Non-Insulin Pharmacotherapy for Type 2 Diabetes Mellitus

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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
ADA Treatment Algorithm

Healthy eating, weight control, increased physical activity, and diabetes education

**Mono-therapy**
- Efficacy
- Hypoglycemia
- Weight
- Side effects
- Costs

**Dual therapy**
- Efficacy
- Hypoglycemia
- Weight
- Side effects
- Costs

**Triple therapy**

**Combination injectable therapy**

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient and disease-specific factors):

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Drug 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Metformin</td>
<td>Metformin</td>
<td>Metformin</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight loss</td>
<td>Hypoglycemia</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>rare</td>
<td>rare</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choices dependent on a variety of patient and disease-specific factors):

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
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<td>high</td>
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<td>intermediate</td>
<td>intermediate</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
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<td>Weight loss</td>
<td>Hypoglycemia</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>rare</td>
<td>rare</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2i.

<table>
<thead>
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<td>intermediate</td>
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</tr>
<tr>
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<td>No</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight loss</td>
<td>Hypoglycemia</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>rare</td>
<td>rare</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

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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

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AACE Treatment Algorithm

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

If not at goal in 3 months proceed to Triple Therapy

Entry A1C > 9.0%

SYMPTOMS
NO
- DUAL Therapy
OR
- TRIPLE Therapy
YES
- INSULIN ± Other Agents

MET or other 1st-line agent

TRIPLE THERAPY*
- GLP-1 RA
- SGLT-2i
- TZD
- Basal insulin
- Colesevelam
- DPP-4i
- SU/GLN

If not at goal in 3 months proceed to or Intensify insulin therapy

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
- Few adverse events and/or possible benefits
- Use with caution

PROGRESSION OF DISEASE

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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 m/gdL; ♂ >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>Low to No risk</td>
<td>$(4 list)</td>
</tr>
</tbody>
</table>
Metformin

Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency

Kasia J. Lipska, MD\textsuperscript{1}
Clifford J. Bailey, PhD, FRCF\textsuperscript{2}
Silvio E. Inzucchi, MD\textsuperscript{3}

• Lactic acidosis extremely rare with metformin, compared to original biguanide phenformin

• Metformin-associated lactic acidosis $\sim$2 per 100,000 patient years

<table>
<thead>
<tr>
<th>Estimated GFR (mL/min)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 45</td>
<td>No renal contraindication to metformin</td>
</tr>
<tr>
<td>30 – 45</td>
<td>Max dose of 1000 mg daily</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Discontinue metformin</td>
</tr>
</tbody>
</table>


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Sulfonylureas

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

- **Available Medications:**
  - **First Generation:** chlorpropamide, tolazamide, tolbutamide
  - **Second Generation:** glyburide, glipizide (40 mg/d max), glipizide XL (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

<table>
<thead>
<tr>
<th>Weight Effect</th>
<th>Hypoglycemia Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>Higher risk (glyburide)</td>
<td>$(4 list)</td>
</tr>
</tbody>
</table>
Now What??

- GLP-1 Agonists
- TZDs
- Glinides
- DPP-4 Inhibitors
- Bile Acid Sequestrant
- α-glucosidase Inhibitors
- SGLT-2 Inhibitors
- Bromocriptine
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 receptors (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 x 1 week</td>
<td>1.8 mg daily</td>
<td>Prefilled pen</td>
</tr>
<tr>
<td></td>
<td>1.2 mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide ER (Bydureon®)</td>
<td>2 mg weekly</td>
<td>2 mg weekly</td>
<td>Kit* or 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>

* Kit can be difficult for patient to use as it requires a number of steps to draw up medication.

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

<table>
<thead>
<tr>
<th>Weight Effect</th>
<th>Hypoglycemia Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>Low Risk</td>
<td>$$$ (~$400/month)</td>
</tr>
</tbody>
</table>
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

www.google.com/images_tips
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%-63% in studies

Decrease basal dose by 10%

Decrease bolus dose by 35%

Required insulin dose reduction ranged from 30%-40% in studies
GLP-1 Agonists
(Glucagon-like peptide-1 agonist)

**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. If it 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
(Dipeptidyl peptidase-4 inhibitor)

• AKA: “gliptins”

• Mechanism:
  • Inhibits the degradation of incretins (GLP-1 and GIP) into their inactive metabolites
DPP-4 Inhibitors
(Dipeptidyl peptidase-4 inhibitor)

- **Efficacy:** ↓ A1c by 0.5% to 1.0%

- **Adverse Effects:** pancreatitis(?)
  - Saxagliptin may worsen heart failure
  - Linagliptin: no dosage adjustment for renal impairment

<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: Jentadueto®</td>
</tr>
<tr>
<td>Saxagliptin (Onglyza®)</td>
<td>2.5 to 5 mg PO daily</td>
<td>+ metformin: Kombiglyze XR®</td>
</tr>
<tr>
<td>Sitagliptin (Januvia®)</td>
<td>100 mg PO daily</td>
<td>+ metformin: Janumet®, simvastatin: Juvisync®</td>
</tr>
</tbody>
</table>

<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>$$ (~$300/month)</td>
</tr>
</tbody>
</table>

PL Detail-Document, Drugs for Type 2 Diabetes. Pharmacist’s Letter/Prescriber’s Letter. August 2013

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GLP-1 Agonists/DPP-4 Inhibitors

http://living-with-pancreatitis.blogspot.com
Pancreatitis Risk

Systematic Review/Meta-analysis (n=59)

- 55 RCTs, 3 Cohorts, 1 Case-Control

<table>
<thead>
<tr>
<th>Study</th>
<th>No of events/total</th>
<th>Peto odds ratio fixed (95% CI)</th>
<th>Weight (%)</th>
<th>Peto odds ratio fixed (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Araki 2013</td>
<td>0/319</td>
<td>0/242</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barnett 2012</td>
<td>0/151</td>
<td>0/76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berger et al. 2010</td>
<td>0/326</td>
<td>2/165</td>
<td></td>
<td></td>
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<tr>
<td>Buneck 2009</td>
<td>1/33</td>
<td>0/33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buse 2011</td>
<td>0/137</td>
<td>0/122</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chacra 2011</td>
<td>0/501</td>
<td>0/267</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diamant 2010</td>
<td>1/233</td>
<td>0/223</td>
<td>2.9</td>
<td>7.08 (0.14 to 357.08)</td>
</tr>
<tr>
<td>Fonseca 2012</td>
<td>0/239</td>
<td>0/122</td>
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<tr>
<td>Gallwitz 2012a</td>
<td>1/76</td>
<td>0/775</td>
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<td>Gallwitz 2012b</td>
<td>1/511</td>
<td>1/508</td>
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<td>Gather 2009</td>
<td>2/497</td>
<td>0/248</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grunberger 2012</td>
<td>0/132</td>
<td>1/32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haak 2012</td>
<td>0/428</td>
<td>0/363</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henry 2012</td>
<td>0/223</td>
<td>0/101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hollander 2011</td>
<td>1/381</td>
<td>0/184</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0/154</td>
<td>0/150</td>
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</tr>
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<td>Kadowaki 2009</td>
<td>0/111</td>
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<td>Kaku 2010</td>
<td>0/176</td>
<td>0/88</td>
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<td>Kikuchi 2010</td>
<td>0/102</td>
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<td></td>
</tr>
<tr>
<td>Kothny 2012</td>
<td>0/216</td>
<td>0/153</td>
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# Pancreatitis Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>D</th>
<th>RR</th>
<th>CI 95%</th>
<th>Test for heterogeneity</th>
<th>Test for overall effect</th>
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<tbody>
<tr>
<td>Nauck 2009</td>
<td>0/248</td>
<td>0/49</td>
<td>Not estimable</td>
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<tr>
<td>Nauck 2013a</td>
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<td>0/322</td>
<td>Not estimable</td>
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<tr>
<td>NCT00061818 2009</td>
<td>1/282</td>
<td>1/367</td>
<td>5.2</td>
<td>0.02 × 0.02 × 5.90</td>
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<tr>
<td>NCT00047700 2009</td>
<td>1/588</td>
<td>1/584</td>
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<td>0.13 × 0.13 × 6.26</td>
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<tr>
<td>NCT00103857 2009</td>
<td>1/551</td>
<td>0/364</td>
<td>2.8</td>
<td>0.12 × 0.12 × 5.26</td>
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<td>NCT00127915 2009</td>
<td>0/978</td>
<td>1/328</td>
<td>2.2</td>
<td>0.02 × 0.02 × 5.71</td>
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<tr>
<td>NCT00123877 2011</td>
<td>1/170</td>
<td>0/132</td>
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<td>0.11 × 0.11 × 5.29</td>
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<td>1/891</td>
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<td>NCT00757389 2011</td>
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<td>2.6</td>
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<tr>
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<td>3/631</td>
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<td>11.7</td>
<td>2.72 × 2.72 × 19.36</td>
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<td>NCT0012812 2013</td>
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<tr>
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<td>1/253</td>
<td>2.9</td>
<td>0.14 × 0.14 × 6.85</td>
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<tr>
<td>Pan 2012</td>
<td>0/284</td>
<td>0/284</td>
<td>Not estimable</td>
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<tr>
<td>Pradley 2013</td>
<td>1/894</td>
<td>0/257</td>
<td>2.6</td>
<td>0.07 × 0.07 × 20.45</td>
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<tr>
<td>Ratner 2010</td>
<td>0/433</td>
<td>0/109</td>
<td>Not estimable</td>
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<tr>
<td>Raz 2012</td>
<td>0/245</td>
<td>0/123</td>
<td>Not estimable</td>
<td></td>
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<tr>
<td>Rosenstock 2009a</td>
<td>0/305</td>
<td>0/51</td>
<td>Not estimable</td>
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<tr>
<td>Rosenstock 2009b</td>
<td>2/260</td>
<td>1/129</td>
<td>5.2</td>
<td>4.43 × 0.24 × 5.42</td>
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<tr>
<td>Ross 2012</td>
<td>0/447</td>
<td>0/44</td>
<td>Not estimable</td>
<td></td>
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<tr>
<td>Russell-Jones 2009</td>
<td>0/230</td>
<td>0/346</td>
<td>Not estimable</td>
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<tr>
<td>Russell-Jones 2012</td>
<td>1/411</td>
<td>0/499</td>
<td>2.9</td>
<td>0.15 × 0.15 × 7.05</td>
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<tr>
<td>Selgo 2010</td>
<td>0/268</td>
<td>0/132</td>
<td>Not estimable</td>
<td></td>
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<tr>
<td>Selgo 2012a</td>
<td>0/188</td>
<td>0/100</td>
<td>Not estimable</td>
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<tr>
<td>Selgo 2012b</td>
<td>0/154</td>
<td>0/157</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpelmez 2011</td>
<td>2/396</td>
<td>0/66</td>
<td>4.4</td>
<td>1.81 × 0.56 × 9.76</td>
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<tr>
<td>Yang 2010</td>
<td>0/697</td>
<td>0/311</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinman 2009</td>
<td>0/356</td>
<td>0/177</td>
<td>Not estimable</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>23/201</td>
<td>14/130</td>
<td>1.11</td>
<td>0.57 × 2.17</td>
<td></td>
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</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 32.40, df = 27, P = 0.22, I^2 = 17\%$

Test for overall effect: $z = 0.31, P = 0.76$
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)
  - Rosiglitazone

- **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>↑</td>
<td>Low Risk</td>
<td>$$$ (~$400/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 cancer was demonstrated with pioglitazone use"
SGLT-2 Inhibitors
(Sodium-glucose Co-transporter 2 Inhibitor)

• Mechanism:

http://courses.washington.edu/conj/bess/polyuria/polyuria.htm
SGLT-2 Inhibitors

• **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

<table>
<thead>
<tr>
<th>Weight Effect</th>
<th>Hypoglycemia Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓</td>
<td>Low Risk</td>
<td>$$$(~$300/month)</td>
</tr>
</tbody>
</table>
SGLT-2 Inhibitors

• **Positive Cardiovascular Effects?**

  • EMPA-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

SGLT-2 Inhibitor ADEs

- **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

*J Clin Endocrinol Metab. 2015 Aug;100(8):2849-52*


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It’s Becoming a Stretch

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

<table>
<thead>
<tr>
<th>Class (Medications)</th>
<th>Mechanism</th>
<th>Efficacy (↓ A1c %)</th>
<th>Adverse Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-glucosidase inh.</td>
<td>Inhibit breakdown of carbohydrates to glucose</td>
<td>0.5%-1.0%</td>
<td>Gas, bloating, diarrhea</td>
<td>Must treat hypoglycemia with simple sugar</td>
</tr>
<tr>
<td>Acarbose (Precose®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miglitol (Glyset®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glinides</td>
<td>Stimulates insulin secretion from pancreas</td>
<td>0.5%-1.0%</td>
<td>Hypoglycemia, increased uric acid</td>
<td>Fast acting with short half-life</td>
</tr>
<tr>
<td>Nateglinide (Starlix®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide (Prandin®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylin Analogs</td>
<td>Delays gastric emptying; increased early satiety</td>
<td>0.5%-1.0%</td>
<td>Nausea, hypoglycemia</td>
<td>Three times daily subQ injection prior to meals</td>
</tr>
<tr>
<td>Pramlintide (Symlin®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile Acid Sequestrant</td>
<td>↓ insulin resistance</td>
<td>0.5%-1.0%</td>
<td>Nausea, constipation, indigestion</td>
<td>Large pill burden; 6 tabs/day</td>
</tr>
<tr>
<td>Colesevelam (Welchol)</td>
<td>↓ glucose production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ glucose absorption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Unknown</td>
<td>0.5%-1.0%</td>
<td>Hypotension, syncope</td>
<td>Same bromocriptine used for Parkinson’s disease</td>
</tr>
</tbody>
</table>
Is Diabetes Management Shifting?

Diagnosis

Lifestyle Intervention + Metformin

A1C≥7%

No

A1C≥7%

Yes*

Add Basal Insulin – Most effective

Add Sulfonylurea – Least expensive

Add Glitazone – No hypoglycemia

Intensify insulin

Add Glitazone

Add Basal Insulin

Add Sulfonylurea

Add Basal or Intensify Insulin

Intensive insulin + Metformin +/- Glitazone

Diabetes Care August 2006 vol. 29 no. 8 1963-1972

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My Algorithm for **MOST**

1st Line
Metformin

2nd Line
Sulfonylurea (not glyburide)

3rd Line
Basal Insulin

3rd Line
GLP-1 Agonists
TZDs
SGLT-2 Inhibitors

4th Line
GLP-1 Agonist

4th Line
Basal Insulin

5th Line
Bolus Insulin

3rd Line
DPP-4 Inhibitors
TZDs
SGLT-2 Inhibitors

4th Line
Basal insulin
GLP-1 agonist

5th Line
Bolus Insulin

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# Candidates for “New Meds”

<table>
<thead>
<tr>
<th>Medication</th>
<th>Appropriate Candidate</th>
<th>Poor Candidate</th>
</tr>
</thead>
</table>
| GLP-1 Agonist | • A1c ≤ 9.0%  
• Concerned about weight gain, and addressing with diet/exercise  
• Dangerous occupation where hypoglycemia could be fatal  
• Relatively newly diagnosed | • History of pancreatitis  
• Compromised renal function (exenatide)  
• History of severe GI disturbance  
• Unwilling to utilize injectable medications  
• Fixed income |
| DDP-4 Inhibitors | • A1c ≤ 8.0%  
• Unwilling to utilize injectable medications  
• Relatively newly diagnosed | • History of pancreatitis  
• Compromised renal function (linagliptin does NOT require dosage adjustment)  
• History of heart failure (saxagliptin)  
• Fixed income |
| SGLT-2 Inhibitors | • A1c ≤ 8.0%  
• May be helpful in patients with heart failure | • Stage 4 CKD or worse  
• History of recurrent UTI  
• Urinary incontinence/BPH  
• Patients with very poorly controlled diabetes (see risk of DKA)  
• History of hyperkalemia (canagliflozin)  
• History of bladder cancer (dapagliflozin) |

*www.google.com/images_angel&devil*

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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

Thank you