Magellan Rx MANAGEMENT℠

Magellan Medicaid Administration

Washington Drug Utilization Review (DUR) Board Meeting

February 28th, 2024

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Agenda Topics

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

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Antibiotics:
- ANTIBIOTICS : AMINOGLYCOSIDES – INHALED
- ANTIBIOTICS : MONOBACTAMS – INHALED

Anticoagulants:
- ANTICOAGULANTS : FACTOR XA AND THROMBIN INHIBITORS – ORAL

Spinal Muscular Atrophy
- NEUROMUSCULAR AGENTS : SPINAL MUSCULAR ATROPHY AGENTS

Bone Resorption Suppression and Related Agents
- BONE DENSITY REGULATORS: SCLEROSTIN INHIBITORS

Bone Resorption Suppression and Related Agents
- BONE DENSITY REGULATORS: SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

Lincosamides/Oxazolidinones/Streptogramins
- ANTIBIOTICS : LINCOSAMIDES – INJECTABLE

Pleuromutilins
- ANTIBIOTICS : PLEUROMUTILINS

Steroids, Topical Very High
- ALLERGY : ANTIHISTAMINE - CORTICOSTEROIDS COMBINATIONS

Cardiovascular, Other
- CARDIOVASCULAR AGENTS : CARDIAC MYOSIN INHIBITORS

Immunomodulators, Topical
- DERMATOLOGICS : MACROLIDE IMMUNOSUPPRESSANTS

Antihyperuricemics
- GOUT AGENTS : PEGYLATED URIC ACID ENZYMES

Disease Modifier, T1DM:
- ANTIDIABETICS : ANTI-CD3 ANTIBODIES

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Antidiabetics:

- SGLT2 Inhibitors
- Amylin Analogs
- 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 37 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

American Diabetes Association, 2020

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

- American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA), 2022
  - Published guidelines for the management of heart failure (HF)
  - SGLT2 inhibitors were given a 2a recommendation in HF with mildly reduced ejection fraction (HFmrEF) with weaker recommendations (2b) in this population for other agents
  - For HFpEF (Heart Failure with Preserved Ejection Fraction), SGLT2 inhibitors received a 2a recommendation, mineralocorticoid receptor antagonists a 2b recommendation, and angiotensin receptor-neprilysin inhibitors a 2b recommendation

Guidelines- Diabetes Mellitus

- American Association of Clinical Endocrinologists (AACE), 2023
  - The 2023 algorithm update separates its recommendations into a complications-centric algorithm and a glucose-centric algorithm
  - Emphasize a comprehensive approach including individualized targets for weight loss, glucose, lipid, and hypertension management
  - AACE supports an HbA1c target of ≤ 6.5% for most patients if it can be reached without substantial hypoglycemia or other adverse effects
  - In the complications-centric algorithm, therapy choice is guided by comorbidity rather than by glycemic target
  - As such, the algorithm suggests that patients with ASCVD or who are at very high risk for ASCVD should be initiated on a GLP-1RA or SGLT2 inhibitor, patients with HF should be prescribed an SGLT2 inhibitor, patients with history of stroke or TIA should be initiated on a GLP-1RA or pioglitazone, and patients with CKD should be prescribed an SGLT2 inhibitor or GLP-1RA
  - In all cases, a drug with proven CV benefit is recommended
  - For these patients, metformin can also be initiated or continued to achieve glycemic targets
  - In the glucose-centric algorithm, patients who require glycemic control should begin with lifestyle therapy plus metformin (if appropriate)
  - Additional therapies may be added to achieve HbA1c target based on individual patient factors
  - For those who are overweight, obese, or at risk for hypoglycemia, a GLP-1RA, dual GLP-1/GIP receptor agonist, or SGLT2 inhibitor is preferred
  - For patients with cost or access issues, a TZD, sulfonylurea, or glinide is preferred
  - For patients with severe hyperglycemia, basal insulin is preferred in combination with either prandial insulin or a GLP-1RA or dual GLP-1/GIP receptor agonist

Guidelines- Diabetes Mellitus

- ADA Standards of Care in Diabetes, 2023
  - Recommends initiation of pharmacologic therapy, along with lifestyle changes, at the time of diagnosis for children with T2DM
  - Metformin is recommended first-line for asymptomatic children with an HbA1c < 8.5%, while those with marked hyperglycemia and an HbA1c ≥ 8.5% should be initiated on metformin along with long-acting insulin
  - If HbA1c goals are not met with metformin (alone or combined with long-acting insulin), the addition of a GLP-1RA approved for youth with T2DM should be considered in patients ≥ 10 years of age
  - Patients who do not meet glycemic targets despite treatment with metformin, a GLP-1RA, and long-acting insulin should then be initiated on multiple daily insulin injections or an insulin pump
  - The current ADA guidelines do not discuss the use of SGLT2 inhibitors in children with T2DM

Guidelines- Diabetes Mellitus

- AHA/ACC/ACCP/ASPC/NLA/PCNA Guidelines, 2023
  - AHA/ACC published guidelines for diagnosis & management for chronic coronary disease (CCD)
  - **They recommend SGLT2 inhibitors & GLP-1RAs in select patients with CCD, including groups without diabetes**
  - Provide new recommendations for beta-blockers for CCD; however, long-term beta-blocker use is not recommended to improve outcomes in patients with CCD in the absence of MI in the past year, LVEF ≤ 50%, or another primary indication for beta-blocker therapy
  - In addition, either a CCB or beta-blocker is recommended as first-line antianginal treatment
  - Statins remain first-line treatment for lipid lowering in patients with CCD
  - Several adjunctive therapies (eg, ezetimibe, PCSK9 inhibitors, inclisiran, bempedoic acid) may be used in select populations, although clinical outcomes data are unavailable for novel agents such as inclisiran
  - Shorter durations of dual antiplatelet therapy are safe and effective in many circumstances, particularly when the risk of bleeding is high and the ischemic risk is low to moderate

Hypoglycemics, SGLT2 Inhibitors

- **bexagliflozin (Brenzavvy)**
  - **January 2023: The FDA approved the SGLT2 inhibitor as an adjunct to diet and exercise to improve glycemic control in adults with T2DM**
  - **Indications**
    - **As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus**
    - **Limitation of Use: Not recommended in patients with type 1 diabetes mellitus. May increase the risk of diabetic ketoacidosis in these patients**
  - **Precautions**
    - **Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters**
    - **Renal Impairment: Higher incidence of adverse reactions related to reduced renal function**
    - **Hepatic Impairment: Not recommended for patients with severe hepatic impairment**
  - **Dosing**
    - **Recommended dose: 20 mg once daily, taken in the morning, with or without food**
  - **Formulations**
    - **Tablets: 20 mg**

Hypoglycemics, SGLT2 Inhibitors

- **dapagliflozin (Farxiga)**
  - **May 2023: The FDA has approved an expanded indication for dapagliflozin to reduce the risk of CV death, hospitalization for heart failure and urgent heart failure visit in adults with heart failure. Previously, it was indicated to reduce the risk of CV death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II to IV)**
  - **Other indications are (1) adjunct to diet and exercise to improve glycemic control in adults with T2DM; (2) to reduce the risk of hospitalization for heart failure in adults with T2DM & either established CV disease or multiple CV risk factors; and (3) to reduce the risk of sustained eGFR decline, end stage kidney disease, CV death, & hospitalization for heart failure in adults with chronic kidney disease at risk of progression**

  - **Precautions**
    - Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters
    - Renal Impairment: Higher incidence of adverse reactions related to volume depletion
    - Hepatic Impairment: Not recommended for patients with severe hepatic impairment
  - **Dosing**
    - To improve glycemic control, the recommended starting dose is 5 mg orally once daily
    - Dose can be increased to 10 mg orally once daily for additional glycemic control
    - For all other indications, the recommended starting dose is 10 mg orally once daily
  - **Formulations**
    - Tablets: 5 and 10 mg

Hypoglycemics, SGLT2 Inhibitors

- **sotagliflozin (Inpefa)**
  - **May 2023: The FDA approved sotagliflozin (Inpefa), a dual SGLT1 & SGLT2 inhibitor, to reduce the risk of CV death, hospitalization for HF, & urgent HF visit in adults with: HF, T2DM, CKD, & other CV risk factors**
  - **Indications**
    - **A sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with:**
      - **Heart failure or**
      - **Type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors**
  - **Precautions**
    - **Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters**
    - **Renal Impairment: Higher incidence of adverse reactions related to volume depletion**
  - **Dosing**
    - **Correct volume status before starting INPEFA at 200 mg daily and titrate to 400 mg as tolerated**
    - **In patients with decompensated heart failure, begin dosing when patients are hemodynamically stable**
    - **Withhold Inpefa at least 3 days, if possible, prior to major surgery or procedures associated with prolonged fasting**
  - **Formulations**
    - **Tablets: 200 and 400 mg**

Hypoglycemics, SGLT2 Inhibitors

- **empagliflozin/metformin (Synjardy)**
  - **February 2023: New indication has been added to state that the empagliflozin component is indicated to reduce the risk of CV death & hospitalization for HF in adults with HF**
  - **June 2023: Synjardy was approved for an expanded indication as adjunct to diet & exercise to improve glycemic control in pediatric patients ≥ 10 years of age with T2DM; previously approved only in adults**
  - **Indications**
    - **A combination of empagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus**
  - **Precautions**
    - BBW: Metformin-associated lactic acidosis
    - Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters
    - Renal Impairment: Higher incidence of adverse reactions related to reduced renal function
  - **Dosing**
    - Individualize the starting dosage based on the patient's current regimen and renal function
    - The maximum recommended dosage is 25 mg/day of empagliflozin and 2,000 mg/day of metformin HCl
  - **Formulations**
    - **Tablets: 5 mg empagliflozin/500 mg metformin HCl, 5 mg empagliflozin/1,000 mg metformin HCl, 12.5 mg empagliflozin/500 mg metformin HCl, 12.5 mg empagliflozin/1,000 mg metformin HCl**

Hypoglycemics, SGLT2 Inhibitors

- **empagliflozin (Jardiance)**
  - **June 2023: Jardiance was approved for an expanded indication as adjunct to diet & exercise to improve glycemic control in pediatric patients ≥ 10 years of age with T2DM; previously approved only in adults**
  - **September 2023: Approved by the FDA to reduce the risk of sustained decline in eGFR, end-stage kidney disease, CV death, & hospitalization in adults with CKD at risk of progression**
  - **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 and pediatric patients aged 10 years and older with type 2 diabetes mellitus**
    - **To reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression**
  - **Precautions**
    - Pregnancy: Advise females of the potential risk to a fetus especially during the second and third trimesters
    - Renal Impairment: Higher incidence of adverse reactions related to reduced renal function
  - **Dosing**
    - Recommended dosage is 10 mg once daily in the morning, taken with or without food
    - For additional glycemic control, dosage may be increased to 25 mg in patients tolerating Jardiance
  - **Formulations**
    - **Tablets: 10 mg, 25 mg**

Hypoglycemics, GLP-1 Agonists

- **semaglutide (Rybelsus)**
  - **January 2023: FDA has approved updated labeling for 7 mg & 14 mg tablets allowing use for first-line treatment of T2DM in adults**
  - **Indications**
    - **Indicated 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
      - Not for treatment of type 1 diabetes mellitus
  - **Precautions**
    - BBW: Thyroid C-cell tumors
    - BBW: Contraindicated in patients with a personal or history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome 2
    - Pregnancy: May cause fetal harm
  - **Dosing**
    - Start with 3 mg once daily for 30 days. After 30 days on the 3 mg dosage, increase the dosage to 7 mg once daily
    - Dosage may be increased to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dosage
  - **Formulations**
    - Tablets: 3 mg, 7mg, 14 mg

Hypoglycemics, GLP-1 Agonists

- **tirzepatide (Mounjaro)**
  - **August 2023: FDA approved a single-use glass vial presentation for all available strengths; previously approved as a single-dose pen. Dosage is 2.5 mg to 15 mg SC once weekly**
  - **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**

Hypoglycemics, DPP-4 Inhibitor

- **sitagliptin (Zituvio)**
  - **August 2023: FDA approved a dipeptidyl peptidase-4 (DPP-4) inhibitor FDA approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM**
  - **Indications**
    - **Indicated 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**
      - **Has not been studied in patients with a history of pancreatitis**
  - **Precautions**
    - **Pancreatitis: There have been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue treatment**
    - **Heart failure: Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of Zituvio in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms**
  - **Dosing**
    - **100 mg orally once daily**
    - **Can be taken with or without food**
    - **Dosage adjustment is recommended for patients with eGFR less than 45 mL/min/1.73 m^2**
  - **Formulations**
    - **Tablets: 100 mg, 50 mg, and 25 mg**

Hypoglycemics, DPP-4 Inhibitor

- **sitagliptin/metformin (Zituvimet)**
  - **November 2023: FDA has approved the dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin) & biguanide (metformin) combo product Zituvimet as an adjunct to diet & exercise to improve glycemic control in adults with T2DM**
  - **Indications**
    - **A combination of sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated 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**
      - **Has not been studied in patients with a history of pancreatitis**
  - **Precautions**
    - **BBW: Lactic Acidosis**
    - **Pancreatitis: There have been post-marketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue treatment**
    - **Heart failure: Heart failure has been observed with two other members of the DPP-4 inhibitor class. Consider risks and benefits of treatment in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms**
  - **Dosing**
    - **Take Zituvimet orally twice daily with meals**
    - **Individualize the dosage on the basis of the patient's current regimen, effectiveness, and tolerability**
    - **The maximum recommended daily dose is 100 mg of sitagliptin and 2,000 mg of metformin HCl**
  - **Formulations**
    - **Sitagliptin 50 mg and metformin HCl 500 mg tablets; sitagliptin 50 mg and metformin HCl 1,000 mg tablets**

Hypoglycemics, GLP-1 Agonists

- **Discontinuation**
  - **Adlyxin (lixisenatide)- February 2023**
    - **Sanofi discontinued distribution of Adlyxin on January 1, 2023. Product expiry is 9/30/2023**
    - **No generics are available**
  - **Onglyza; Kombiglyze XR (saxagliptin; saxagliptin/metformin)- March 2023**
    - **AstraZeneca made a business decision to discontinue Onglyza & Kombiglyze XR**

- **FDA Communication**
  - **Ozempic (semaglutide)- April 2023**
    - **FDA is reporting availability of 1 mg, 2 mg, & 0.25 mg/0.5 mg (2 mg/3mL) products**
    - **The 0.25 mg/0.5 mg (2 mg/1.5 mL) product is to be discontinued; prescribers should transition to the 2 mg/3 mL presentation**
  - **Ozempic, Rybelsus, Wegovy (semaglutide)- June 2023**
    - **FDA released drug safety information regarding medications containing semaglutide marketed for T2DM or weight loss**
    - **FDA has received reports of compounded products using sodium & acetate salt forms of semaglutide, which have different active ingredients from the approved semaglutide products (Ozempic, Rybelsus, Wegovy)**

Hypoglycemics, GLP-1 Agonists

- **Weight Management**
  - **Ozempic; Wegovy (semaglutide)- June 2023**
    - **Novo Nordisk issued a statement alerting the public of a counterfeit Ozempic (semaglutide) pen purchased at a retail pharmacy which contained insluin glargine rather than semaglutide**
    - **The company advises pharmacies to purchase semaglutide products through authorized distributor and encourages patients to check product label and contents against the description provided**
  - **Statement, 2023**
    - **The American Society of Anesthesiologists (ASA) released a statement which suggests to hold GLP-1RAs (semaglutide, etc.) prior to surgery for patients undergoing anesthesia due to risk of regurgitation & aspiration of food**
    - **This suggestion is based on anecdotal reports; increased risk may be due to delayed gastric emptying & residual gastric contents**
    - **Per ASA, daily GLP-1RAs should be held on the day of the surgery and weekly GLP-1RAs should be held for 1 week prior to surgery**
  - **Wegovy (semaglutide)- August 2023**
    - **Novo Nordisk announced that it will continue to restrict starter doses of Wegovy into 2024**

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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

Hypoglycemics, GLP-1 Agonists

- **Discontinuation**
  - **Levemir (insulin detemir)- November 2023**
    - **FDA has announced that Novo Nordisk will discontinue manufacture of Levemir 100 unit/mL FlexPen & vials**
    - **Discontinuation of Levemir FlexPen will occur on Apr 1, 2024; however, supply disruptions are expected starting in mid-Jan 2024**
    - **Vials were available until the end of 2024**
    - **Full brand discontinuation occurred on Dec 31, 2024**

- **New Presentation**
  - **Fiasp (insulin aspart)- June 2023**
    - **FDA approved the 1.6 mL PumpCart cartridge for use in compatible insulin pumps**

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Sedative Hypnotics:

- SLEEP DISORDER AGENTS : SELECTIVE MELATONIN RECEPTOR AGONISTS
- SLEEP DISORDER AGENTS : TRICYCLIC AGENTS
- SLEEP DISORDER AGENTS : NON-BENZODIAZEPINE
- ANTIPSYCHOTICS / ANTIMANIC AGENTS : ANTIPSYCHOTICS - ALPHA AGONISTS
- SLEEP DISORDER AGENTS : OREXIN RECEPTOR ANTAGONISTS

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

Sedative Hypnotics

- **zolpidem tartrate**
  - **May 2023:**
    - **FDA has approved a new generic, zolpidem tartrate capsule (C-IV), a gamma-aminobutyric acid (GABA) A receptor positive modulator, for the short-term treatment of transient insomnia characterized by difficulties with sleep initiation in adults < 65 years of age.**
    - **Supplied as an oral capsule in the strength of 7.5 mg; if a 5 mg or 10 mg dosage is needed, another zolpidem tartrate immediate-release (IR) product should be used.**
    - **The lowest effective dosage of zolpidem should be utilized & use should be avoided in geriatric patients.**
    - **The capsules are for short-term use only & are taken once per night before bedtime with ≥ 7 or 8 hours remaining before planned awakening.**
      - **In females, the recommended starting dosage is 5 mg once nightly; as a result, use another zolpidem IR product for dosage initiation in these patients.**
      - **Males can initiate zolpidem at a dose of 5 mg IR, 7.5 mg IR, or 10 mg IR once nightly.**
      - **For males & females, if a 5 mg dosage is not effective, the dose can be increased to 7.5 mg or 10 mg once nightly (max recommended dosage of 10 mg IR once nightly).**
    - **Boxed warning for complex sleep behaviors**

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Hemophilia:

- ANTIHEMOPHILIC PRODUCTS : GENE THERAPY AGENTS

Disease State Description - Hemophilia

- **Hemophilia**
  - A rare, inherited bleeding disorder where the blood does not clot properly due to an absence of 1 of the coagulation factors present in normal blood
  - Hemophilia is identified as an X-linked congenital bleeding disorder that has an estimated frequency of 1 in 5,000 to 10,000 births
    - Typically affects males on the maternal side due to X-linked inheritance; however, females may also rarely be affected but are more commonly carriers of the disease
    - Up to 30% of newly diagnosed cases occur with no prior family history and are attributed to spontaneous mutations in either the F8 or F9 gene
  - The World Federation of Hemophilia estimates the global prevalence of hemophilia at around 400,000 persons
    - It is estimated there are approximately 17,000 to 20,000 persons in the United States are afflicted with hemophilia
  - There are 2 main types of hemophilia
    - Type A
      - Also known as Factor VIII deficiency, classical hemophilia, or standard hemophilia
      - Far more common than hemophilia B with hemophilia A presenting in 80 to 85% of all hemophilia patients
      - Patients with type A hemophilia exhibit low or missing levels of clotting Factor VIII (8)
    - Type B
      - Also known as Factor IX deficiency or Christmas disease
      - Those with type B have low or missing levels of clotting factor IX (9)

National Heart, Lung, and Blood Institute, 2018
World Federation of Hemophilia, 2013

Disease State Description - Hemophilia

- Hemophilia can also encompass several other rare factor deficiencies
  - These disorders include deficiencies involving the following factors:
    - Factor I (1) – fibrinogen deficiency
    - Factor II (2) – prothrombin deficiency
    - Factor V (5) – proconvertin deficiency
    - Factor X (10) – Stuart-Prower deficiency
    - Factor XI (11) – hemophilia C or plasma thromboplastin deficiency
    - Factor XII (12) – Hageman factor deficiency
    - Factor XIII (13) fibrin stabilizing deficiency
  - These disorders are far less common than hemophilia A and B, exemplified by factor XIII deficiency which is estimated to occur in 1 in 5 million persons

National Heart, Lung, and Blood Institute, 2018
World Federation of Hemophilia, 2013

Disease State Description - Hemophilia

- Von Willebrand disease (vWD)
  - Similar to hemophilia A, this is a group of inherited bleeding disorders related to the absence or defects of von Willebrand Factor, a clotting protein, needed to achieve hemostasis
    - Von Willebrand factor binds to Factor VIII and platelets to generate a platelet plug during the clotting process
    - The disease leads to bleeding from impaired platelet adhesion and aggregation, which may be accompanied by reduced levels of Factor VIII
  - The prevalence of the disease is estimated to affect between 1 in 100 to 10,000 individuals; equal in males and females
  - There are 3 major subtypes of vWD identified
    - Type 1 is a partial quantitative deficiency of vWF deficiency and accounts for 75% of all patients
    - Type 2 is a more pronounced qualitative deficiency and comprises almost all the remaining 25% of patients
      - Type 2 disease is further divided into 4 variants named 2A, 2B, 2M, 2N on the basis of identified phenotypes
    - Type 3 is characterized as a complete vWF deficiency and occurs very rarely
      - For type 3 vWD patients, their inherent Factor VIII levels are typically very low

National Heart, Lung, and Blood Institute, 2018
World Federation of Hemophilia, 2013

Treatment Guidelines - Hemophilia

- The Medical and Safety Advisory Committee (MASAC), 2022
  - Published guidelines provide recommendations regarding prophylaxis for patients with hemophilia A or B with and without inhibitors
  - Because of the benefits demonstrated by prophylactic therapy, MASAC recommends that prophylaxis be considered optimal therapy for individuals with severe hemophilia A or B where endogenous factor levels are found to be less than 1%
  - Prophylaxis can also be used in patients with mild or moderate hemophilia who have a severe phenotype
  - Prophylactic therapy should be initiated early (e.g., prior to the age of 3 years and before the second joint bleed) and may be considered within the first 6 months after birth to decrease the potential for intracranial hemorrhage (e.g., emicizumab prophylaxis for hemophilia A)
  - Prophylactic options include standard half-life factor, extended half-life factor, and non-factor replacement (emicizumab)
  - Bypassing agents (BPAs) may be used for prophylaxis in those with inhibitors; however, for hemophilia A patients with inhibitors, BPAs are less effective than prophylaxis with emicizumab
  - For prophylaxis in hemophilia A patients, standard half-life factors are usually given 2 to 4 times per week, and extended half-life factors are usually given 1 to 3-times per week with the goal trough values for factor VIII levels of at least 1% (> 3% to 5% or higher if possible) and minimal or no spontaneous bleeds
  - When factors are utilized for prophylaxis, the dose and frequency can be individualized based on pharmacokinetic studies. In contrast, laboratory-based assays are not currently approved for assessing response in patients receiving non-factor replacement (emicizumab)
  - Standard half-life and extended half-life factor VIII prophylaxis can be given in the morning to prevent bleeding events during the day; however, timing of the dose is not considered as relevant for the extended half-life factor IX products
  - Adherence to prophylactic regimens should be monitored, and a patient's regimen may need to be adjusted across the patient's life based on changes in physical activity and risk of traumatic bleeding

Hemophilia

- etranacogene dezaparvovec-drlb (Hemgenix)
  - **December 2022: FDA approved etranacogene dezaparvovec-drlb (Hemgenix), an adeno-associated virus vector-based gene therapy, for use in adults with hemophilia B (congenital factor IX deficiency) who currently use factor IX prophylaxis therapy, or have current or history of life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes**
  - **Indication**
    - **An adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:**
      - **Currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes**
  - **Warnings and Precautions**
    - **Infusion reactions: Monitor during administration and for at least 3 hours after end of infusion. If symptoms occur, slow or interrupt administration. Re-start administration at a slower infusion once resolved**
  - **Dosage**
    - **Perform baseline testing to select patients, including testing for Factor IX inhibitor presence and liver health tests**
    - **The recommended dose of HEMGENIX is 2 x 10^{13} genome copies (gc) per kg of body weight**
    - **Administer as an intravenous infusion after dilution with 0.9% normal saline at a constant infusion rate of 500 ml/hour (8 mL/min)**
  - **Availability**
    - **Intravenous suspension**

Hemophilia

- antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl (Altuviiio)
  - **February 2023: FDA approved recombinant DNA-derived, factor VIII concentrate (Altuviiio) for use in adults & pediatric patients with hemophilia A (congenital factor VIII deficiency) for routine prophylaxis to reduce frequency of bleeding episodes, on-demand treatment and control of bleeding episodes, & perioperative management of bleeding**
  - **Indication**
    - **A recombinant DNA-derived, Factor VIII concentrate indicated for use in adults and children with hemophilia A (congenital factor VIII deficiency) for:**
      - **Routine prophylaxis to reduce the frequency of bleeding episodes**
      - **On-demand treatment & control of bleeding episodes**
      - **Perioperative management of bleeding**
    - **<u>Limitation of Use</u>: Not indicated for the treatment of von Willebrand disease**
  - **Warnings and Precautions**
    - **Hypersensitivity reactions, including anaphylaxis, may occur. Should symptoms occur, immediately discontinue treatment and initiate appropriate treatment**
  - **Dosage**
    - **For routine prophylaxis: 50 IU/kg once weekly**
    - **For on-demand treatment and control of bleeding episodes and perioperative management: 50 IU/kg**
  - **Availability**
    - **For injection: nominally 250, 500, 750, 1000, 2000, 3000, or 4000 IU, lyophilized powder in single-dose vials for reconstitution**

Hemophilia

- coagulation factor X (human) (Coagadex)
  - **April 2023: FDA approved the indication for perioperative management of bleeding to include patients with severe hereditary factor X deficiency; previously approved for perioperative management of bleeding only in patients with mild or moderate hereditary factor X deficiency**
  - **Indication**
    - **A plasma-derived human blood coagulation factor indicated in adults and children with hereditary Factor X deficiency for:**
      - Routine prophylaxis to reduce the frequency of bleeding episodes
      - On-demand treatment and control of bleeding episodes
      - **Perioperative management of bleeding in patients with** mild, moderate and **severe hereditary Factor X deficiency**
  - **Warnings and Precautions**
    - Development of neutralizing antibodies (inhibitors) may occur
    - If expected plasma Factor X activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor X inhibitor concentration
  - **Dosage**
    - Stratified by indication, age and weight (Found in TCR/PI)
  - **Availability**
    - Available as a lyophilized powder for reconstitution in single-dose vials containing nominally (approximately) 250 IU or 500 IU of Factor X activity
    - When reconstituted using the Sterile Water for Injection supplied with the kit, the final concentration is approximately 100 IU/mL

Hemophilia

- valoctocogene roxaparvovec (Roctavian)
  - **June 2023: FDA approved valoctocogene roxaparvovec, an adeno-associated virus vector-based gene therapy, for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test**
  - **Indication**
    - **An adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test**
  - **Warnings and Precautions**
    - **Infusion-related reactions**
  - **Dosage**
    - **For one-time single-dose intravenous use only**
    - **Perform baseline testing to select patients, including testing for pre-existing antibodies to adeno-associated virus serotype 5 (AAV5), factor VIII inhibitor presence, and liver health assessments**
    - **The recommended dose is 6 × 1013 vector genomes (vg) per kg of body weight**
    - **Start the infusion at 1 mL/min. If tolerated, the rate may be increased every 30 minutes by 1 mL/min up to a maximum rate of 4 mL/min**
  - **Availability**
    - **A suspension for intravenous infusion**
    - **Has a nominal concentration of 2 × 1013 vg valoctocogene roxaparvovec-rvox per mL, each vial contains an extractable volume of not less than 8 mL (16 × 1013 vg)**

Appendices

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