Type 2 Diabetes — Pathophysiology and Pharmacology Review

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Type of Activity: Knowledge
Media: Internet

New Horizons in Diabetes Care:
Reducing Cardiovascular Risks Through Advances in Pharmacotherapy

This valuable and engaging 3-part webinar series was designed to inform and educate pharmacists in all practice settings who are involved in the care of patients with T2DM, bridging the gap of learning about the new classes of medications for T2DM including their pathophysiologic basis of action, the optimal combinations of these agents, and the cardiovascular safety of these glucose-lowering medications.

Attend one, two, or all three webinars and gain confidence in applying the results of recent studies to clinical practice.

Part 1 — “Type 2 Diabetes—Pathophysiology and Pharmacology Review”
Wednesday, March 22, 2017 at 1:00 PM EDT

Part 2 — “Intensifying Therapy after Basal Insulin Optimization in Type 2 Diabetes—Options for Targeting Postprandial Control”
Thursday, March 30, 2017 at 1:00 PM EDT

Part 3 — “Cardiovascular Outcome Trials (CVOTs): Practical Considerations for your Type 2 Diabetes Patients”
Wednesday, April 5, 2017 at 1:00 PM EDT
Disclosures to Participants

Conflicts of Interest and Financial Relationships

Presenter and Program Chair:
Joshua J. Neumiller, PharmD, CDE, FASCP
- Advisory Board/Consultant: Eli Lilly & Boehringer Ingelheim
- Research Grant Support to WSU: Novo Nordisk

Content Reviewer:
Tricia Russell, PharmD, BCPS, CDE has nothing to disclose.

Learning Objectives

After completing this webinar, participants will be able to:
1. Describe the clinical pharmacology of the dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors
2. Understand the concept of implementing combination pharmacotherapy by addressing complementary pathophysiologic targets
3. Describe the role of DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors as monotherapy and in combination with other medications for the treatment of type 2 diabetes (T2DM)

Normal Regulation of Glucose Homeostasis
Dysregulation of Glucose Homeostasis in T2DM

- Glucagon (α-cell)
- Insulin (β-cell)
- Muscle

Hyperglycemia

Natural History of T2DM

- Years from diagnosis
- Insulin resistance
- Insulin secretion
- Pre-diabetes
- T2DM
- Microvascular complications
- Macrovascular complications

Pathophysiologic Defects in T2DM

- Increased glucose uptake
- Increased glucose reabsorption
- Increased hepatic glucose production
- Impaired insulin secretion
- Decreased incretin effect
- Increased glucagon secretion
- Increased lipolysis

Sources:
Select Antihyperglycemic Pharmacotherapy Options

**Oral medications**
- Biguanides
- Sulfonylureas
- Meglitinides
- α-Glucosidase inhibitors (AGIs)
- DPP-4 inhibitors
- SGLT-2 inhibitors

**Insulin**
- Prandial insulin
  - Insulin lispro
  - Insulin aspart
  - Insulin glulisine
- Basal insulin
  - Insulin human inhaled
  - Regular human insulin
  - Insulin NPH
  - Insulin detemir
  - Insulin glargine U-100
  - Insulin glargine U-300
  - Insulin degludec

**Non-insulin injectable agents**
- GLP-1 receptor agonists
- Amylin mimetic

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Pathophysiologic Defects in T2DM

- Decreased incretin effect
- Neurotransmitter dysfunction
- Islet β-cell impairment
- Impaired insulin secretion
- Decreased glucose uptake
- Increased glucagon secretion
- Increased lipolysis
- Increased glucose reabsorption
- Increased hepatic glucose production
- Hyperglycemia

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Decreased incretin effect
Neurotransmitter dysfunction
Islet β-cell impairment
Impaired insulin secretion
Decreased glucose uptake
Increased glucagon secretion
Increased lipolysis
Increased glucose reabsorption
Increased hepatic glucose production
Hyperglycemia
The Incretin Effect

Control subjects (n = 8)

Oral glucose load
Intravenous glucose infusion

People with T2DM (n = 14)

Endogenous GLP-1: Effects in Humans

After food ingestion...

GLP-1 is secreted from L-cells of the jejunum and ileum

GIP-1 then...

- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Increases satiety

Pharmacological Strategies to Augment the Incretin Effect

- GLP-1 secretion is impaired in T2DM
- Natural GLP-1 has an extremely short half-life

Block DPP-4 to slow the enzymatic degradation of GLP-1:
- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)

Add GLP-1 analogues with longer half-life:
- Exenatide (Byetta)
- Liraglutide (Victoza)
- Lixisenatide (Adlyxin)
- Once-weekly Exenatide (Bydureon)
- Albiglutide (Tanzeum)
- Dulaglutide (Trulicity)
Comparison of Incretin-based Therapies

Select clinical properties of DPP-4 inhibitors and GLP-1 receptor agonists

<table>
<thead>
<tr>
<th></th>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Receptor Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow gastric emptying</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect on postprandial</td>
<td>Yes (variable)</td>
<td></td>
</tr>
<tr>
<td>hyperglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Weight neutral</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Associated with</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>hypoglycemia when used</td>
<td></td>
<td></td>
</tr>
<tr>
<td>as monotherapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Comparison of DPP-4 Inhibitors Currently Available in the United States (U.S.)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sitagliptin (Januvia)</th>
<th>Saxagliptin (Onglyza)</th>
<th>Linagliptin (Tradjenta)</th>
<th>Alogliptin (Nesina)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia risk</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Initial dose (normal CrCl)</td>
<td>100 mg daily</td>
<td>5 mg daily</td>
<td>5 mg daily</td>
<td>25 mg daily</td>
</tr>
<tr>
<td>Dose adjustment for renal impairment</td>
<td>&lt;CrCl &lt; 50 mL/min: 50 mg daily</td>
<td>CrCl ≤ 30 mL/min: 2.5 mg daily</td>
<td>No adjustment recommended on the basis of renal function</td>
<td>&lt;CrCl &lt; 60 mL/min: 12.5 mg daily</td>
</tr>
</tbody>
</table>

Effects of Currently Available DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sitagliptin (Januvia)</th>
<th>Saxagliptin (Onglyza)</th>
<th>Linagliptin (Tradjenta)</th>
<th>Alogliptin (Nesina)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average A1C lowering*</td>
<td>0.60% to 0.79%</td>
<td>0.36% to 0.82%</td>
<td>0.50% to 0.69%</td>
<td>0.47% to 0.85%</td>
</tr>
<tr>
<td>Average weight change*</td>
<td>+0.3 to +1.2 kg</td>
<td>-0.55 to +1.3 kg</td>
<td>+0.33 to +1.1 kg</td>
<td>+0.14 to +0.51 kg</td>
</tr>
</tbody>
</table>

*A1C = Hemoglobin A1C.
Key Considerations for the Use of DPP-4 Inhibitors

- Oral administration
- Generally weight neutral
- Side effects:
  - Headache
  - Nasopharyngitis/upper respiratory tract infections
  - Generally well tolerated
- Warnings/precautions:
  - Pancreatitis
  - Hypoglycemia (when added to secretagogues or insulin)
  - Allergic reactions
  - Heart failure? (saxagliptin & alogliptin)

Comparison of A1C Reductions with GLP-1 Receptor Agonists

GLP-1 Receptor Agonists: Weight Change Ranges in Phase III Trials

- Exenatide BID
- Exenatide QW
- Liraglutide
- Dulaglutide 0.75 mg QW
- Dulaglutide 1.5 mg QW
- Lixisenatide
- Albiglutide
- Liraglutide

*Adapted from Triplitt C, Solis-Herrera C. Diabetes Educ. 2015;41(suppl 1):32S-46S.*
Comparison of Exenatide Products (30-week Data)

<table>
<thead>
<tr>
<th></th>
<th>Exenatide extended-release suspension</th>
<th>Exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction (%)</td>
<td>1.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.5</td>
</tr>
<tr>
<td>FPG reduction (mg/dL)</td>
<td>41&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25</td>
</tr>
<tr>
<td>PPG reduction (mg/dL)</td>
<td>96</td>
<td>124&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Achievement of A1C &lt; 7%</td>
<td>77&lt;sup&gt;b&lt;/sup&gt;</td>
<td>81&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Change in body weight (kg)</td>
<td>-3.7</td>
<td>-3.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> P = 0.0023; <sup>b</sup> P < 0.0001; <sup>c</sup> P = 0.0124; <sup>d</sup> P = 0.0039 versus comparator.

Key Considerations for the Use of GLP-1 Receptor Agonists

- Subcutaneous administration
- Can result in weight loss
- Side effects:
  - Nausea/vomiting
  - Injection site reactions
- Contraindications:
  - Personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (long-acting products)
- Warnings/precautions:
  - Pancreatitis
  - Hypoglycemia (when added to secretagogues or insulin)

Pathophysiologic Defects in T2DM
Renal Glucose Reabsorption Under Normal Conditions

*~180 grams of glucose filtered per day

**SGLT-2**
- Virtually no urinary glucose excretion

**SGLT-1**
- Reabsorption of ~90% of filtered glucose
- Reabsorption of ~10% of filtered glucose

Renal Glucose Reabsorption Under Normal Conditions


SGLT-2 Inhibition

~90% of filtered glucose is reabsorbed through SGLT-2 transporters in the early proximal tubule

Inhibition of SGLT-2 transporters in the proximal tubule blocks the reabsorption of filtered glucose, leading to increased glucose excretion via urine


Canagliflozin versus Glimepiride as Add-on to Metformin: Change in A1C


CANA = canagliflozin; GLIM = glimepiride.
Canagliflozin versus Glimepiride as Add-on to Metformin: Change in Weight

Comparison of SGLT-2 Inhibitors Currently Available in the U.S.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Canagliflozin (Invokana)</th>
<th>Dapagliflozin (Farxiga)</th>
<th>Empagliflozin (Jardiance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia risk (as monotherapy)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Dose</td>
<td>100 mg daily before breakfast; increase to 300 mg daily, if needed</td>
<td>5 mg daily in the morning; increase to 10 mg daily, if needed</td>
<td>10 mg daily in the morning; increase to 25 mg, if needed</td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Weight loss</td>
<td>Weight loss</td>
<td>Weight loss</td>
</tr>
</tbody>
</table>

Renal Dose Adjustment of SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Canagliflozin (Invokana)</th>
<th>Dapagliflozin (Farxiga)</th>
<th>Empagliflozin (Jardiance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ≥ 60 mL/min/1.73 m²</td>
<td>No dosage adjustment needed</td>
<td>No dosage adjustment needed</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>eGFR 45 - 59 mL/min/1.73 m²</td>
<td>Do not exceed 100 mg/day by mouth</td>
<td>Do not exceed 100 mg/day by mouth</td>
<td>Do not exceed 100 mg/day by mouth</td>
</tr>
<tr>
<td>eGFR &lt; 45 mL/min/1.73 m²</td>
<td>Do not initiate and discontinue in patients currently receiving drug</td>
<td>Do not initiate and discontinue in patients currently receiving drug</td>
<td>Do not initiate and discontinue in patients currently receiving drug</td>
</tr>
</tbody>
</table>
Canagliflozin: Less A1C Reduction with Declining eGFR

Key Considerations for the Use of SGLT-2 Inhibitors

- Unique mechanism of action
  - Have been studied in combination with a variety of other medication classes
- Oral administration
- Low hypoglycemia risk as monotherapy
  - Caution when used with secretagogues or insulin
- Can result in weight loss and modest decrease in blood pressure
- Side effects:
  - Genital mycotic infections
  - Urinary tract infections
  - Orthostasis (especially in elderly, chronic kidney disease, diuretic use)
  - Watch volume status
  - Increased levels of low-density lipoproteins
  - Euglycemic diabetic ketoacidosis
### Comparison of Glucose-lowering Abilities of T2DM Pharmacotherapy Options

<table>
<thead>
<tr>
<th>Medication</th>
<th>Route of administration</th>
<th>Targets insulin resistance</th>
<th>Target glucose (FPG or PPG)</th>
<th>A1C reduction* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>Oral</td>
<td>No</td>
<td>Both</td>
<td>1.5 – 2.0</td>
</tr>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>Yes</td>
<td>FPG</td>
<td>1.0 – 1.5</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Oral</td>
<td>No</td>
<td>FPG</td>
<td>0.5 – 1.0</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Oral</td>
<td>No</td>
<td>FPG</td>
<td>0.5 – 0.7</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Oral</td>
<td>No</td>
<td>FPG</td>
<td>0.4</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors</td>
<td>Oral</td>
<td>No</td>
<td>FPG</td>
<td>0.5 – 0.7</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Oral</td>
<td>Yes</td>
<td>Both</td>
<td>1.0 – 1.5</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.5 – 2.0</td>
</tr>
<tr>
<td>Gluconates</td>
<td>Oral</td>
<td>No</td>
<td>FPG</td>
<td>0.4</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>Injectable</td>
<td>No</td>
<td>Both</td>
<td>0.7 – 1.5</td>
</tr>
<tr>
<td>Amylin analog</td>
<td>Injectable</td>
<td>No</td>
<td>FPG</td>
<td>0.8</td>
</tr>
<tr>
<td>Insulin</td>
<td>Injectable</td>
<td>No</td>
<td>FPG</td>
<td>0.6</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>Injectable</td>
<td>No</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>Amylin analog</td>
<td>Injectable</td>
<td>No</td>
<td>FPG</td>
<td>0.8</td>
</tr>
<tr>
<td>Insulin</td>
<td>Injectable</td>
<td>No</td>
<td>FPG</td>
<td>0.6</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>Injectable</td>
<td>No</td>
<td>PPG</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*All reduction data are not from head-to-head comparative studies.

Once FBG is optimized, start addressing PPG excursions:
- Add GLP-1 receptor agonist
- Add 1 rapid-acting insulin injection to largest meal
- Change to premixed insulin twice daily

### GLP-1 Receptor Agonist vs. Bolus Insulin in Patients with T2DM and Optimized Basal Insulin

**Exenatide caused more gastrointestinal issues (47% vs. 13%) but fewer non-nocturnal episodes of hypoglycemia (15% vs. 34%) than insulin liraglutide.**

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**Notes:**
- p < 0.001 for exenatide BID vs. insulin lispro
- p < 0.001 for exenatide BID vs. insulin liraglutide
- p < 0.001 for exenatide BID vs. insulin liraglutide

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Don’t Miss the Upcoming Webinars in This Series!

• Intensifying Therapy after Basal Insulin Optimization in Type 2 Diabetes – Options for Targeting Postprandial Control  
  **Presenter:** Dr. Susan Cornell

• Cardiovascular Outcome Trials (CVOTs): Practical Considerations for Your Type 2 Diabetes Patients  
  **Presenter:** Dr. Curtis Triplitt

Thank you!

**Special Thanks:**
- Postgraduate Healthcare Education, LLC
- Susan Cornell, PharmD
- Curtis Triplitt, PharmD

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