

Endocrine/Diabetes Pharmacology Review
May 8, 2015


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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



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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

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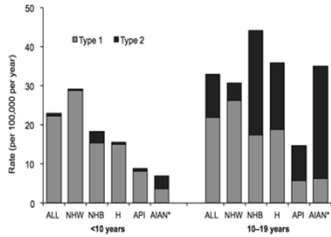
Background

- ▶ 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)
 - ▶ 1st line therapy is basal-bolus insulin regimen
- ▶ Type 2 diabetes mellitus (T2DM)
 - ▶ Therapeutic lifestyle changes preferred over pharmacologic intervention
 - ▶ Metformin is currently the only FDA approved oral agent for children

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Diabetes Care 2015; 38(5):e11
 Endocrine Practice 2015; 21(5):e18-21
 Pediatrics 2013; 131(2):364-372
 Center for Disease Control Online

Rate of new cases of type 1 and type 2 diabetes among people younger than 20 years, by age and race/ethnicity, 2008-2009



*The American Indian/Alaska Native (AI/AN) youth who participated in the SEARCH study are not representative of all AI/AN youth in the United States. Thus, these rates cannot be generalized to all AI/AN youth nationwide.
 Source: SEARCH for Diabetes in Youth Study
 NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics; API=Asians/Pacific Islanders; AIAN=American Indians/Alaska Natives.

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Center for Disease Control - National Diabetes Statistics Report 2014

Background

- ▶ Factors to consider in juvenile DM
 - ▶ Education level
 - ▶ Behavior 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?

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Diabetes Care 2015; 38(5):e11
 Diabetes Care 2005;28(1):186-212

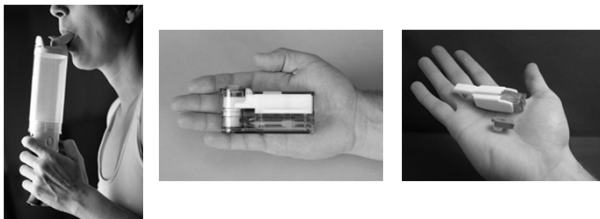
New Pharmacotherapy Options

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

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Insulin Inhalation Powder

Inhaled insulin over time



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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

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How does insulin work?

11 Medscape

Inhaled Insulin

- ▶ 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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Alrezza [package insert] 2014

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

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Atrioza [package insert] 2014

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

SQ mealtime bolus units	Inhaled insulin units
Up to 4	4
5-8	8
9-12	12
13-16	16
17-20	20
21-24	24

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Package Insert

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
 - ▶ Dialysis
- ▶ 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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Package Insert

SGLT2 Inhibitors

▶ 17 Medscape

SGLT2 Inhibitors

Enterocyte + S3 proximal renal tubule

S1 segment proximal renal tubule

▶ 18 Medscape

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 eGFR < 45ml/min/1.73m²
 - ▶ Signs and symptoms of hypotension
- ▶ Patient Counseling
 - ▶ With or without food

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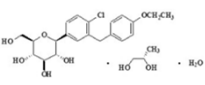
SGLT2 Inhibitors

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

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Upcoming Clinical Trials

- ▶ Dapagliflozin in Type I Diabetes (DapaT1DM)
 - ▶ Currently recruiting patients
 - ▶ Randomized, double blind, crossover trial
 - ▶ Estimated completion: January 2015
 - ▶ 18-60 year old males



The image shows the chemical structure of Dapagliflozin, a loop diuretic. It consists of a central benzene ring with a chlorine atom at the 1-position, a propyl group at the 4-position, and a 2-(4-hydroxyphenyl)ethyl group at the 3-position. This central ring is connected to a 2,3,4-trihydroxy-5-(hydroxymethyl)tetrahydrofuran ring system.


▶ 21 ClinicalTrials.gov NCT02311742
Farxiga [Package Insert] 2014

Glucagon-Like-Peptide-1 (GLP-1) Receptor Agonists

GLP-1 Agonists

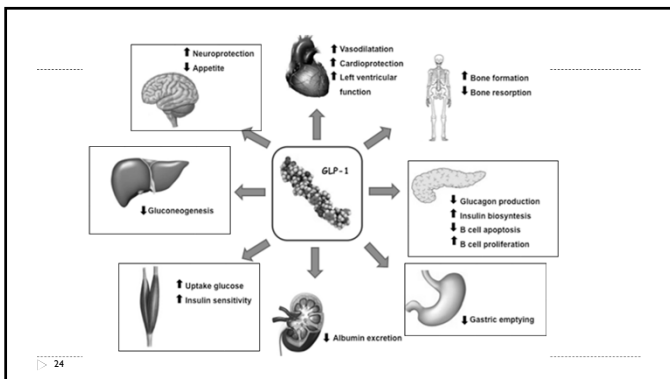
▶ Mechanism:

- ▶ 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



Heloderma suspectum

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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

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GLP-1 Agonists

- ▶ 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

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Trulicity [package insert] 2014.

GLP-1 Agonists

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

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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

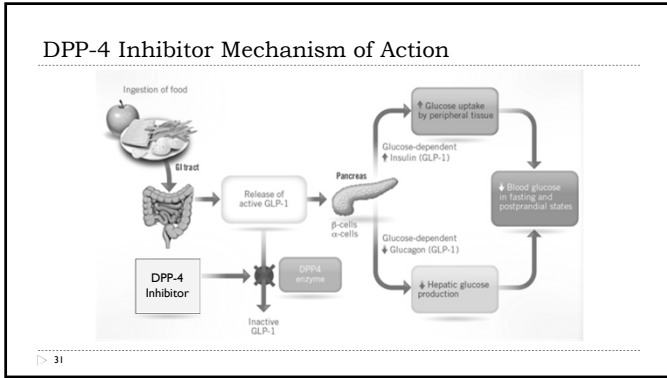
28 Clinicaltrials.gov ID: NCT01722227
Clinicaltrials.gov ID: NCT01411115

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

DPP-4 Inhibitors

- ▶ Mechanism:
 - ▶ Inhibition of dipeptidyl peptidase-4
 - ▶ DPP-4 enzyme is responsible for conversion and inactivation 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

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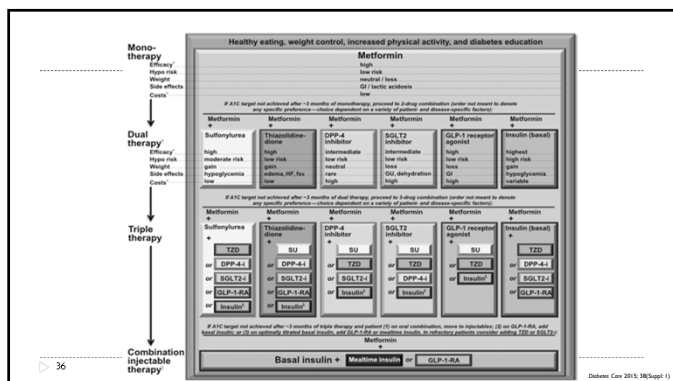
- ### DPP-4 Inhibitors
- ▶ Pregnancy category B
 - ▶ Lactation – No information
 - ▶ Pediatric Information – No information
 - ▶ Adverse effects
 - ▶ Headache
 - ▶ N/V/D
 - ▶ Peripheral edema
 - ▶ Urinary retention, oliguria, pancreatitis
 - ▶ Report immediately
 - ▶ Monitoring
 - ▶ A1C and BG
 - ▶ Signs/symptoms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

Place in Therapy



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- ▶ INVOKAMET (canagliflozin and metformin) [package insert]. Titusville, NJ; Janssen; Revised Aug, 2014.
- ▶ INVOKANA (canagliflozin) [package insert]. Titusville, NJ; Revised May, 2015.
- ▶ FARXIGA (dapagliflozin) [package insert]. Wilmington, DE; AstraZeneca Revised Aug, 2014.

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