NEW DIABETES MEDICATIONS: WHERE DO THEY FIT IN THE PARADIGM?

Nabila Ahmed-Sarwar, Pharm.D., BCPS, CDE
Elizabeth Sutton Burke, Pharm.D., BCACP, CDE
Wegmans School of Pharmacy
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Disclosure Statement

No relevant financial relationships to disclose
Learning Objectives

Upon completion of this educational session, participants will be able to:

• Summarize current and new targets for drug action that influence glucose homeostasis

• Explain the clinical impact of the new therapeutic agents and determine their place in therapy for the treatment of diabetes mellitus
## Current Treatment Options

<table>
<thead>
<tr>
<th>Location</th>
<th>Medications</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Secretagogues</td>
<td>Increase serum insulin levels</td>
</tr>
<tr>
<td></td>
<td>DPP-IV Inhibitors</td>
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<tr>
<td></td>
<td>Insulin</td>
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<tr>
<td></td>
<td>Metformin</td>
<td>Decrease gluconeogenesis</td>
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<tr>
<td></td>
<td>Thiazolidinediones</td>
<td>Increase glucose uptake</td>
</tr>
<tr>
<td></td>
<td>Alpha-glucosidase Inhibitors</td>
<td>Decrease glucose absorption</td>
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<td></td>
<td>Pramlintide</td>
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</tbody>
</table>
Where do we go from here??

New Anti-hyperglycemic Agents

Desirable Administration Regimens

Improved Safety

Improved Efficacy

Alternative targets for glucose homeostasis
# New Treatment Options

<table>
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<tr>
<th>Location</th>
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<tbody>
<tr>
<td></td>
<td>Basal Insulins GLP-1 Analogs</td>
<td>Increase serum insulin levels&lt;br&gt;Decrease glucagon release</td>
</tr>
<tr>
<td></td>
<td>SGLT-2 Inhibitors</td>
<td>Increase urinary glucose excretion</td>
</tr>
</tbody>
</table>
Where do we go from here??

Desirable Administration Regimens

Improved Safety

Improved Efficacy

Alternative targets for glucose homeostasis

New Anti-hyperglycemic Agents
Basal-Rapid Acting Regimen

Provides continuous basal coverage
## Basal Insulins

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Dosage Formulation and Regimens</th>
<th>Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin glargine (Toujeo®)</td>
<td>Pen: 300 units/ml subcut every 24 hours</td>
<td>42 days opened at room temp</td>
</tr>
<tr>
<td>Insulin degludec (Tresiba®)</td>
<td>Pens: 100 units/ml or 200 units/ml subcut once daily</td>
<td>56 days opened at room temp</td>
</tr>
</tbody>
</table>

*Approved for Type 1 and Type 2 Diabetes, Adults only*

Prescribing Information: TOUJEEO (insulin glargine)
Prescribing Information: TRESIBA (insulin degludec)
Pharmacokinetics and Pharmacodynamics

Insulin degludec
Onset: 1 hour
Steady State: 3-4 days

Insulin glargine 300 units/ml
Onset: 6 hours
Steady State: 5 days

Prescribing Information: TOUJEEO (insulin glargine)
Prescribing Information: TRESIBA (insulin degludec)
Clinical Efficacy

Insulin glargine 300 units/ml

- Dosing regimen remains every 24 hours
- No difference in HbA1c reduction in compared to Insulin glargine 100 units/ml

Insulin degludec

- Dosed every 24 hours in comparison to insulin detemir and insulin glargine, no difference in HbA1c reduction
- Dosed alternating timings in comparison to insulin glargine 100 units/ml, no difference in HbA1c reduction

Prescribing Information: TOUJEO (insulin glargine)
Prescribing Information: TRESIBA (insulin degludec)
Which one do you choose?

**Insulin glargine 300 units/ml**
- Patients at risk for nocturnal hypoglycemia

**Insulin degludec**
- Patients requiring >80 units/day
- Patients that are unable to maintain every 24 hour dosing regimen
Where do we go from here??

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Improved Safety

Improved Efficacy

Alternative targets for glucose homeostasis

New Anti-hyperglycemic Agents
GLP-1 Effects in Humans

GLP-1 secreted upon the ingestion of food

↓ Beta-cell workload

Promotes satiety and reduces appetite

α cells:
↓ Postprandial glucagon secretion

Liver:
↓ Glucagon reduces hepatic glucose output

Stomach:
Helps regulate gastric emptying

β cells:
Enhances glucose-dependent insulin secretion

↑ Beta-cell response

Adapted from Nauck MA, et al. Diabetologia. 1996;39:1546-1553
Adapted from Drucker DJ. Diabetes. 1998;47:159-169
# GLP-1 Analogs

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Dosing Formulation and Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>exanatide</td>
<td>Byetta® Bydureon®</td>
<td>Pen: subcut BID Single Dose Pen?: subcut qweek*</td>
</tr>
<tr>
<td>liraglutide</td>
<td>Victoza®</td>
<td>Pen: subcut qday</td>
</tr>
<tr>
<td>dulaglutide</td>
<td>Trulicity®</td>
<td>Single Dose Pen: subcut qweek</td>
</tr>
<tr>
<td>albiglutide</td>
<td>Tanzeum®</td>
<td>Single Dose Pen: subcut qweek*</td>
</tr>
<tr>
<td>lixisenatide</td>
<td>Adlyxin®</td>
<td>Pen: subcut qday</td>
</tr>
</tbody>
</table>

*Medication must be reconstituted prior to administration

Prescribing Information: BYETTA (exanatide), Prescribing Information: BYDUREON (exanatide), Prescribing Information: VICTOZA (liraglutide), Prescribing Information: TRULICITY (dulaglutide), Prescribing Information: TANZEUM (albiglutide), Prescribing Information: ADLYXIN (lixisenatide)
Clinical Efficacy

Additional HbA1c Reduction when added to Metformin

- **LIRAGlutide**: 1.1%
- **DULAGlutide**: 1.1%
- **ALBIGlutide**: 0.9%
- **LIXISENATIDE**: 0.9%

### GLP-1 Analogs with Insulin??

<table>
<thead>
<tr>
<th>Type 2 Diabetes</th>
<th>Type 1 Diabetes</th>
</tr>
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<tbody>
<tr>
<td>• HbA1c reduction</td>
<td>• HbA1c reduction</td>
</tr>
<tr>
<td>• Liraglutide 0.9% vs. placebo 0%</td>
<td>• Liraglutide 0.5% vs. placebo 0.3%</td>
</tr>
<tr>
<td>• No significant difference in weight, total daily insulin dose, or occurrence of hypoglycemia</td>
<td>• Weight change</td>
</tr>
<tr>
<td></td>
<td>• Liraglutide -5.9 kg vs. placebo +0.2 kg</td>
</tr>
<tr>
<td></td>
<td>• Insulin dose</td>
</tr>
<tr>
<td></td>
<td>• Liraglutide +4.1 units/kg vs. placebo +13.4 units/kg</td>
</tr>
</tbody>
</table>

Safety Profile

• Contraindications
  - Medullary thyroid carcinoma history or family history
  - Multiple endocrine neoplasia syndrome type 2
  - Type 1 Diabetes?
  - Pancreatitis?

• Risk of Hypoglycemia
  - Greater when used in combination with insulin or sulfonylureas
  - Reduce dose of sulfonylurea by half

• Adverse effects
  - Nausea, vomiting, dyspepsia
  - Weight Loss ranges from -1.8 kg to -3.1 kg (~4-7 lbs)
GLP-1 Analogs: Place in therapy

Baseline A1c between 7-8%

Add to metformin therapy as second line agent in obese patients

May have better efficacy in patient’s earlier in disease process

Potential to lower A1c in patient’s with T2DM on insulin therapy
Where do we go from here??

Desirable Administration Regimens

Improved Safety

Improved Efficacy

Alternative targets for glucose homeostasis

New Anti-hyperglycemic Agents
Sodium/Glucose Cotransporter 2 (SGLT-2) Inhibitors

SGLT2 inhibitors suppress the action of SGLT2

Reduce glucose reabsorption

Increase urinary glucose excretion

Lost in urine
# SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Dosing Regimen</th>
</tr>
</thead>
</table>
| canagliflozin   | Invokana® | eGFR ≥ 60ml/min: 100mg-300mg po qam  
|                 |           | eGFR 45-59ml/min: 100mg po qam 
|                 |           | eGFR < 45ml/min: not recommended                                               |
| dapagliflozin   | Farxiga®  | eGFR ≥60ml/min: 5mg-10mg po qam  
|                 |           | eGFR <60ml/min: not recommended                                                |
| empagliflozin   | Jardiance®| eGFR ≥ 45ml/min: 10mg, 25mg po qam  
|                 |           | eGFR < 45ml/min: not recommended                                              |
Clinical Efficacy

HbA1c Reduction as add on to Metformin

- DAPAGLIFLOZIN: 0.84%, p<0.0001
- EMPAGLIFLOZIN: 0.77%, p<0.001

Clinical Efficacy

HbA1c Reduction compared to 2nd Line Agents

- CANAGLIFLOZIN: 0.93%
- GLIMEPERIDE: 0.81%
- SITAGLIPTIN: 0.73%

Clinical Efficacy

HbA1c Reduction as add on to metformin vs. metformin and sitagliptin

Jabour SA, et. al. Diabetes Care 2014
## SGLT-2 inhibitors with Insulin??

**Type 2 Diabetes**
- **HbA1c reduction**
  - empagliflozin 0.6% greater A1c reduction than insulin alone at 78 weeks
- No significant difference in occurrence of hypoglycemia, no reports of DKA

**Type 1 Diabetes**
- **HbA1c reduction**
  - empagliflozin 0.35% to 0.49% greater than placebo (p<0.01)
- Weight change reported was between -1.5 kg and -1.9 kg
- Reduction in total daily insulin dose and hypoglycemic episodes

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Safety Profile

- Incidence of hypoglycemia
  - Monotherapy: 0.9% to 1.8%
  - In combination with metformin: 1.8% to 6%

- Incidence of Urinary Tract Infections
  - Monotherapy: 3.8% to 6.4%
  - In combination with metformin: 4% to 12.7%

- Incidence of genital infection (mycotic)
  - Monotherapy: 3.7% to 5.8%
  - In combination with metformin: 3% to 13%
  - More frequent in women

SGLT-2 Inhibitors: Place in therapy

Baseline A1c between 7-8%, possibly more effective at higher A1c values (>10%)

Patient’s at risk for hypoglycemia

Patient’s later in the disease process (duration of disease > 10 years) with normal renal function

Added to metformin, slightly more efficacious than sulfonylureas, preferred over DPP-IV inhibitors

Limited clinical benefit when added as a third line agent
Patient and Provider Education

- Monitoring requirements
- Cost restraints
- Complexity of regimen
- Health literacy

Optimal Drug Outcomes
Conclusions

- New agents are approved for the treatment of Type 2 DM, and would be appropriate as second line agents added to metformin.

- The HbA1c reduction achieved by GLP-1 agonist and SGLT-2 inhibitors indicate they would be most appropriate in patients with moderately uncontrolled diabetes.

- Data for use of GLP-1 agonist and SGLT-2 inhibitors in Type 1 DM is limited, but appears to provide some clinical benefits.

- Patient and provider education is key in optimizing medication outcomes.
Questions

e-mail: nahmed-sarwar@sjfc.edu