Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Washington Drug Utilization Review (DUR) Board Meeting

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Agenda Topics

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

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Antibiotics:
- Aminoglycosides- Inhaled
- Monobactams- Inhaled

Respiratory Agents:
- Cystic Fibrosis Agents

Disease State Description - Cystic Fibrosis

- Cystic Fibrosis (CF) is a serious autosomal recessive multiorgan disorder
- Affects ~31,411 children and adults in the U.S. and is the most common fatal genetic disease in Caucasians
  - The median survival in patients with CF is 50 years with 80% of patients reaching adulthood
  - Children are anticipated to live to approximately 40 years of age with current treatments
  - In 2020, adults comprised approximately 57.2% of the CF population, while in 1990, they comprised approximately 32.1%
- Mutations lead to the disease of the exocrine gland function, resulting in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body
  - CF transmembrane conductance regulator (CFTR) functions as a chloride channel
  - Mutations in CFTR results in abnormalities of chloride transport across epithelial cells on mucosal surfaces
- Goals of CF treatment include:
  - Maintaining lung function by controlling infection and clearing mucus in the airway
  - Maintaining appropriate growth by providing nutritional support (e.g., enzyme, mineral, and multivitamin supplements)
  - Managing disease complications (e.g., insulin therapy in patients who develop diabetes)

Cystic Fibrosis Foundation, 2020

Guidelines - Cystic Fibrosis

- Goals of CF treatment include maintaining lung function by controlling infection and clearing mucus in the airway, maintaining appropriate growth by providing nutritional support (e.g., enzyme, mineral, and multivitamin supplements) and managing disease complications (e.g., insulin therapy in patients who develop diabetes)
- *CFTR* modulators (potentiators or correctors) are the newest class of medications available for this disease and improve chloride ion transport abnormalities

- Cystic Fibrosis Foundation, 2013
  - Inhaled treatments (e.g., tobramycin, dornase alfa, hypertonic saline, corticosteroids) and oral treatments (e.g., antibiotics, corticosteroids) for treatment of symptoms, exacerbations, and/or infections
  - Chronic treatment of ivacaftor for individuals 6 years of age and older with at lease one *G551d CFTR* mutation to improve lung function and quality of life and to reduce exacerbations

- Clinical Pharmacogenetics Implementation Consortium (CPIC), 2014
  - Recommend ivacaftor therapy based on *CFTR* genotype in CF patients ≥ 6 years old who are homozygous or heterozygous for the *G551D CFTR* variant
  - CPIC further states that there are no data regarding whether or not ivacaftor can replace other established therapy

- Please note: Orkambi, Symdeko, and Trikafta were not approved in 2013/2014 and were not addressed in either guideline

Updated Information - Cystic Fibrosis

- **lumacaftor/ivacaftor (Orkambi)**
  - **September 2022: FDA approved an expanded indication for Orkambi for the treatment of cystic fibrosis in patients ≥ 1 year of age who are homozygous for the F508del mutation in the CFTR gene; previously indicated for patients ≥ 2 years of age**
  - **Indication**
    - **Treatment of cystic fibrosis (CF) in patients age 1 year of age and older who are homozygous for the F508del mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene**
  - **Dosage**
    - **Pediatric patients 1 to 2 years of age:**
      - **7 to < 9 kg: 1 packet of lumacaftor 75 mg/ivacaftor 94 mg granules**
      - **9 to < 14 kg: 1 packet of lumacaftor 100 mg/ivacaftor 125 mg granules**
      - **≥ 14 kg: 1 packet of lumacaftor 150 mg/ivacaftor 188 mg granules**
    - Pediatric patients 2 to 5 years of age:
      - < 14 kg: 1 packet of lumacaftor 100 mg/ivacaftor 125 mg granules; ≥ 14 kg: 1 packet of lumacaftor 150 mg/ivacaftor 188 mg granules
    - Pediatric patients 6 to 11 years of age:
      - 2 tablets of lumacaftor 100 mg/ivacaftor 125 mg granules
    - Pediatric patients 12 years of age or older:
      - 2 tablets of lumacaftor 200 mg/ivacaftor 125 mg granules
  - **Availability**
    - Tablets: 100 mg/125 mg; 200 mg/125 mg
    - Oral granules: Unit-dose packets of lumacaftor 100 mg and ivacaftor 125 mg; lumacaftor 150 mg and ivacaftor 188 mg

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Anticoagulants:
- Factor Xa and Thrombin Inhibitors - Oral

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Antidiabetics:

- Amylin Analogs
- SGLT2 Inhibitors
- DPP4 Inhibitor
- DPP4 Inhibitor/ SGLT2 Inhibitor Combinations
- DPP4 Inhibitor/ TZD Combinations
- GLP1 Agonists
- GLP1 Agonist/ Insulin Combinations

Disease State Description - Diabetes Mellitus

- It is estimated that over 34 million Americans have diabetes mellitus (DM)
  - Of which, 90-95% have Type 2 Diabetes
  - Diabetes is responsible for increased morbidity and mortality
- Adequate glycemic control is crucial to minimize chronic microvascular (e.g., blindness, renal dysfunction) and macrovascular (e.g., cardiovascular disease [CVD]) complications
- Exogenous insulin supplements deficient levels of endogenous insulin, and temporarily restores the ability of the body to properly utilize carbohydrates, fats, and proteins
- Multiple insulin products are available and are used as replacement therapy in the management of both T1DM and T2DM when glycemic goals are not met with oral antidiabetic agents
- In addition to exogenous insulin, there are several pathways by which blood glucose may be regulated in diabetic patients
- The sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion

American Diabetes Association, 2020

Guidelines- Diabetes Mellitus

- American Gastroenterological Association (AGA), 2021
  - Estimates that up to 70% of individuals with T2DM have nonalcoholic fatty liver disease (NAFLD)
  - The AGA inform that GLP-1RAs, SGLT2 inhibitors, and pioglitazone can improve the cardiometabolic profile and reverse steatosis in patients with diabetes and NAFLD
  - They recommend an GLP-1RA or pioglitazone in patients with indeterminate or high risk clinically significant liver fibrosis
  - SLGT2 inhibitors appear to provide benefit in patients with nonalcoholic steatohepatitis (NASH) and associated comorbidities (e.g. congestive heart failure, CKD)
  - AGA advises to prescribe GLP-1RAs and SGLT2 inhibitors according to the ADA guidelines

Guidelines- Diabetes Mellitus

- American Diabetes Association (ADA), 2021
  - In 2021, the American Diabetes Association (ADA) Standards of Medical Care in Diabetes continued to include the sodium-glucose cotransporter 2 (SGLT2) inhibitors in the management algorithm for T2DM
  - The position statement recommends HbA1c < 7% as a reasonable target for most nonpregnant adult patients
  - **In patients using ambulatory glucose profile/glucose management indicator to assess glycemia, a parallel goal is a time in range of > 70% with time below range < 4%**
  - A more stringent HbA1c goal of < 6.5% may be considered for select patients (e.g., those with short duration of diabetes, long life expectancy, and no significant cardiovascular disease [CVD]) if this can be achieved without significant hypoglycemia
  - Less-stringent HbA1c goals (< 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with longstanding diabetes in whom the general goal is difficult to attain
  - **During pregnancy, the ADA recommends a target HbA1c of 6% to 6.5% is reasonable, but can be adjusted based on hypoglycemia risk; more frequent (e.g., monthly) HbA1c monitoring may be required**
  - **For diabetes technology, an automated insulin delivery system should be considered in adults with T1DM who have the skills to use the device in order to improve time in range and reduce A1C and hypoglycemia (A-rated recommendation)**
    - **These systems may also be useful to improve glycemia in children (B-rated recommendation)**
  - **Regarding obesity management, ADA states that lorcaserin should no longer be used, as the FDA requested its market withdrawal**
  - **For pharmacologic T2DM therapy, ADA advises to interrupt SGLT2 inhibitor therapy before scheduled surgery to avoid diabetic ketoacidosis, this aligns with label revisions for SGLT2 inhibitors**
  - **For management of CVD in patients with T2DM, ADA advises to consider an SGLT2 inhibitor in patients with HF with reduced ejection fraction to reduce risk of worsening HF and CV death**

Guidelines- Diabetes Mellitus

- The American Heart Association (AHA), 2022
  - Published a scientific statement on comprehensive management of CV risk factors for adults with T2DM
  - In terms of drug therapy, weight loss medications are discussed as adjuncts to diet, physical activity, and behavioral therapy for certain patients with T2DM and BMI ≥ 27 kg/m^2
  - FDA-approved drugs for weight management with CV safety and A1c lowering include orlistat, lorcaserin, liraglutide, naltrexone/bupropion sustained release, and phentermine/topiramate
  - Although long-term CV event reduction has not been evaluated, notable CV risk reduction has been demonstrated for liraglutide at lower doses in pts with ASCVD or high CV risk
  - Additionally, once weekly semaglutide 2.5 mg has also shown weight loss and CV risk factor improvement; it is FDA-approved for chronic weight management in adults with a BMI ≥30 kg/m^2 or BMI ≥ 25 kg/m^2 with a comorbid condition
  - The CV outcome trial data for newer antihyperglycemics agents is also reviewed; selection of diabetes agent should be individualized based on patients' risk and preference
  - BP management, lipid-lowering therapies, and antithrombotic therapy are also addressed

Guidelines- Diabetes Mellitus

- The American Heart Association (AHA) and American College of Cardiology (ACC), 2022
  - In 2022, the AHA and ACC, along with the Heart Failure Society of America (HFSA) published guidelines for the management of HF that includes SGLT2 inhibitors as a new treatment strategy in HF
  - The agencies recommend treatment with SGLT2 inhibitors in patients with T2DM and HF for hyperglycemia management
  - These agents are also recommended in patients with T2DM and established CVD or at high CV risk to prevent HF hospitalization
  - While the mechanism is not clearly understood, the HF benefit that SGLT2 inhibitors provide appears to be independent of glucose lowering
  - Notably, SGLT2 inhibitors are recommended to reduce hospitalization for HF and CV mortality in patients with symptomatic chronic HFrEF, regardless of the presence of T2DM.

Updated Information - SGLT2 Inhibitors

- **empagliflozin (Jardiance)**
  - **February 2022: The FDA has expanded the indication for empagliflozin to reduce the risk of CV death and hospitalization for HF in adults with HF. Previously, the indication was to reduce the risk of CV death plus hospitalization for HF in adults with HF and reduced ejection fraction**
  - **Indications**
    - **To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure**
    - To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease
    - As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
    - Limitations of Use: Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients; Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2
  - **Precautions**
    - Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters
    - Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Serious, life-threatening cases have occurred in patients with diabetes, both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise
    - Volume depletion: Before initiating, assess volume status and renal function in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics
  - **Dosing**
    - The recommended dose is 10 mg once daily in the morning, taken with or without food
    - For additional glycemic control, dose may be increased to 25 mg in patients tolerating medication
  - **Formulations**
    - Tablets: 10 and 25 mg

Updated Information - Glucagon-like-Peptide 1 (GLP-1)

- **semaglutide (Ozempic)**
  - **April 2022: Package Insert updated to add a 3rd maintenance dose of Ozempic (2 mg SC once weekly) (2.68 mg/mL concentration); previously, the maximum recommended dosage was 1 mg once weekly. However, now, if additional glycemic control is needed after ≥ 4 weeks on the 1 mg dosage, the dosage may be increased to 2 mg once weekly and the updated maximum recommended dosage is 2 mg once weekly.**
  - **April 2022: Along with the new dosage regimen the FDA-approved a new strength, 8 mg/3 mL (2.68 mg/mL) in a new single-patient-use pen that delivers 2 mg per injection**
  - **Indications**
    - An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease
  - **Precautions**
    - BBW: Thyroid C-cell tumors
    - BBW: Contraindicated in patients with personal of family history of Multiple Endocrine Neoplasia
    - Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated
  - **Dosing**
    - **Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly**
    - **If additional glycemic control is needed, increase the dose to 1 mg once weekly after at least 4 weeks on the 0.5 mg dose**
    - **If additional glycemic control is needed, increase the dose to 2 mg once weekly after at least 4 weeks on the 1 mg dose**
  - **Formulations**
    - Injection: 2 mg/1.5 mL (1.34 mg/mL) available in: Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection
    - Injection: 4 mg/3 mL (1.34 mg/mL) available in: Single-patient-use pen that delivers 1 mg per injection
    - **Injection: 8 mg/3 mL (2.68 mg/mL) available in: Single-patient-use pen that delivers 2 mg per injection**

Updated Information - Glucagon-like-Peptide 1 (GLP-1)

- **tirzepatide (Mounjaro)**
  - **May 2022: FDA approved Mounjaro, a glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM; limitations of use include that it has not been studied in patients with a history of pancreatitis and is not indicated for use in patients with T1DM**
  - **Indications**
    - **As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus**
    - **Limitations of Use: Has not been studied in patients with a history of pancreatitis; Is not indicated for use in patients with type 1 diabetes mellitus**
  - **Precautions**
    - **BBW: Thyroid C-cell tumors**
    - **BBW: Contraindicated in patients with personal of family history of Multiple Endocrine Neoplasia**
    - **Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated**
  - **Dosing**
    - **The recommended starting dosage is 2.5 mg injected subcutaneously once weekly**
    - **After 4 weeks, increase to 5 mg injected subcutaneously once weekly**
    - **If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose**
    - **The maximum dosage is 15 mg subcutaneously once weekly**
  - **Formulations**
    - **Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen**

Updated Information - Glucagon-like-Peptide 1 (GLP-1)

- **dulaglutide (Trulicity)**
  - **November 2022: FDA approved as adjunct to diet and exercise to improve glycemic control in patients ≥ 10 years of age with T2DM; previously approved in adults for this indication**
  - **December 2022: FDA is reporting potential intermittent periods of backorder for Trulicity 3 mg/0.5 mL and 4.5 mg/0.5 mL pens due to increased demand for the drug. Delays in full shipments may occur until early Jan 2023. Trulicity 0.75 mg/0.5 mL and 1.5 mg/0.5 mL pens are available**
  - **Indications**
    - **As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus**
    - To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors
  - **Precautions**
    - BBW: Thyroid C-cell tumors
    - BBW: Contraindicated in patients with personal of family history of Multiple Endocrine Neoplasia
  - **Dosing**
    - **Pediatric Dosage: Recommended starting dosage is 0.75 mg injected subcutaneously once weekly**
    - Adult Dosage: Found in TCR/PI
  - **Formulations**
    - Injection: 0.75 mg/0.5 mL solution in a single-dose pen
    - Injection: 1.5 mg/0.5 mL solution in a single-dose pen
    - Injection: 3 mg/0.5 mL solution in a single-dose pen
    - Injection: 4.5 mg/0.5 mL solution in a single-dose pen

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Insulins:

- ANTIDIABETICS : INSULIN - INTERMEDIATE ACTING
- ANTIDIABETICS : INSULIN - LONG ACTING
- ANTIDIABETICS : INSULIN - PRE-MIXED
- ANTIDIABETICS : INSULIN - RAPID ACTING
- ANTIDIABETICS : INSULIN - SHORT ACTING

Updated Information - Insulins

- **insulin glargine-aglr (Rezvoglar)**
  - **December 2021: The FDA has approved the 2nd biosimilar insulin product to Lantus (insulin glargine), insulin glargine-aglr (Rezvoglar). It is a long-acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 DM and in adults with type 2 DM**
  - **Indications**
    - **To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus**
    - **Limitations of use: Not recommended for treating diabetic ketoacidosis**
  - **Precautions**
    - **Hyperglycemia or hypoglycemia with changes in insulin regimen: Make changes to a patient's insulin regimen (e.g., insulin strength, manufacturer, type, injection site or method of administration) under close medical supervision with increased frequency of blood glucose monitoring**
    - **Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk of hypokalemia and treat if indicated**
    - **Fluid retention and heart failure with concomitant use of thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation of TZD if heart failure occurs**
  - **Dosing**
    - **Individualize dosage based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, prior insulin use**
  - **Formulations**
    - **Injection: 100 units/mL (U-100) available as:**
      - **3 mL single-patient-use prefilled pen**

Updated Information - Insulins

- **Discontinuations**
  - **insulin lispro(Humalog Mix 50/50)- July 2022**
    - **Eli Lilly has decided to discontinue manufacturing of the Humalog Mix 50/50 (10 mL vial)**
    - **The 10 mL vial will continue to be available until August 2023**
    - **Humalog Mix 50/50 will continue to be available in 3 mL prefilled pens (Kwikpen)**

- **Recalls**
  - **insulin glargine-yfgn (Semglee)**
    - **January 2022: Mylan is voluntarily recalling 1 batch of its non-interchangeable Semglee (insulin glargine injection), 100 units/ml (U-100), 3 mL prefilled pens, packaged in a labeled carton of 5 pens due to the potential for the label to be missing on some prefilled pens within the labeled carton for this batch. Notably, it is not the branded Semglee vial but the unbranded Insulin Glargine-yfgn vial**
    - **April 2022: Mylan issued voluntary recall of 1 batch (NDC: 49502-393-80; Batch: BF21002800; Exp: Aug 2023) of Insulin glargine-yfgn Injection, 100 units/mL (U-100), packaged in a 10 mL vial that is inside a carton due to the potential for the label to be missing on some vials. Notably, it is not the branded Semglee vial but the unbranded Insulin Glargine-yfgn vial**
    - **July 2022: Mylan is voluntarily recalling 1 batch (NDC 49502-0394-75; BF21002895; Exp. 8/2023) of unbranded insulin glargine-yfgn 3 ml prefilled pens due to the potential for the label to be missing on some pens. This is a wholesaler, retailer, and consumer level recall. No adverse events related to the recall have been reported**

Updated Information - Insulins

- **insulin lispro-aabc (Lyumjev)**
  - **October 2022: FDA has approved an expanded indication to improve glycemic control in diabetes mellitus has been expanded to include pediatric patients. Lyumjev may be administered by SC injection, continuous SC infusion, or IV infusion**
  - **Indications**
    - To improve glycemic control in adult and **pediatric patients** with diabetes mellitus
  - **Precautions**
    - Hypokalemia: May be life-threatening. Monitor potassium levels in patients at risk for hypokalemia and treat if indicated
    - Fluid retention and heart failure with concomitant use of thiazolidinediones (TZDs): Observe for signs and symptoms of heart failure; consider dosage reduction or discontinuation of TZD if heart failure occurs
  - **Dosing**
    - Individualize and adjust the dosage based on the patient's metabolic needs, glucose monitoring results, and glycemic control goal
  - **Formulations**
    - Injection: 100 units/mL (U-100) available as:
      - 10 mL multiple-dose vial
      - 3 mL single-patient-use KwikPen
      - 3 mL single-patient-use Junior KwikPen
      - 3 mL single-patient-use Tempo Pen
      - 3 mL single-patient-use cartridges
    - Injection: 200 units/mL (U-200) available as:
      - 3 mL single-patient-use KwikPen

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Antiparkinson’s Agents:

- ANTIPARKINSON AGENTS : ADENOSINE RECEPTOR ANTAGONISTS
- ANTIPARKINSON AGENTS : DOPAMINERGICS
- ANTIPARKINSON AGENTS : MONOAMINE OXIDASE INHIBITORS (MAOI)

Disease State Description - Antiparkinson's Agents

- **Parkinson's disease (PD)**
  - A progressive, neurodegenerative disorder with cardinal motor features of tremor, bradykinesia, and rigidity
  - This disease affects approximately 1% of individuals older than 60 years and the incidence increases significantly with age
  - The term "parkinsonism" describes the motor syndrome of bradykinesia, rigidity, tremor, and balance and gait disturbances
  - Secondary parkinsonism, which has a different etiology and pathology than PD, is the predominant clinical manifestation of a number of disorders, including brain tumors near the basal ganglia, cerebral atherosclerosis, head trauma, and progressive supranuclear palsy
  - Secondary parkinsonism can also be caused by toxins and drugs, especially antipsychotic agents
  - Despite advances in treatments over the years, there is no cure for PD
    - Symptomatic therapy can provide benefit for quite some time, but the continued, however slow, progression of PD eventually results in significant disability
    - Patients may not require treatment in the early stages of PD if symptoms do not cause functional impairment
    - As the disease progresses, however, therapy becomes more complex, requiring dosage adjustments, incorporation of multiple medications, and the use of rescue treatments

Disease State Description - Antiparkinson's Agents

- **Restless Leg Syndrome**
  - A neurological sensory disorder in which patients experience irrepressible sensations in the legs or arms while sitting or lying still to cause them to move their arm or legs
  - Providers will need to rule out other movement disorders with similar symptoms to RLS, such as periodic limb movement disorder (PLMD), antipsychotic drug adverse effects, and dyskinesis, to correctly diagnose and treat these symptoms
  - Studies suggest that RLS is associated with the dopamine system and depletion of iron stores
  - Historically, RLS has been treated with opioids, benzodiazepines, anticonvulsants (including the immediate-release formulation of gabapentin), iron replacement (in patients with low serum ferritin levels), and dopaminergic agents (e.g., carbidopa/levodopa)
  - Prior to 2000, levodopa was the dopaminergic agent most studied for RLS
  - Pramipexole (Mirapex), ropinirole (Requip), and rotigotine (Neupro) are approved for an indication of RLS and there has been increased focus on the use of dopamine agonists in the treatment of this disorder
  - Gabapentin enacarbil (Horizant) is also FDA-approved for RLS

Guidelines - Antiparkinson's Agents

- **American Academy of Neurology (AAN), 2021**
  - The guideline updates state that treatment with levodopa provides superior benefit at reducing motor symptoms when compared to treatment with either dopamine agonists or MAO-B inhibitors
  - While incidence is low, levodopa is more likely than other agents to cause dyskinesia in the first 5 years of therapy
  - Discontinuation rates are lower with levodopa than dopamine agonists and MAO-B inhibitors
  - Immediate-release levodopa is preferred over controlled-release levodopa or levodopa/carbidopa/entacapone for early PD
  - Guidelines for the treatment initiation for Parkinson disease is under development

Updated Information - Antiparkinson's Agents

- **New Generic**
  - **Apomorphine hydrochloride- February 2022**
    - **First new generic (drug cartridges only) of MDD Pharma's Apokyn (apomorphine hydrochloride) from Sage Chemical**
    - **The ANDA approval is for the drug cartridges only; these are compatible with the Apokyn Pen (brand-name pen injector)**

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Sedative Hypnotics:

- SLEEP DISORDER AGENTS : SELECTIVE MELATONIN RECEPTOR AGONISTS
- SLEEP DISORDER AGENTS : TRICYCLIC AGENTS
- SLEEP DISORDER AGENTS : NON-BENZODIAZEPINE

Disease State Description - Sedative Hypnotics

- **Insomnia**
  - A complex symptom that comprises difficulties falling asleep, staying asleep, or non-refreshing sleep in combination with daytime dysfunction or distress
  - The symptom complex can be an independent disorder (primary insomnia) or the result of another condition (secondary insomnia)
  - Insomnia is commonly divided into 3 types based on duration
    - Transient insomnia lasts up to 1 week and is often referred to as adjustment sleep disorder because it is caused most often by an acute situational stress, such as a test or deadline
      - It is often recurrent with the same or similar stresses
    - The second type, short-term insomnia, by definition lasts 1 to 6 months and is usually associated with more persistent stressful situational (death or illness) or environmental (noise) factors
    - Finally, chronic insomnia is insomnia lasting more than 6 months
  - Children
    - The incidence of insomnia in children ranges from 1% to 6%
      - In children with neurodevelopmental or psychiatric comorbidities, the incidence is as high as 50% to 75%
    - Insomnia in children may result in irritability, restlessness, lack of concentration, suicide risk, and poor memory

Neurotherapeutics, 2012
Developmental Psychology, 2000

Updated Information - Sedative Hypnotics

- **daridorexant (Quviviq)**
  - **January 2022: FDA approved Quviviq, an orexin receptor antagonist indicated for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance**
  - **Indication**
    - **The treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance**
  - **Limitation**
    - **CNS Depressant Effects and Daytime Impairment: Impairs alertness and motor coordination including morning impairment. Risk increases when used with other central nervous system (CNS) depressants. For patients taking QUVIVIQ, caution against next-day driving and other activities requiring complete mental alertness**
    - **Sleep Paralysis, Hypnogogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms: May occur with use of Quviviq**
    - **Complex Sleep Behaviors: Behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur. Discontinue immediately if a complex sleep behavior occurs**
    - **Compromised Respiratory Function: Effect on respiratory function should be considered**
  - **Dosage**
    - **The recommended dosage is 25 mg to 50 mg once per night, taken orally within 30 minutes before going to bed, with at least 7 hours remaining prior to planned awakening**
  - **Availability**
    - **Tablets: 25 mg, 50 mg**

Updated Information - Sedative Hypnotics

- **Discontinuation**
  - **zolpidem tartrate (Zolpimist) – June 2022**
    - **Atyu BioPharma will be discontinuing Zolpimist 5 mg oral spray**
    - **Product is anticipated to be available until December 31, 2022**
    - **There are no available generics**

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Spinal Muscular Atrophy

- NEUROMUSCULAR AGENTS : SPINAL MUSCULAR ATROPHY - GENE THERAPY AGENTS
- NEUROMUSCULAR AGENTS : SPINAL MUSCULAR ATROPHY AGENTS - ANTISENSE OLIGONUCLEOTIDES

Disease State Description - Spinal Muscular Atrophy

- **Spinal Muscular Atrophy (SMA)**
  - A rare, debilitating neuromuscular disease characterized by motor neuron degeneration, muscle weakness, and atrophy
    - The disease mainly affects the motor neurons in the spinal cord
    - It is not believed to impact a person's capacity to think, learn, and build interpersonal relationships
  - It is the leading monogenic cause of infant mortality and is the second most common autosomal-recessive inherited disorder, with an incidence ranging from 4 to 10 per 100,000 live births
    - It is more common in males than females, particularly with the early onset forms
  - Patients experience motor function decline with disease progression, and morbidity and mortality rates are inversely correlated with the age of onset
    - Mortality due to SMA is most commonly related to respiratory infections and complications
  - Genetic testing is used to establish diagnosis in patients with suspected SMA based on symptoms, and universal newborn screening for SMA is part of the federal Recommended Uniform Screening Panel (RUSP)
    - Clinical classification is typically based on age of onset and maximum motor function achieved

SMA Type	Age of Symptom Onset	Highest Motor Function Achieved	Life Expectancy
Type 0	At birth/prenatal	None	< 6 months
Type 1 (Werdnig-Hoffman disease)	0 to 6 months	Sits with support only	< 2 years (without respiratory support)
Type 2 (Dubowitz disease)	6 to 18 months	Independent sitting	> 2 years (≈70% are alive at age 25 years)
Type 3 (Kugelberg-Welander disease)	> 18 months	Independent ambulation	Normal
Type 4	Late onset (typically third decade of life)	Normal	Normal

Updated Information - Spinal Muscular Atrophy

- **risdiplam (Evrysdi)**
  - **June 2022: FDA approved expanded use to include patients < 2 months of age for the treatment of spinal muscular atrophy (SMA)**
  - **Indications**
    - **A survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients**
  - **Warnings/Precautions**
    - Pregnancy: Based on animal data, may cause fetal harm
    - Avoid coadministration with drugs that are substrates of multidrug and toxin extrusion (MATE) transporters
  - **Dosage**
    - **< 2 months of age: 0.15 mg/kg**
    - 2 months to < 2 years of age: 0.2 mg/kg
    - 2 years of age and older weighing < 20 kg: 0.25 mg/kg
    - 2 years of age and older weighing ≥ 20 kg: 5 mg
  - **Availability**
    - For Oral Solution: 60 mg of risdiplam as a powder for constitution to provide 0.75 mg/mL solution

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Bone Resorption Suppression and Related Agents

- BONE DENSITY REGULATORS: SCLEROSTIN INHIBITORS

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Antidepressants, Other

- ANTIDEPRESSANTS : GABA RECEPTOR MODULATOR - NEUROACTIVE STEROID

Disease State Description - Antidepressants

- Prevalence of 12-month and lifetime MDD is approximately 21 million American adults or 8.4% of the U.S. population
  - Women experience depression more often than men
  - In addition, the prevalence of depression in 2020 was estimated at 4.1 million adolescents (ages 12 to 17 years)
  - With appropriate treatment, 70% to 80% of patients experiencing MDD achieve response
  - However, as many as one-half of all patients do not experience sufficient symptom improvement with initial treatment
- Among patients who remit, residual symptoms are common and associated with impaired psychosocial functioning and increased relapse rates
- Until recently, known differences among antidepressant drugs were generally limited to safety and tolerability issues
  - However, over the past handful of years, a number of studies have emerged to evaluate possible differences among antidepressant classes in their ability to resolve specific symptoms of depression
- Each of the groups of drugs in this class has a potential role in the treatment of MDD, primarily as a result of their heterogeneous spectrums of activity
  - As with many psychotropic drugs, patients failing to respond to 1 type of antidepressant may respond to a switch to, or augmentation with, an antidepressant with another mechanism of action

National Institute of Mental Health, 2020

Updated Information - Antidepressants

- **brexanolone (Zulresso)**
  - **June 2022: The FDA approved an expanded indication for postpartum depression to include patients ≥ 15 years of age**
  - **Indication**
    - **A neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in patients 15 years and older**
  - **Warnings**
    - BBW: Patients are at risk of excessive sedation or sudden loss of consciousness during administration of Zulresso
    - Pregnancy: May cause fetal harm
    - Avoid use in patients with end stage renal disease (ESRD)
  - **Dosage**
    - Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:
      - 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
      - 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
      - 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)
      - 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
      - 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour
    - Dilution required prior to administration
  - **Availability**
    - Injection: 100 mg/20 mL (5 mg/mL) single-dose vial

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Leukotriene Modifiers

- ASTHMA AND COPD AGENTS : LEUKOTRIENE MODIFIERS

Appendices

Treatment Guidelines - Anticoagulants

American College of Chest Physicians (ACCP), 2018

- Guidelines suggest no antithrombotic therapy
  - In patients with AF without valvular heart disease, including those with paroxysmal AF, who are at low risk for stroke (CHA2DS2VASc ≥ 0 in males or ≥ 1 in females)
- Guidelines recommend oral anticoagulation therapy
  - Patients with AF, including those with paroxysmal AF, without valvular heart disease who have 1 non-sex CHA2DS2VASc stroke risk factor are suggested to receive oral anticoagulation while patients considered at high risk of stroke (e.g., CHA2DS2VASc ≥ 2 in males or ≥ 3 in females)
- Where oral anticoagulation is recommended or suggested, ACCP suggests using a novel oral anticoagulant (NOAC) rather than adjusted-dose vitamin K antagonist therapy

AHA/ACC/HRS Guidelines, 2019 Update

- All NOACs are now preferred over warfarin in NOAC-eligible patients with AF; exceptions to this are patients with moderate-to-severe mitral stenosis or a mechanical heart valve
  - In NOAC-eligible patients, NOACs were shown to be at least noninferior to warfarin in preventing stroke and systemic embolism and have a lower risk of bleeding
  - Apixaban is preferred in patients with end-stage renal disease or on dialysis while the other NOACs are not recommended in this population due to lack of evidence
  - Edoxaban is now included in the guidelines as an option for stroke prevention
  - The anticoagulant reversal agents idarucizumab (Praxbind) and andexanet alfa (Andexxa) are recommended in the event of life-threatening bleeding or an urgent procedure

Guidelines- Diabetes Mellitus

- American Diabetes Association (ADA), 2020
  - For diabetes technology, an automated insulin delivery system should be considered in adults with T1DM who have the skills to use the device in order to improve time in range and reduce A1C and hypoglycemia (A-rated recommendation)
    - These systems may also be useful to improve glycemia in children (B-rated recommendation)
  - Regarding obesity management, ADA states that lorcaserin should no longer be used, as the FDA requested its market withdrawal
  - For pharmacologic T2DM therapy, ADA advises to interrupt SGLT2 inhibitor therapy before scheduled surgery to avoid diabetic ketoacidosis, this aligns with label revisions for SGLT2 inhibitors
  - For management of CVD in patients with T2DM, ADA advises to consider an SGLT2 inhibitor in patients with Heart Failure (HF) with reduced ejection fraction to reduce risk of worsening HF and CV death

Guidelines- Diabetes Mellitus

- American College of Cardiology, 2020
  - The ACC published an expert consensus decision pathway for CV risk reduction in patients with T2DM
  - They identify opportunities to initiate an SGLT2 inhibitor or GLP-1RA with demonstrated CV or renal benefit in patients with T2DM
    - A medication from either class may be initiated in any patient with T2DM and ASCVD at the time of diagnosis of T2DM or ASCVD or any time after diagnosis, including at hospital discharge for ASCVD
    - An agent from either class can also be started in patients with T2DM without established ASCVD but who are at high risk of ASCVD
  - In addition, initiation of an SGLT2 inhibitor with demonstrated CV or renal benefit is recommended in patients with Heart Failure and/or diabetic kidney disease
  - A GLP-1RA is an alternative in patients with eGFR < 30 ml/min/1.73 m^2

- Kidney Disease: Improving Global Outcomes (KDIGO), 2020
  - Published its first guidelines on managing diabetes in patients with chronic kidney disease (CKD)
  - Key recommendations include:
    - Patients with diabetes, hypertension, and albuminuria should start treatment with an ACEI or ARB
    - Monitor glycemic control using HbA1c in patients with diabetes and CKD
      - Target HbA1c range from < 6.5% to < 8% in those not on dialysis depending on hypoglycemia risk
    - Metformin and a SGLT2 inhibitor are recommended in patients with eGFR ≥ 30 mL/min/1.7 m2
      - If glycemic targets are not met, then a long-acting GLP-1 agonist is recommended

Guidelines- Diabetes Mellitus

- Kidney Disease Improving Global Outcomes (KDIGO), 2020
  - Guidelines on managing diabetes in CKD
  - Recommend an individualized HbA1c target from < 6.5% to < 8% in diabetic patients with CKD, based on CKD severity, macrovascular complications, comorbidities, life expectancy, hypoglycemia awareness and management resources, and hypoglycemic risk of medication
  - In addition to lifestyle therapy, KDIGO recommends first-line treatment with metformin and an SGLT2 inhibitor in most patients with an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m2
  - A GLP-1RA (generally preferred), DPP-4 inhibitor, insulin, SU, TZD, and/or AGI may be added as needed for glycemic control
  - These additions are guided by patient preference, comorbidities, eGFR, and cost. They advise against use of a GLP-1RA with a DPP-4 inhibitor

- The American College of Cardiology (ACC), 2020
  - Published an expert consensus decision pathway for CV risk reduction in patients with T2DM
  - They identify opportunities to initiate an SGLT2 inhibitor or GLP-1RA with demonstrated CV or renal benefit in patients with T2DM
  - A medication from either class may be initiated in any patient with T2DM and ASCVD at the time of diagnosis of T2DM or ASCVD or any time after diagnosis, including at hospital discharge for ASCVD
  - An agent from either class can also be started in patients with T2DM without established ASCVD but who are at high risk of ASCVD
  - In addition, initiation of an SGLT2 inhibitor with demonstrated CV or renal benefit is recommended in patients with HF and/or diabetic kidney disease; a GLP-1RA is an alternative in patients with eGFR < 30 ml/min/1.73 m2

Guidelines - Sedative Hypnotics

- US Department of Veterans Affairs (VA) and Department of Defense (DoD), 2020
  - Published guidelines on management of patients with chronic insomnia disorder and obstructive sleep apnea (OSA) that provides three 1-page algorithms, and 41 recommendations around diagnosis and assessment of OSA and chronic insomnia disorder
  - Obstructive Sleep Apnea
    - Positive airway pressure (PAP) is recommended as well as caution or avoidance of opioids and sedative hypnotics
  - Chronic insomnia
    - Cognitive behavioral therapy is recommended first-line
    - Weak recommendations are given for low-dose doxepin, or zolpidem, zaleplon, and eszopiclone (at the lowest effective dose for the shortest possible duration)
    - There is insufficient evidence to recommend for/against ramelteon or suvorexant
    - Recommend against use of herbal supplements, antipsychotics, benzodiazepines, and diphenhydramine

Disease State Description & Guidelines - Sedative Hypnotics

- Non-24-hour sleep-wake disorder (N24SWD or non-24)
  - A chronic circadian rhythm disorder that causes problems with the timing of sleep and sleep patterns
  - It occurs in approximately 55% to 70% of people who are completely blind, but can also be experienced in sighted people; prevalence among people with sight is unknown
  - States that the condition is characterized by the failure of a person's biological clock to synchronize to a 24-hour day light-dark cycle
  - In people who are completely blind (e.g., have no perception of light), this is due to their eyes inability to register light signals
  - In sighted people N24SWD may be due to a number of factors, such as altered sensitivity of light on circadian rhythm; self-selected changes in light exposure late in the day; and hormonal factors
  - Those with the disorder may have difficulty falling or staying asleep, and may wake up feeling as if they need more rest
  - People with N24SWD may find their sleep patterns reversed (e.g., needing to sleep during the day and to be awake at night)
  - N24SWD onset most often occurs in late teen or early twenties but can occur at any age and appears to be a life-long effect

National Organization for Rare Disorders (NORD), 2017

- The American Academy of Sleep Medicine (AASM), 2017
  - In 2015, the AASM updated their guidelines for the treatment of intrinsic circadian rhythm sleep-wake disorders, which includes N24SWD
  - They endorse strategically-timed melatonin or light therapy for select patients with Circadian Rhythm Sleep-Wake Disorders (CRSWD), including N24SWD
  - The AASM Task Force also strongly recommends avoiding the use of sleep-promoting medications to treat elderly patients with dementia and Irregular Sleep-Wake Rhythm Disorder (ISWRD)
  - Tasimelteon (Hetlioz), FDA approved in October 2014 to treat N24SWD, was not addressed in the guidelines

Guidelines - Sedative Hypnotics

- The American Academy of Sleep Medicine (AASM), 2017
  - Treatment for insomnia should first consist of identification and treatment and/or control of secondary sources
    - Whenever possible, non-pharmacological measures should be used to treat insomnia
    - When such measures fail to address the condition, use of pharmacologic hypnotics may be necessary
    - Recommend psychological and behavioral strategies, which are effective in both primary and secondary insomnia, as are pharmacological interventions
      - Initial behavioral interventions should include stimulus control therapy or relaxation therapy, or a combination of therapies referred to as cognitive behavioral therapy for insomnia (CBT-I) and should always include good sleep hygiene
      - Cognitive behavioral therapy for insomnia includes traditional cognitive behavioral therapy (CBT), stimulus control, and sleep restriction therapy (with or without relaxation therapy)
    - Additionally, the AASM guideline recommends that pharmacotherapy should be used to treat patients who failed to respond to CBT (Grade: weak recommendation, low-quality evidence)
      - Recommends zaleplon, triazolam, and ramelteon versus no treatment for sleep onset insomnia (weak recommendations), suvorexant and doxepin over no treatment for sleep maintenance insomnia (weak recommendations), and eszopiclone, zolpidem, and temazepam for both sleep onset and sleep maintenance insomnia
      - Recommend against the use of trazodone or tiagabine for sleep onset or sleep maintenance insomnia in adults (Grade: weak recommendation, low-quality evidence)
      - AASM recommends against the use of over-the-counter (OTC) medications or supplements (e.g., diphenhydramine, tryptophan, melatonin) or herbal products (e.g., valerian) as a treatment for sleep onset and sleep maintenance for chronic insomnia (Grade: weak recommendation, low-quality evidence)
      - Choice of agent should be based on symptom pattern, treatment goals, past treatment response, patient preference, cost, availability of other treatments options, comorbid conditions, contraindications, potential interaction with concurrent medication, and side effects

Spinal Muscular Atrophy - Guidelines

- **International SMA Care Group, 2018**
  - Regarding targeted therapy directed at the disease itself, only nusinersen (Spinraza) is specifically addressed in the guidelines, while the concept of vector-based gene therapy is briefly mentioned
  - Spinraza was not available at the time of guideline development
  - The group states that the early clinical outcomes data are promising, but Spinraza is limited clinically by its intrathecal administration, post-administration monitoring, and other practical considerations

- **American Academy of Neurology (AAN), 2018**
  - Published an Evidence in Focus document regarding Spinraza for SMA
  - The group determined there was Class III evidence to support that Spinraza improved ventilation-free survival at 24 months in infants with homozygous deletions or mutations of SMN1
  - There is Class I evidence that it improves motor milestone response and event-free survival in patients who initiate treatment at < 7 months of age
  - Further, in children ages 2 to 12 years of age with symptom onset after 6 months, it improved motor function at 15 months
  - Overall, they determined Spinraza was well-tolerated

Disease State Description - Antidepressants

Panic Disorder

- Panic disorder is a severe, chronic anxiety disorder characterized by recurrent episodes of panic and the development of fear or anxiety regarding the possibility of future panic attacks
- Incidence range between 3 to 6 million people per year with one-half to two-thirds of those affected being female
- Up to 15% of the general population experience isolated panic attacks, whereas up to 3.5% develop full panic disorder during their lifetime

Vasomotor Symptoms (VMS) Associated with Menopause

- VMS, such as hot flashes and night sweats, often are considered the most bothersome symptoms of menopause and affect approximately 75% of women over the age of 50 years

- Treatment
  - The Endocrine Society Recommends SSRIs, SNRIs, gabapentin, or pregabalin for moderate to severe vasomotor symptoms (VMS) in patients with contraindications to hormone therapy or who choose not to use hormone therapy
  - Paroxetine mesylate (Brisdelle) is the only SSRI approved to treat VMS
  - American Association of Clinical Endocrinologists (AACE) state that therapeutic trials of nonhormonal medications (e.g. clonidine, SSRIs, gabapentin) may be considered for the relief of menopausal symptoms in women with no contraindications
  - The American College of Obstetricians and Gynecologists (ACOG) also states SSRIs, SNRIs, clonidine, and gabapentin are effective alternatives to hormone therapy for the treatment of VKS related to menopause

Endocrine Society, 2015
American Association of Clinical Endocrinologists (AACE), 2011
American College of Obstetricians and Gynecologists (ACOG), 2014

Disease State Description - Antidepressants

Generalized Anxiety Disorder (GAD)

- Affects ~2.7% of the adult US population annually, and women are 60% more likely to be affected by anxiety over their lifetime
- The disorder develops gradually and can begin across the life cycle, though the risk is highest between childhood and middle age
- GAD is diagnosed when a person worries excessively about a variety of everyday problems for at least 6 months
- Unable to get rid of their concerns, even though they usually realize that their anxiety is more intense than the situation
- Physical symptoms that often accompany the anxiety include fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, and hot flashes

Social Anxiety Disorder (SAD)

- In the U.S., SAD is the most common anxiety disorder, affecting approximately 5.3 million people per year
- It is the third most common psychiatric disorder after depression and alcohol abuse
- Characterized by a marked and persistent fear of social or performance situations in which embarrassment may occur
- Women and men are equally likely to develop the disorder, which usually begins in childhood or early adolescence
- Social anxiety disorder is often accompanied by other anxiety disorders or depression, and substance abuse may develop if people try to self-medicate their anxiety

American Academy of Child and Adolescent Psychiatry (AACAP), 2020

- Recommends that SSRIs should be offered to patients 6-18 years of age with SAD, GAD, separation anxiety, or panic disorder
- Suggest that the combination of CBT and an SSRI could be offered preferentially over either CBT or an SSRI alone in the same population
- Data supporting the use of other antidepressants are fewer; however, AACAP states that SNRIs could be offered to patients ≥ 6 years of age with social anxiety, generalized anxiety, separation anxiety, or panic disorder
- Notably, the SNRI in this class approved for use in a pediatric population for an anxiety disorder is duloxetine, which is approved for use in children ≥ 7 years of age with generalized anxiety disorder.

Guidelines - Antidepressants

- **GAD**
  - International Consensus Group on Depression and Anxiety (ICGDA) recommends SSRIs, SNRIs, TCAs, and CBT as first-line treatments
- **SAD**
  - ICGDA expert panel guidelines recommend SSRIs as first-line therapy
- **Panic Disorder**
  - 2009 APA treatment guidelines state that SSRIs, SNRIs, TCAs, and benzodiazepines are roughly comparable in efficacy
  - SSRIs or SNRIs are frequently preferred as initial therapy due to their favorable safety and adverse effect profile
  - The APA does not distinguish a particular SSRI amongst those that are approved by the Food and Drug Administration (FDA) for panic disorder
- **OCD**
  - SSRIs are preferred as a first medication trial for OCD
  - All SSRIs appear to be equally effective; however, individual patients may respond well to one and not to another
- **PTSD**
  - SSRIs are the recommended first-line medications for the treatment of PTSD

ICGDA, 2018

Guidelines - Antidepressants

- **Treatment-Resistant Depression (TRD)- American Psychiatric Association, 2020**
  - During patient evaluation and ongoing follow-up, providers must monitor patients for suicide risk, which should include inquiries regarding suicidal thoughts, plans, intents, means, and behaviors; specific psychiatric symptoms and medical conditions that may impact the likelihood of a suicide attempt; past suicidal ideation and family history of mental illness; currents stressors or protective considerations; and patient support system and independence, among others
  - The treatment approach in patients with depressive symptoms with acute suicidal ideation or behavior remains similar, but the APA depression guidelines recommend establishing a therapeutic alliance, close surveillance, and consideration of an increased intensity of treatment (e.g., complete or partial hospitalization, psychotherapy plus pharmacotherapy)
  - Antidepressants are the mainstay of therapy. In select cases of acute suicide risk, ECT also may be considered
  - Treatment selection may also be impacted by medication safety in an overdose
  - Additional agents may be used to augment antidepressants but are not approved for depression (e.g., lithium, mood stabilizers) or for the prevention of suicide (e.g., antipsychotics)
  - The only agent approved in this class specifically for depressive symptoms with acute suicidal ideation or behavior is esketamine (Spravato); for approval, its use was studied in combination with initial inpatient hospitalization and comprehensive standard of care treatment, including a newly initiated or optimized antidepressant (e.g., antidepressant, antidepressant plus augmentation therapy).

ICGDA, 2018