Updates in Diabetes Mellitus Pharmacotherapy

Jennifer Grelle, Pharm.D., BCPS
Clinical Pharmacist, Abilene Regional Medical Center
Assistant Professor, Adult Medicine Division
Disclosures

• None
Learning Objectives

• Review the newly approved anti-glycemic agents.

• Discuss the impact of new agents on current treatment recommendations.

• Design a regimen using the new medications when given a patient case.
Recent FDA Drug Approvals

2013

- Invokana® (canagliflozin)
- Nesina® (alogliptin)

2014

- Bydureon® (exenatide ER)
- Afrezza® (insulin human)
- Trulicity® (dulaglutide)

- Farxiga® (dapagliflozin)
- Tanzeum® (albiglutide)
- Jardiance® (empagliflozin)
New Drugs by Pharmacologic Class

• **Sodium-glucose co-transporter 2 (SGLT2) Inhibitors**
  - Invokana® (canagliflozin)
  - Farxiga® (dapagliflozin)
  - Jardiance® (empagliflozin)

• **Glucagon-Like Peptide 1 Agonist**
  - Bydureon® (exenatide extended-release)
  - Tanzeum® (albiglutide)
  - Trulicity® (dulaglutide)

• **Dipeptidyl peptidase-4 inhibitor**
  - Nesina® (alogliptin)

• **Rapid Acting Inhaled Insulin**
  - Afrezza® (technosphere insulin)
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

Invokana® (canagliflozin)
Farxiga® (dapagliflozin)
Jardiance® (empagliflozin)
SGLT2 Inhibitor Mechanism of Action

SGLT2 Inhibitors: How do they work?

Plasma glucose (mg/dL)

200
300
400

Glucose filtration/reabsorption/excretion (mg/min)

200
300
400

SGLT2 Inhibition

Diabetic glucose transport rate

Diabetic Threshold

Normal glucose transport rate

Normal Threshold

SGLT2 Inhibition

# SGLT2 Inhibitor Dosing

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invokana® (canagliflozin)</td>
<td>100 mg PO daily prior to 1\textsuperscript{st} meal of day</td>
<td>300 mg PO daily</td>
</tr>
<tr>
<td>Farxiga® (dapagliflozin)</td>
<td>5 mg PO daily with/without food</td>
<td>10 mg PO daily</td>
</tr>
<tr>
<td>Jardiance® (empagliflozin)</td>
<td>10 mg PO daily with/without food</td>
<td>25 mg PO daily</td>
</tr>
</tbody>
</table>
# SGLT2 Inhibitor Renal Adjustments

<table>
<thead>
<tr>
<th></th>
<th>&lt; 60 mL/min/1.73 m²</th>
<th>&lt; 45 mL/min/1.73 m²</th>
</tr>
</thead>
</table>
| **Invokana®** (canagliflozin) | 100 mg PO daily*  
*Screen for UGT enzyme inducer meds – do not use                                        | X                   |
| **Farxiga®** (dapagliflozin)                          | X                                                                                     | X                   |
| **Jardiance®** (empagliflozin)                      | No adjustment                                                                         | X                   |
Canagliflozin: HgA1c Changes

% Change in A1c in 26 or 52* wks

PLACEBO  GLIM*  SITA 100 mg*  MET-SU*  MET-PIO

Comparator  CANA 100 mg  CANA 300 mg

Canagliflozin: Weight Changes

![Weight Change Graph](image)

**Weight Change from Baseline (kg)**

- PLACEBO
- GLIM*
- SITA 100 mg*
- MET-SU*
- MET-PIO

**Comparators**:
- CANA 100 mg
- CANA 300 mg

**Add-On**

- Diabetology, 2014;16:467-477
SGLT-2 Inhibitor Class Efficacy/Safety Data

- **A1c**: Reduction up to 1% with monotherapy. Reduction of 0.6-0.8% as “add-on” therapy.
- **Kg**: Average of 3 kg weight loss.
- **SBP**: Diuretic effect results in ~5 mmHg decrease.
- **Glu**: Hypoglycemia not anticipated based on MOA.
SGLT2 Adverse Effects

Genital mycotic & urinary tract infections
  - Females > males

Orthostatic hypotension & postural dizziness
  - Infrequent but greater risk with older age, concomitant loop diuretics, and decreased renal function

Lipid Parameters
  - ↑ LDL, ↑ HDL, ↓ TGs (wash?)

Malignancies
  - Dapagliflozin was associated with an increased number of breast and bladder cancers.
**SGLT2 Inhibitors Summary**

- **Place in therapy:** Add-on therapy or intolerant to metformin

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>High efficacy</td>
<td>Costly</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Reduced efficacy w/CKD</td>
</tr>
<tr>
<td>Very low risk of hypoglycemia</td>
<td>May result in hypotension</td>
</tr>
</tbody>
</table>

- **Counseling Points**
  - Monitor for signs/symptoms of yeast infections & UTIs
  - Changes in usual urination patterns (volume, frequency)
  - Dehydration
Glucagon-Like Peptide 1 Agonist

Bydureon® (exenatide extended-release)
Tanzeum® (albiglutide)
Trulicity® (dulaglutide)
GLP-1 Agonist Mechanism of Action

- inappropriate glucagon secretion
- glucose-dependent insulin secretion
- satiety
- gastric emptying

### GLP-1 Agonists Dosing

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta® (exenatide)</td>
<td>5-10 mcg SubQ BID</td>
</tr>
<tr>
<td>Bydureon® (exenatide ER)</td>
<td>2 mg SubQ weekly</td>
</tr>
<tr>
<td>Tanzeum® (albiglutide)</td>
<td>30-50 mg SubQ weekly</td>
</tr>
<tr>
<td>Trulicity® (dulaglutide)</td>
<td>0.75-1.5 mg SubQ weekly</td>
</tr>
<tr>
<td>Victoza® (liraglutide)</td>
<td>0.6-1.2 mg SubQ daily</td>
</tr>
</tbody>
</table>
At 30 weeks, no difference in weight loss between ER and IR (-3.7 vs. -3.6 kg).
Exenatide ER Efficacy

**DURATION 4**
(26 weeks)

- Mean A1c Change (%): -1.5, -1.5, -1.2
- p < 0.001

**DURATION 6**
(26 weeks)

- Mean A1c Change (%): -1.3, -1.5
- 95% CI 0.08-0.33
- Non-Inferiority CI Margin < 0.25%

LIRA resulted in 0.9 kg weight loss (p=0.0005).

Tanzeum® (albiglutide) Efficacy

HARMONY 2
(52 weeks)

Mean A1c Change (%)

HARMONY 7
(32 weeks)

Non-Inferiority
p value = 0.08

LIRA resulted in 1.55 kg > weight loss (p<0.05).

Trulicity® (dulaglutide) Efficacy

**AWARD 1**
52 weeks

**Non-Inferiority**
p value < 0.0001

**AWARD 6**
26 weeks

LIRA resulted in 0.71 kg > weight loss (p=0.011).

GLP-1 Agonist Adverse Effects

- **Gastrointestinal (Most common)**
  - Nausea, vomiting and/or diarrhea
  - Dose dependent and usually resolves after 8 weeks of therapy
  - Exenatide IR > liraglutide ~ dulaglutide ~exenatide ER > albiglutide

- **Pancreatitis (Rare)**
  - If suspect pancreatitis, discontinue therapy.
  - If pancreatitis confirmed and unknown etiology, do not resume therapy.

- **Thyroid Tumors (**all agents w/labeling except Byetta®**)**
  - Contraindicated in patients with history or family history of:
    - Medullary thyroid carcinoma (MTC)
    - Multiple endocrine neoplasia syndrome Type 2 (MEN2)
GLP-1 Agonist Summary

• **Place in therapy:** Add-on

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>High efficacy</td>
<td>GI side effects</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Injectable</td>
</tr>
<tr>
<td>Low risk of hypoglycemia</td>
<td>Costly</td>
</tr>
</tbody>
</table>

• **Clinical Pearls**
  
  • Concurrent use of sulfonylurea and/or insulin increases risk for hypoglycemia.
  
  • If dose missed, administer within 3 days of regularly scheduled time.
  
  • May administer each of the new GLP-1 agonists without regard for meals.
  
  • Byetta® → Bydureon®: may observe increased glucose levels for ~ 2 weeks.
Dipeptidyl peptidase-4 inhibitors

Nesina® (alogliptin)
Tradjenta® (linagliptin)
Onglyza® (saxagliptin)
Januvia® (sitagliptin)
Dipeptidyl Peptidase IV Inhibitors Mechanism of Action

DPP-4 Inhibitors

GLP-1 “Active”

GLP-1 “Active”

inappropriate glucagon secretion

satiety gastric emptying

glucose-dependent insulin secretion

Liver

Stomach

Duodenum

Pancreas

insulin

stomach

intestine

inappropriate glucagon secretion

satiety gastric emptying

glucose-dependent insulin secretion

Liver

Stomach

Duodenum

Pancreas

insulin

stomach

intestine
Nesina® (alogliptin)

- FDA approved for Type 2 DM
- Recommended Dose
  - 25 mg PO daily
- Renal Impairment
  - CrCl $\geq$ 30 to $< 60$ mL/minute: 12.5 mg PO daily
  - CrCl $\geq$ 15 to $< 30$ mL/minute: 6.25 mg PO daily
  - CrCl $< 15$ mL/minute or hemodialysis: 6.25 mg PO daily
  - Peritoneal dialysis: Not studied
- Hepatic Impairment
  - Mild-Moderate (Child-Pugh A & B): no adjustment needed
  - Severe (Child-Pugh C): avoid use (*not studied*)
Nesina® (alogliptin) Efficacy

% Change in A1c in 26 wks

PLACEBO
PIO
PIO
MET-PIO
Insulin

ALOG 12.5 mg
ALOG 25 mg
Comparator
Nesina® (alogliptin) Safety

- Hypoglycemia
  - Rates of 1.5-3% observed in clinical studies

- Common Adverse Effects
  - Headache (4-5%)
  - Upper respiratory tract infection (4%)

- Serious Adverse Effects
  - Fatal & non-fatal liver failure (draw liver enzymes at baseline)
  - Pancreatitis
  - Steven-Johnson Syndrome
  - Angioedema
Nesina® (alogliptin) Summary

• Place in Therapy: **Add-On**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight neutral</td>
<td><em>Moderate efficacy</em></td>
</tr>
<tr>
<td>Low risk of hypoglycemia</td>
<td>Costly</td>
</tr>
</tbody>
</table>

• **Combination Agents**
  • Kazano® (alogliptin + metformin)
  • Oseni® (alogliptin + pioglitazone)

• **Comparison to other DPP-4 inhibitors**
  • Similar efficacy, hypoglycemia rates and $$$
Rapid-Acting Inhaled Insulin

Afrezza® (technosphere insulin)
Time to Peak Insulin Level

- Early insulin response in healthy individuals
- AFREZZA™
- Rapid-Acting Analog
- Regular Human Insulin

Data from different studies

2. Insulin Aspart, 0.2 U/kg. Regular Human Insulin, 0.2 U/kg units. Subcutaneous injection in abdomen. Adapted from Mudaliar SR et al. Diabetes Care. 1999;22:1501-1506.
## Afrezza® Dosing

<table>
<thead>
<tr>
<th>Injected Mealtime Insulin Dose</th>
<th>AFREZZA® Dose</th>
<th># of 4 unit (blue) cartridges needed</th>
<th># of 8 unit (green) cartridges needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 4 units</td>
<td>4 units</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Afrezza® (technosphere) Efficacy Data

T1DM

-0.2

-0.41

T2DM

-0.58

-0.7

Afrezza® Therapy Considerations

• **Contraindications**
  - Asthma
  - Chronic obstructive pulmonary disease

• **Warning**
  - Smokers
  - Lung cancer

• **Monitoring**
  - Assess pulmonary function tests: baseline, at 6 months, and annually
Afrezza® (rapid-acting inhaled insulin)

- Place in Therapy (approval in adults only):
  - Uncontrolled T2DM after adequate oral therapy trial
  - Use in T1DM management in place of injectable rapid/intermediate-acting insulin

Anticipate arrival to United States market in 1st quarter of 2015
Putting the pieces together:
Therapy Selection
## T2DM Treatment Strategies

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>1st Add-On Therapy</th>
<th>2nd Add-On Therapy</th>
<th>Multi-Dose Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Sulfonylurea (SU)</td>
<td>Thiazolidinedione (TZD)</td>
<td>Basal insulin</td>
</tr>
<tr>
<td></td>
<td>DPP-4 Inhibitor (DPP-4i)</td>
<td>GLP-1 Agonist (GLP-1-RA)</td>
<td>SGLT2-i</td>
</tr>
<tr>
<td>PLUS 1 of the following:</td>
<td>TZD DPP-4i GLP-1-RA SGLT2-i Basal Insulin</td>
<td>SU DPP-4i GLP-1-RA SGLT2-i Basal Insulin</td>
<td>SU TZD SGLT2-i Basal Insulin</td>
</tr>
<tr>
<td></td>
<td>TZD DPP-4i GLP-1-RA SGLT2-i</td>
<td>Basal Insulin</td>
<td>TZD DPP-4i GLP-1-RA SGLT2-i</td>
</tr>
<tr>
<td>Efficacy (HgA1c)</td>
<td>Insulin &gt; MET-TZD-SU-GLP-1-RA &gt; DPP-4i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>GLP-1-RA &gt; MET &gt; DPP-4 &gt; SU-TZD-Insulin (gain)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Insulin &gt; SU &gt; MET-TZD-GLP-1-RA-DPP-4i</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient Case

A 52 year-old female with T2DM presents to your clinic. She is currently receiving metformin 1000 mg PO BID and her HbA1c today is 8.5%.

PMH: HTN, COPD, thyroid carcinoma, chronic pancreatitis
Vitals: BP 138/89  HR 75  eGFR: 95 mL/min/m²

Which of the following would be the most appropriate add-on therapy?

a. Invokana® 100 mg PO daily
b. Tanzeum® 30 mg SubQ weekly
c. Nesina® 6.25 mg PO daily
d. Afrezza® 5 units AC + Lantus 10 units QPM
QUESTIONS

Jennifer.grelle@ttuhsc.edu