Conflict of Interest Disclosure

- A conflict of interest exists when an individual is in a position to profit directly or indirectly through application of authority, influence, or knowledge in relation to the affairs of PENS. A conflict of interest also exists if a relative benefits or when the organization is adversely affected in any way.

Conflicts of Interest:
- Nothing to disclose
  - Christopher Winslow, PharmD, MBA
  - Amanda Brown, PharmD

Program Objectives

- Analyze newly approved medications and their respective classes including the risks and benefits of therapy
- Investigate the role of new drugs in medication therapy plans for endocrine patients including indications, adverse effects, and contraindications
- Compose a treatment strategy for difficult patients and evaluate the use of non-traditional treatments when conventional therapy fails
Background

- Each year, there are 23,000 new cases of pediatric/adolescent diabetes
- Increase in prevalence of type 2 diabetes mellitus in adolescents
  - 1 in 3 cases
  - 2.3% increase yearly, leading to a quadruple incidence in just 40 years
- ADA goal of A1C < 7.5% for all pediatric patients
  - Modify based on benefit-risk assessment
- Type 1 diabetes mellitus (T1DM)
- Type 2 diabetes mellitus (T2DM)
- Therapeutic lifestyle changes preferred over pharmacologic intervention
- Metformin is currently the only FDA approved oral agent for children

Factors to consider in juvenile DM

- Education level
- Behavioral factors
  - Ambivalence, impulsiveness and mood swings of adolescence
- Emotional factors
  - Maturity
  - Fear
- Psychosocial factors
  - Family stressors that could impact adherence
  - Peer acceptance
- Environmental factors
  - Is the school or daycare able to provide the correct care?
New Pharmacotherapy Options

- Insulin inhalation powder
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors
- Glucagon-like-peptide-1 (GLP-1) agonists
- Dipeptidyl peptidase-4 (DPP-4) inhibitors

Insulin Inhalation Powder

Inhaled insulin over time

Biodrugs 2010;24(3):165-172
Insulin (Human) Inhalation Powder

- Approved in June 2014
- Indicated for Diabetes Mellitus
- Mechanism:
  - Closely resembles endogenous insulin
  - Regulates metabolism of carbohydrates, protein, and fats
- Technosphere Insulin (TI) technology
  - Particles formed by fumaryl diketopiperazine (FDKP) crystals
  - The crystals absorb the insulin

How does insulin work?

Contraindications
- Hypersensitivity
- Chronic lung disease
- Asthma/COPD
- Lung cancer or risk of lung cancer

Warnings/Precautions
- Black Box: Risk of acute bronchospasm
- Risk of hypoglycemia

Interactions
- Hypoglycemic agents
- Beta blockers
- GLP-1 agonists
- MAOIs
- Corticosteroids
- Diuretics

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- Diuretics
Inhaled Insulin

- Pregnancy category C
- Lactation – excreted in breast milk, but not contraindicated
- Pediatric Information – No information
- Adverse effects
  - Headache
  - N/V/D
  - Hypoglycemia
  - Hypokalemia
  - Fluid retention and weight gain
  - Acute bronchospasm
  - Cough, throat pain, irritation
- Monitoring
  - Baseline spirometry (FEV1)
  - Blood glucose, A1C
- Patient Counseling
  - Demonstrating proper DPI use
  - Symptoms of hypoglycemia

Conversion from SQ to inhaled insulin

- Currently, only 2 DPI inhalation cartridges are available
- 4 units/inhalation
- 8 units/inhalation
- Combination of these may be needed to reach needed dose

<table>
<thead>
<tr>
<th>SQ mealtime bolus units</th>
<th>Inhaled insulin units</th>
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<tbody>
<tr>
<td>Up to 4</td>
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<td>5-8</td>
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Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors
SGLT2 Inhibitors

- **Mechanism:**
  - Inhibits glucose reabsorption in the kidneys by inhibiting SGLT2
  - Increased glucose remaining in the glomerular filtrate leading to elimination through the urine

- **Contraindications:**
  - Hypersensitivity or allergy to components
  - Severe renal impairment or ESRD
  - Diabetic

- **Warnings/Precautions:**
  - Not recommended in type 1 or treatment of DKA

- **Interactions:**
  - Diuretics – increased urine frequency and volume
  - Increased risk of volume depletion
  - Insulin or secretagogues – increased risk of hypoglycemia

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SGLT2 Inhibitors

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SGLT2 Inhibitors

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SGLT2 Inhibitors

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SGLT2 Inhibitors

- Pregnancy category C
- Lactation – No information
- Pediatric Information – No information
- Adverse effects
  - Decreased estimated GFR
  - Increased SCr
  - Hypotension
  - Increased risk of UTI or genital mycotic infection
  - Increased LDL
- Monitoring
  - Need baseline GFR and periodic monitoring
  - Do not initiate therapy if GFR < 45 ml/min/1.73 m²
  - Signs and symptoms of hypotension
- Patient Counseling
  - With or without food

Products:
- Empagliflozin (Jardiance)
  - With linagliptin (Glyxambi)
- Canagliflozin (Invokana)
  - With metformin (Invokamet)
- Dapagliflozin (Farxiga)
  - With metformin (Xigduo XR)

Upcoming Clinical Trials

- Dapagliflozin in Type 1 Diabetes (DapaTIDM)
  - Currently recruiting patients
  - Randomized, double blind, crossover trial
  - Estimated completion: January 2015
  - 18-60 year old males
Glucagon-Like-Peptide-1 (GLP-1) Receptor Agonists

**GLP-1 Agonists**

- **Mechanism:**
  - GLP-1 analog mimicking action of endogenous GLP-1
  - Increase in cAMP in beta cells
  - Leading to glucose-dependent insulin secretion
  - Increase in beta cell growth/replication
  - Increase in satiety
  - Decrease in glucagon secretion
  - Delayed gastric emptying

Image: Heloderma suspectum
GLP-1 Agonists

- **Contraindications**
  - Hypersensitivity
  - Thyroid cancer
  - Type 1 DM

- **Warnings/Precautions**
  - Pancreatitis
  - Renal dysfunction risk
    - Contraindicated if CrCl<30mL/min
  - Interactions
    - Insulin and insulin secretagogues
    - Long acting oral meds
    - SSRI, MAOI
    - Corticosteroids
    - Diuretics
    - Quinolones
  - Caution: Renal dysfunction risk if CrCl<30mL/min

- **Pregnancy category C** (Saxenda X)
- **Lactation** - No information
- **Pediatric Information** - No information

- **Adverse effects**
  - N/V/D, abdominal pain, decreased appetite
  - Weight loss independent of A1C

- **Monitoring**
  - A1C
  - Renal function
  - Signs/symptoms of pancreatitis

- **Patient Counseling**
  - Subcutaneous injection
  - Avoid concomitant, close proximity insulin injections
  - Adjunct to diet and exercise

**Products:**
- Liraglutide (Victoza, Saxenda)
- Exenatide (Byetta, Bydureon)
- Dulaglutide (Trulicity)
- Albiglutide (Tanzeum)
Upcoming Clinical Trials

- Anti-diabetic Effects of Liraglutide in Adolescents and Young Subjects With Type 1 Diabetes
  - Currently being conducted
  - Randomized, double-blind, placebo controlled trial
  - Insulin + liraglutide vs. Insulin + placebo
  - Patients ages 15-30
  - Estimated completion May 2018

- Efficacy and Safety of Liraglutide in Combination With Metformin Compared to Metformin Alone, in Children and Adolescents With Type 2 Diabetes
  - Currently recruiting patients
  - Randomized, double-blind, placebo controlled trial
  - Metformin + liraglutide vs. metformin + placebo
  - Patients ages 10-16
  - Estimated completion June 2020

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

**Mechanism:**
- Inhibition of dipeptidyl peptidase-4
- DPP-4 enzyme is responsible for converting and inactivating of GLP-1 and GIP
- Results in an increase of active incretin hormones in the bloodstream
- Glucose-dependent increase in insulin
- Decrease in glucagon secretion

**Contraindications:**
- Hypersensitivity
- Pancreatitis

**Warnings/Precautions:**
- Renal adjustment needed if CrCl <50mL/min

**Interactions:**
- CYP3A4 substrates
- Antidiabetic agents
- Beta-blockers
- Diuretics
- Corticosteroids
DPP-4 Inhibitor Mechanism of Action

DPP-4 Inhibitors
- Pregnancy category B
- Lactation – No information
- Pediatric Information – No information
- Adverse effects
  - Headache
  - N/V/D
  - Peripheral edema
  - Urinary retention, oliguria, pancreatitis
    - Report immediately
- Monitoring
  - A1C and BG
  - Signs/symptoms of pancreatitis
  - Renal function at baseline and periodic checks
- Patient Counseling
  - Adjunct to diet and exercise
  - With or without food

DPP-4 Inhibitors
- Products:
  - Alloglupin (Nesina)
    - With metformin (Kazano)
    - With pioglitazone (Oseni)
  - Linagliptin (Tradjenta)
    - With metformin (Jentaduo)
    - With empagliflozin (Glyxambi)
  - Saxagliptin (Onglyza)
    - With metformin (Kombiglyze XR)
  - Sitagliptin (Januvia)
    - With metformin (Janumet, Janumet XR)
Upcoming Clinical Trials

- Study to Assess Safety & Efficacy of Sitagliptin as Initial Oral Therapy for Treatment of Type 2 Diabetes Mellitus in Pediatric Participants
  - Currently recruiting patients
  - Randomized, double-blind, placebo-controlled study
  - Patients ages 10-17 years
  - Expected completion: November 2017

Clinicaltrials.gov ID# NCT01485614

Place in Therapy
Questions
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