Non-Insulin Pharmacotherapy for Type 2 Diabetes Mellitus

Kevin T. Schleich, Pharm.D., BCACP
Clinical Pharmacy Specialist, Department of Family Medicine
University of Iowa Hospitals and Clinics

Objectives

• Become more familiar with guideline recommendations for treatment of type 2 diabetes mellitus

• More fully understand the following aspects of different medications available for the treatment of type 2 diabetes mellitus:
  • Mechanism of action
  • Place in therapy
  • Expected efficacy
  • Potential adverse effects
  • Cost of therapy

• Get introduced to emerging therapies for the treatment of type 2 diabetes mellitus

ADA Treatment Algorithm

• ADA includes the following non-insulin medication options:
  • Metformin
  • Sulfonylureas
  • Thiazolidinedione
  • DPP-4 Inhibitors
  • SGLT-2 Inhibitors
  • GLP-1 Receptor Agonists
AACE Treatment Algorithm

- AACE includes the following non-insulin medication options:
  - Metformin
  - GLP-1 Receptor Agonists
  - DPP-4 Inhibitors
  - Alpha-glucosidase Inhibitors
  - SGLT-2 Inhibitors
  - Thiazolidinediones
  - Sulfonylureas
  - Glinides
  - Bile Acid Sequestrants
  - Bromocriptine

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician.
Permission from the author must be sought before reuse or redistribution.
What Are All These Medications?

Metformin
(First-Line Unless Contraindicated)

• **Mechanism:**
  • Inhibits hepatic gluconeogenesis
  • Enhances insulin sensitivity in muscle and fat

• **Efficacy:** ↓ A1c by 1.0% to 1.5%

• **Adverse Effects:**
  • **Common:** nausea and GI upset (take with food, start at low dose)
  • **Severe:** lactic acidosis (SCr ↓ >1.4 mg/dL; ↑ >1.5 mg/dL)

• **Dose:** start at 500 mg daily, increase slowly to max 2550 mg/d
  • Max of 2000 mg/d of XR version

<table>
<thead>
<tr>
<th>Weight Effect</th>
<th>Hypoglycemia Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral to ↓</td>
<td>Lactic acidosis</td>
<td>$544</td>
</tr>
</tbody>
</table>
Sulfonylureas

- **Mechanism:** stimulates the pancreas to secrete more insulin

- **Available Medications:**
  - **First Generation:** chlorpropamide, tolazamide, tolbutamide
  - **Second Generation:** glipizide, glipizide XR (20 mg/d max), glimepiride (8 mg/d max)

- **Efficacy:** ↓ A1c by 1.0% to 1.5% (reduced efficacy over time)

- **Adverse Effects:** hypoglycemia, weight gain

### Efficacy

<table>
<thead>
<tr>
<th>Weight Effect</th>
<th>Hypoglycemic Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>higher risk (tend to)</td>
<td>$340</td>
</tr>
</tbody>
</table>

Now What??

Incretin-Based Therapies

- **GLP-1 Agonists**
  - Exenatide (Byetta®)
  - Exenatide ER (Bydureon®)
  - Liraglutide (Victoza®)
  - Albiglutide (Tanzeum®)
  - Dulaglutide (Trulicity®)

- **DPP-4 Inhibitors**
  - Alogliptin (Nesina®)
  - Linagliptin (Tradjenta®)
  - Saxagliptin (Onglyza®)
  - Sitagliptin (Januvia®)
GLP-1 Agonists
(Glucagon-like peptide-1 agonist)

• AKA: “incretin mimetics”

• Mechanism: Stimulates GLP-1 receptor (GLP = incretin hormone)
  - ↑ insulin production/secretion
  - ↓ glucagon release/glucose production
  - Slowing of gastric emptying
  - Increased satiety

GLP-1 Agonists

• All Subcutaneous Injectables

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Max Dose</th>
<th>Supplied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta®)</td>
<td>5 mcg twice daily</td>
<td>10 mcg twice daily</td>
<td>Prefilled pen</td>
</tr>
<tr>
<td>Liraglutide (Victoza®)</td>
<td>0.6 mg daily</td>
<td>1.8 mg daily</td>
<td>Prefilled pen</td>
</tr>
<tr>
<td>Exenatide ER (Bydureon®)</td>
<td>2 mg weekly</td>
<td>2 mg weekly</td>
<td>Prefilled pen</td>
</tr>
<tr>
<td>Albiglutide (Tanzeum®)</td>
<td>30 mg weekly</td>
<td>50 mg weekly</td>
<td>Prefilled pen/kit*</td>
</tr>
<tr>
<td>Dulaglutide (Trulicity®)</td>
<td>0.75 mg weekly</td>
<td>1.5 mg weekly</td>
<td>Prefilled pen</td>
</tr>
</tbody>
</table>

- **Efficacy:** ↓ A1c by 1.0% to 1.5%
- **Adverse Effects:** Headache, nausea, diarrhea, pancreatitis?
- Nausea may be least pronounced with exenatide ER

GLP-1 Agonists

“3’s the Magic Number”

• **Helpful Tips**
  - **Exenatide** (IR and ER) should be avoided with CrCl < 30 mL/min
  - If patient omits > 3 doses of liraglutide, initial titration should be restarted to avoid GI upset
  - For weekly formulations, if > 3 days late, wait for next dose to administer
  - Can be used in combination with insulin
    - Basal insulin + GLP-1 agonist
    - Bolus insulin + GLP-1 agonist

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician.
Permission from the author must be sought before reuse or redistribution.
GLP-1 Agonists
Combined with Insulin

- Basal
- Bolus

Shown to decrease:
- Fasting blood glucose
- Post-prandial blood glucose
- Hemoglobin A1c

- Required insulin dose reduction ranged from 15%–45% in studies
- Decrease basal dose by 10%
- Decrease bolus dose by 35%

Required insulin dose reduction ranged from 30%–40% in studies

Black Box Warning
Thyroid C-cell tumors have been observed in animal studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown if any of the commercially available GLP-1 agonists cause thyroid C-cell tumors in humans, including medullary thyroid carcinoma (MTC). These are contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2.

DPP-4 Inhibitors
(Dipeptidylpeptidase-4 inhibitor)

- AKA: "gliptins"
- Mechanism:
  - Inhibits the degradation of incretins (GLP-1 and GIP) into their inactive metabolites

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician. Permission from the author must be sought before reuse or redistribution.
DPP-4 Inhibitors
(Dipeptidylpeptidase-4 inhibitor)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial &amp; Max Dose</th>
<th>Combos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin (Nesina®)</td>
<td>25 mg PO daily</td>
<td>metformin: Kazano® + pioglitazone: Oseni®</td>
</tr>
<tr>
<td>Linagliptin (Tradjenta®)</td>
<td>5 mg PO daily</td>
<td>metformin, pioglitazone</td>
</tr>
<tr>
<td>Napaglipitin (Single®)</td>
<td>2.5 mg PO daily</td>
<td>metformin, saxagliptin</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza®)</td>
<td>2.5 to 5 mg PO daily</td>
<td>metformin, saxagliptin, linagliptin</td>
</tr>
<tr>
<td>Sitagliptin (Januvia®)</td>
<td>100 mg PO daily</td>
<td>metformin, saxagliptin, linagliptin</td>
</tr>
</tbody>
</table>

- **Efficacy**: ↓ A1c by 0.5% to 1.0%
- **Adverse Effects**: pancreatitis(?)
  - Saxagliptin may worsen heart failure
  - Linagliptin: no dosage adjustment for renal impairment

## Weight Effect

<table>
<thead>
<tr>
<th>Weight Effect</th>
<th>Hypoglycemia Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral</td>
<td>Low Risk</td>
<td>$$$</td>
</tr>
</tbody>
</table>

## GLP-1 Agonists/DPP-4 Inhibitors

Pancreatitis Risk

Systematic Review/Meta-analysis (n=59)
- 55 RCTs, 3 Cohorts, 1 Case-Control

<table>
<thead>
<tr>
<th>Study</th>
<th>PancreatitisRisk</th>
<th>Heterogeneity</th>
<th>Meta analysis with fixed effects</th>
<th>Meta analysis with random effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>datum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician. Permission from the author must be sought before reuse or redistribution.
Pancreatitis Risk

• “The available evidence suggests that the incidence of pancreatitis in patients taking incretin-therapy is low and that these drugs do not increase the risk of pancreatitis”

• “The current body of evidence is not definitive…”

• Prudent to avoid in patients with a history of pancreatitis

• Control risk factors known to contribute to pancreatitis
  • Moderation of EtOH
  • Low-fat diets
  • Weight management

Thiazolidinediones (TZDs)

• **Mechanism:** ↑insulin sensitivity in muscles by ↑glucose transporter expression

• **Efficacy:** ↓A1c by 1.0 to 1.5% (similar to sulfonylureas)

• **Available Medications:**
  • Pioglitazone (Actos®): initial dose of 15 mg daily (max 45 mg/day)

• **Adverse Effects:** edema, heart failure, ↑fracture risk, URI
  • Linked to possibility of bladder cancer

<table>
<thead>
<tr>
<th>Weight Effect</th>
<th>Hypoglycemia Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>Low Risk</td>
<td>$$$ (≈$00/month)</td>
</tr>
</tbody>
</table>
Thiazolidinediones (TZDs)

Bladder Cancer

- Rosiglitazone implicated more than pioglitazone
- Pioglitazone has been associated with bladder cancer
- Duration of use is positively associated with increasing incidence
- "Pioglitazone: No Longer a Worry for Bladder Cancer?"
  - "...no statistically significant increased risk of bladder cancers was demonstrated with pioglitazone use"

SGLT-2 Inhibitors (Sodium-glucose Co-transporter 2 Inhibitor)

- **Mechanism:**
  - Normal glucose handling
  - In diabetes mellitus

- **Efficacy:**
  - ↓ A1c by 0.7% to 1.0%

- **Available Medications**
  - Canagliflozin (Invokana®): 100 mg daily (up to 300 mg/day)
  - Dapagliflozin (Farxiga®): 5 mg daily (up to 10 mg/day)
  - Empagliflozin (Jardiance®): 10 mg daily (up to 25 mg/day)

- **Common Adverse Effects:**
  - Genital fungal infections, UTI, increased urination, hypotension

- **Renal dysfunction:**
  - GFR < 60 mL/min: avoid dapagliflozin
  - GFR < 45 mL/min: avoid canagliflozin, empagliflozin

- **Contraindicated GFR < 30 mL/min**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Hypoglycemia Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40</td>
<td>Low Risk</td>
<td>$$$</td>
</tr>
<tr>
<td>40-90</td>
<td>Low Risk</td>
<td>$$$</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>Low Risk</td>
<td>$$$</td>
</tr>
</tbody>
</table>
SGLT-2 Inhibitors

- Positive Cardiovascular Effects?
  - EMPI-REG OUTCOME Trial
    - Empagliflozin patients had less
      - Heart failure hospitalizations
      - Cardiovascular events
      - Cardiovascular deaths
      - All-cause deaths
  - Effect was only seen early in the trial, and not sustained throughout
  - Positive effects have been argued to occur due to diuretic effect of SGLT-2 inhibitors

SGLT-2 Inhibitor ADEs

- LDL Elevation: dose-related increase
  - Canagliflozin 100 mg: ↑ LDL 2.9%
  - Canagliflozin 300 mg: ↑ LDL 7.1%

- Stroke
  - High number of CV events during the first 30 days of treatment with canagliflozin
  - Subsequent meta-analysis showed no further significant increase in cardiovascular adverse events during extended use

- Cancer
  - In a post-marketing surveillance program, a disproportionate amount of breast and bladder cancers were noted in patients receiving dapagliflozin
  - Neither types of cancer were previously identified as possible ADE's in randomized trials

---

Diabetic Ketoacidosis

- May 2015, FDA issued a warning that treatment with SGLT2 inhibitors may increase the risk of ketoacidosis
- > 20 cases reported as of June 2014
- 3 proposed mechanisms
  1. When combined with insulin, often decrease insulin dose to avoid hypoglycemia. Lower dose of insulin may not fully suppress lipolysis and ketogenesis
  2. SGLT-2 is expressed in pancreatic α-cells; SGLT-2 inhibition may promote glucagon secretion
  3. Phlorizin, a nonselective inhibitor of SGLT family transporters decreases urinary excretion of ketone bodies
It's Becoming a Stretch

http://www.cloudsidekick.com/blog/stretch-armstrong.html

Class (Medications) Mechanism Efficacy (∆ A1c %) Adverse Effects Comments

α-glucosidase inh. Acarbose (Precose®) Miglitol (Glyset®) Inhibit breakdown of carbohydrates to glucose 0.5% – 1.0% Gas, bloating, diarrhea Must treat hypoglycemia with simple sugar

Glutamate analogs Nateglinide (Starlix®) Repaglinide (Prandin®) Stimulate insulin secretion from pancreas 0.5% – 1.0% Hypoglycemia, increased uric acid Fast acting with short half-life

Amylin Analogs Pramlintide (Symlin®) Delays gastric emptying; increased early satiety 0.5% – 1.0% Nausea, hypoglycemia Three times daily subQ injection prior to meals

Bile Acid Sequestrant Colesevelam (Welchol®) ↓ insulin resistance ↓ glucose production ↓ glucose absorption 0.5% – 1.0% Nausea, constipation, indigestion Large pill burden; 6 tabs/day

Is Diabetes Management Shifting?

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician. Permission from the author must be sought before reuse or redistribution.
My Algorithm for **MOST**

1. **Metformin**
   - Yes
   - Metformin ineffective
   - Sulfonylurea (not glyburide)
   - Basal insulin

2. **Sulfonylurea**
   - Yes
   - Metformin ineffective
   - GLP-1 agonist
   - TZD/SGLT-2 inhibitors
   - Basal insulin

3. **GLP-1 agonist**
   - Yes
   - Metformin ineffective
   - DPP-4 inhibitors
   - TZDs/SGLT-2 inhibitors
   - Basal insulin

4. **DPP-4 Inhibitors**
   - Yes
   - Metformin ineffective
   - SGLT-2 inhibitors
   - GLP-1 agonist
   - Basal insulin

5. **SGLT-2 Inhibitors**
   - Yes
   - Metformin ineffective
   - GLP-1 agonist
   - DPP-4 inhibitors
   - Basal insulin

Candidates for “New Meds”

<table>
<thead>
<tr>
<th>Medication</th>
<th>Appropriate Candidate</th>
<th>Poor Candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 Ag</td>
<td>A1c ≤ 8.0%</td>
<td>History of pancreatitis</td>
</tr>
<tr>
<td></td>
<td>No concern about weight gain, and adherence with diet/exercise</td>
<td>Compromised renal function (exenatide)</td>
</tr>
<tr>
<td></td>
<td>Sluggish response when top agents could be tested</td>
<td>History of severe GI disturbance</td>
</tr>
<tr>
<td></td>
<td>Relative contraindication</td>
<td>History of heart failure</td>
</tr>
</tbody>
</table>

| DPP-4 Inhibitors | A1c ≤ 8.0% | Stage 4 CKD or worse |
|                  | No concern about weight gain, and adherence with diet/exercise | History of hyperkalemia (canagliflozin) |
|                  | Compromised renal function (linagliptin does NOT require dosage adjustment) | History of bladder cancer (dapagliflozin) |

| SGLT-2 Inhibitors | A1c ≤ 8.0% | Stage 4 CKD or worse |
|                   | No concern about weight gain, and adherence with diet/exercise | History of hyperkalemia (canagliflozin) |
|                   | Compromised renal function (exenatide) | History of bladder cancer (dapagliflozin) |

Wrap-Up

- Many still largely turn to metformin and sulfonylureas as first and second line agents

- Consideration should be given to emerging agents when insurance allows and safety is considered

- No agent is the “miracle drug” that will cure diabetes

- Dietary modifications and physical activity MUST be cornerstones of diabetic therapy
Questions/Discussion

Kevin T. Schleich, Pharm.D., BCACP
Clinical Pharmacy Specialist, Department of Family Medicine
University of Iowa Hospitals and Clinics

These materials provided for reference use at the 43rd Annual Family Medicine Refresher Course for the Family Physician.
Permission from the author must be sought before reuse or redistribution.