treatments			
Treatment-Experienced (previous failure of PEG-IFN / RBV + a HCV protease inhibitor [NS3], including telaprevir, boceprevir, or simeprevir)	Patients **without** cirrhosis: ▪ ledipasvir/sofosbuvir ▪ sofosbuvir/velpatasvir ▪ glecaprevir/pibrentasvir Patients **with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir ▪ glecaprevir/pibrentasvir	 12 12 12 12 12	 Class I, Level A Class I, Level A Class IIa, Level B Class I, Level A Class IIa, Level B
Treatment-Experienced (previous failure of non-NS5A inhibitor, sofosbuvir-containing regimen)	Patients **without cirrhosis or with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir/voxilaprevir (genotype 1a only) ▪ glecaprevir/pibrentasvir ▪ sofosbuvir/velpatasvir (genotype 1b only)	 12 12 12	 Class I, Level A Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous failure of any NS5A inhibitor excluding glecaprevir/pibrentasvir failure)	Patients **without cirrhosis or with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir/voxilaprevir	 12	 Class I, Level A

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 1 (Continued)

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 1 (regardless of subtype, unless noted) – Alternative Treatments			
Treatment-Experienced (previous failure of PEG-IFN / RBV + a HCV protease inhibitor [NS3], including telaprevir, boceprevir, or simeprevir)	Patients **without** cirrhosis: ▪ elbasvir/grazoprevir + weight-based RBV (genotype 1b or 1a without baseline NS5A RAVs) ▪ elbasvir/grazoprevir + weight-based RBV (genotype 1a with baseline NS5A RAVs) Patients **with compensated** cirrhosis: ▪ ledipasvir/sofosbuvir + weight-based RBV ▪ elbasvir/grazoprevir + weight-based RBV (genotype 1b or 1a without baseline NS5A RAVs) ▪ elbasvir/grazoprevir + weight-based RBV (genotype 1a with baseline NS5A RAVs)	12 16 12 12 16	Class IIa, Level B Class IIa, Level B Class I, Level A Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous failure of non-NS5A inhibitor, sofosbuvir-containing regimen)	Patients **without** cirrhosis: ▪ ledipasvir/sofosbuvir + weight-based RBV (excluding simeprevir failures)	12	Class IIa, Level B
Treatment-Experienced (previous failure of any NS5A inhibitor excluding glecaprevir/ pibrentasvir failures)	Patients **without or with compensated** cirrhosis: ▪ glecaprevir/pibrentasvir (excluding prior therapy with NS3/4 protease inhibitor inclusive combination regimens)	16	Class IIa, Level B

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 2

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 2 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪ glecaprevir/pibrentasvir ▪ sofosbuvir/velpatasvir Patients **with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir ▪ glecaprevir/pibrentasvir	 8 12 12 8	 Class I, Level A Class I, Level A Class I, Level A Class I, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without** cirrhosis: ▪ glecaprevir/pibrentasvir ▪ sofosbuvir/velpatasvir Patients **with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir ▪ glecaprevir/pibrentasvir	 8 12 12 12	 Class I, Level A Class I, Level A Class I, Level A Class I, Level B
Treatment-Experienced (previous failure of sofosbuvir + RBV)	Patients **without cirrhosis or with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir ▪ glecaprevir/pibrentasvir	 12 12	 Class I, Level B Class IIb, Level B
Treatment-Experienced (previous failure of sofosbuvir + NS5A inhibitor [excluding glecaprevir/ pibrentasvir failure])	Patients **without cirrhosis or with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir/voxilaprevir	 12	 Class I, Level B

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 3

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 3 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis: ▪ glecaprevir/pibrentasvir ▪ sofosbuvir/velpatasvir Patients **with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir (without Y93H present) ▪ glecaprevir/pibrentasvir	 8 12 12 8	 Class I, Level A Class I, Level A Class I, Level A Class I, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without** cirrhosis: ▪ sofosbuvir/velpatasvir (without Y93H present) Patients **with compensated** cirrhosis: ▪ glecaprevir/pibrentasvir ▪ sofosbuvir/velpatasvir/voxilaprevir	 12 16 12	 Class I, Level A Class IIa, Level B Class IIb, Level B
Treatment-Experienced (previous failure of sofosbuvir + ribavirin [± peginterferon])	Patients **without cirrhosis or with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir/voxilaprevir ▪ glecaprevir/pibrentasvir	 12 16	 Class I, Level B Class IIb, Level B
Treatment-Experienced (previous failure of DAAs, including NS5A inhibitors excluding glecaprevir/pibrentasvir failure)	Patients **without cirrhosis or with compensated** cirrhosis: ▪ sofosbuvir/velpatasvir/voxilaprevir ▪ sofosbuvir/velpatasvir/voxilaprevir + weight-based RBV (those with NS5A inhibitor failure and compensated cirrhosis)	 12 12	 Class I, Level A Class IIa, Level C

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 3

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 3 – Alternative Treatments			
Treatment-Naïve	Patients **with compensated** cirrhosis: ▪sofosbuvir/velpatasvir/voxilaprevir (when Y93H present) ▪sofosbuvir/velpatasvir ± weight-based RBV (when Y93H present)	 12 12	 Class IIa, Level B Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without** cirrhosis: ▪glecaprevir/pibrentasvir ▪sofosbuvir/velpatasvir/voxilaprevir (when Y93H present) Patients **with compensated** cirrhosis: ▪elbasvir/grazoprevir + sofosbuvir ▪sofosbuvir/velpatasvir + weight-based RBV	 16 12 12 12	 Class IIa, Level B Class IIb, Level B Class I, Level B Class I, Level B

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 3

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 4 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ ledipasvir/sofosbuvir	12	Class I, Level A
	▪ elbasvir/grazoprevir	12	Class I, Level B
	Patients **with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level B
	▪ elbasvir/grazoprevir	12	Class IIa, Level B
	▪ ledipasvir/sofosbuvir	12	Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without** cirrhosis:		
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ glecaprevir/pibrentasvir	8	Class I, Level B
	▪ elbasvir/grazoprevir (without on-treatment failure only)	12	Class IIa, Level B
	▪ ledipasvir/sofosbuvir	12	Class IIa, Level B
	Patients **with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir	12	Class I, Level A
	▪ elbasvir/grazoprevir (without on-treatment failure only)	12	Class IIa, Level B
	▪ glecaprevir/pibrentasvir	12	Class IIa, Level B
Treatment-Experienced (previous failure of DAAs, including NS5A inhibitors except glecaprevir/ pibrentasvir)	Patients **without or with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir/voxilaprevir	12	Class I, Level A
Genotype 4 – Alternative Treatments			
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **with compensated** cirrhosis		
	▪ ledipasvir/sofosbuvir + weight-based RBV	12	Class IIa, Level B

Guidelines – Hepatitis C Agents

- Summary of the AASLD/IDSA HCV Guidelines Recommendations
  - Genotype 3

Treatment Experience	Treatment	Duration (weeks)	Rating
Genotype 5/6 – Recommended Treatments			
Treatment-Naïve	Patients **without** cirrhosis:		
	▪ glecaprevir/pibrentasvir	8	Class I, Level A
	▪ sofosbuvir/velpatasvir	12	Class I, Level B
	▪ ledipasvir/sofosbuvir (not recommended for genotype 6c)	12	Class IIa, Level B
	Patients with compensated cirrhosis:		
	▪ glecaprevir/pibrentasvir	8	Class I, Level B
	▪ sofosbuvir/velpatasvir	12	Class I, Level B
	▪ ledipasvir/sofosbuvir (not recommended for genotype 6c)	12	Class IIa, Level B
Treatment-Experienced (previous failure of PEG-IFN/ RBV)	Patients **without** cirrhosis:		
	▪ glecaprevir/pibrentasvir	8	Class IIa, Level B
	▪ sofosbuvir/velpatasvir	12	Class IIa, Level B
	▪ ledipasvir/sofosbuvir	12	Class IIa, Level B
	Patients **with compensated** cirrhosis:		
	▪ glecaprevir/pibrentasvir	12	Class I, Level B
	▪ sofosbuvir/velpatasvir	12	Class IIa, Level B
	▪ ledipasvir/sofosbuvir	12	Class IIa, Level B
Treatment-Experienced (previous failure of DAAs, including NS5A inhibitors except glecaprevir/ pibrentasvir)	Patients **without or with compensated** cirrhosis:		
	▪ sofosbuvir/velpatasvir/voxilaprevir	12	Class IIa, Level B

Treatment Guidelines, European Society of Cardiology (ESC) and the European Respiratory Society (ERS), February 2016

- **At the time of diagnosis of PAH**, the **suggested initial approach is the adoption of general measures** (exercise training, psychosocial support, rehabilitation) **and the initiation of supportive therapy** (oral anticoagulation, diuretics, digoxin, and long-term oxygen therapy, if needed
- **Patients who are at low or intermediate risk for 1-year mortality can be treated with either initial monotherapy or initial oral combination therapy**
- **If initial monotherapy** is chosen, **no evidence-based first-line monotherapy can be proposed** because there are no head-to-head comparisons
- If **initial combination therapy** is chosen, **ambrisentan plus tadalafil has been given a higher grade recommendation** because the combination has proven to be superior to initial ambrisentan or tadalafil monotherapy in delaying clinical failure

Treatment Guidelines, European Society of Cardiology (ESC) and the European Respiratory Society (ERS), February 2016

Therapy	Recommendation	Strength of Recommendation
Initial monotherapy	WHO-FC II: ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), sildenafil (Revatio), tadalafil (Adcirca), riociguat (Adempas), and selexipag (Uptravi) WHO-FC III: ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, selexipag, IV epoprostenol (Flolan®/Veletri®), inhaled iloprost (Ventavis), SC or inhaled treprostinil (Remodulin®, Tyvaso) and oral or IV treprostinil (Orenitram, Remodulin) WHO-FC IV: IV epoprostenol (Level I, Grade A), ambrisentan, bosentan, macitentan, sildenafil, tadalafil, riociguat, inhaled iloprost, SC, IV or inhaled treprostinil	Level I, Grade A or B for all Level I, Grade A or B Level IIa or IIb, Grade B or C for treprostinil Level IIb, Grade C
Initial combination therapy	WHO-FC II: • Ambrisentan + tadalafil • Other endothelin receptor antagonist (ERA) + phosphodiesterase type 5 inhibitor (PDE-5i) WHO-FC III: • Ambrisentan + tadalafil • Other ERA + PDE-5i, bosentan + sildenafil + IV epoprostenol, bosentan + IV epoprostenol, other ERA or PDE-5i + SC treprostinil, other ERA or PDE-5i + other IV prostacyclin analogues WHO-FC IV: • Ambrisentan + tadalafil • Other ERA + PDE-5i, bosentan + sildenafil + IV epoprostenol, bosentan + IV epoprostenol, other ERA or PDE-5i + SC treprostinil, other ERA or PDE-5i + other IV prostacyclin analogues	Grade I, Level B Grades IIa, Grade C Grade I, Level B Grades IIa, or IIb Grade C Grades IIa, or IIb Grade C

American College of Chest Physicians (CHEST), 2014 (Updated 2018)

- At the time of diagnosis of PAH
  - The suggested **initial approach** is
    - **Treatment of contributing causes of PAH** (e.g., sleep apnea, systemic hypertension)
    - The **adoption of general measures** (supervised exercise activity, influenza and pneumonia vaccinations, and avoidance of pregnancy, high altitudes, and non-essential surgery)
    - The **initiation of supportive therapy** (oxygen therapy if needed to maintain oxygen saturations > 91%)
    - Palliative care

- Unless there is a contraindication, acute vasoreactivity testing should be performed at a facility with experience in performing and interpreting the test (UCBS)
  - **A trial of high dose oral calcium channel blockers (CCB), such as amlodipine, diltiazem, or nifedipine, is recommended in patients with a positive acute vasoreactive test**
  - Furthermore, **CCBs should not be used empirically to treat PAH** in the absence of demonstrated acute vasoreactivity (UCBS)
  - Patients should be followed closely for response and side effects of therapy. Alternative or additional PAH therapy should be initiated if improvement to WHO FC I or II are not seen after the trial of a CCB

American College of Chest Physicians (CHEST), 2014 (Updated 2018)

- In treatment-naive patients who are not candidates for, or who have failed CCB therapy, treatment is based on WHO functional class (UCBS)
  - In treatment-naïve patients with WHO FC I
    - Continued monitoring for disease progression is advised (UCBS)
  - **In treatment-naïve patients with WHO FC II**
    - **Initial combination therapy with ambrisentan and tadalafil to improve 6-minute walk distance (6MWD) is suggested (weak recommendation, moderate quality evidence)**
    - **In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, sildenafil (strong recommendations, low quality evidence for both), bosentan, macitentan, tadalafil, or riociguat (UCBS for all 4 products) is recommended**
  - **In treatment-naïve patients with WHO FC III without rapid disease progression or poor prognosis**
    - **Initial combination therapy with ambrisentan and tadalafil to improve 6MWD is suggested (weak recommendation, moderate quality evidence)**
    - **In patients who are unwilling to take or cannot tolerate combination therapy, then monotherapy with ambrisentan, bosentan, sildenafil (strong recommendations, low or moderate quality to improve 6MWD for all 3 products), macitentan, tadalafil, or riociguat (UCBS for all 3 products) is recommended**
  - For treatment-naïve patients with WHO FC IV
    - Initial therapy with a parenteral prostanoid agent is recommended (UCBS)
    - In patients who cannot comply with parenteral administration, inhaled prostanoid in combination with an oral endothelin receptor antagonist or an oral PDE-5 inhibitor are alternatives (UCBS)