Non-Insulin Pharmacotherapy for Type 2 Diabetes Mellitus

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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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>high</td>
<td>low</td>
<td>neutral / loss</td>
<td>GI / lactic acidosis</td>
<td>low</td>
</tr>
</tbody>
</table>

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>Metformin +</th>
<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 Inhibitor</th>
<th>SGLT2 Inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>low risk</td>
<td>low risk</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>intermediate</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
<td>variable</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>rare</td>
<td>rare</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>hypoglycemia</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>hypoglycemia</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>Metformin +</th>
<th>Sulfonylurea + TZD</th>
<th>Sulfonylurea + DPP-4 Inhibitor</th>
<th>Thiazolidinedione + SU</th>
<th>Thiazolidinedione + DPP-4 Inhibitor</th>
<th>DPP-4 Inhibitor + SGLT2 Inhibitor</th>
<th>GLP-1 receptor agonist + SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin +</td>
<td>Metformin +</td>
<td>Metformin +</td>
<td>Metformin +</td>
<td>Metformin +</td>
<td>Metformin +</td>
<td>Metformin +</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low</td>
<td>rare</td>
<td>rare</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>hypoglycemia</td>
<td>hypoglycemia</td>
<td>high</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>low</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>
<tr>
<th>Metformin +</th>
<th>Basal insulin + Mealtime Insulin + GLP-1-RA</th>
</tr>
</thead>
</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
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%

TRIPLE THERAPY*
- GLP-1 RA
- SGLT-2i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGI
- SU/GLN

If not at goal in 3 months proceed to Intensify Insulin therapy

SYMPTOMS
NO
- DUAL Therapy
OR
- TRIPLE Therapy

YES
- ADD OR INTENSIFY INSULIN
- Refer to Insulin Algorithm

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

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
Clifford J. Bailey, PhD, FRCP
Silvio E. Inzucchi, MD

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

• Metformin-associated lactic acidosis ~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®)

Injectables

Orals

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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>
</tbody>
</table>
| Liraglutide (Victoza®)| 0.6 mg daily x 1 week
1.2 mg daily       | 1.8 mg daily                      | Prefilled pen     |
| Exenatide ER (Bydureon®) | 2 mg weekly                   | 2 mg weekly       | Kit* or prefilled pen |
| Albiglutide (Tanzeum®)| 30 mg weekly                      | 50 mg weekly      | Prefilled pen/kit*  |
| Dulaglutide (Trulicity®)| 0.75 mg weekly             | 1.5 mg weekly    | Prefilled pen       |

* 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

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GLP-1 Agonists
Combined with Insulin

**Basal**
- Shown to decrease
  - Fasting blood glucose
  - Post-prandial blood glucose
  - Hemoglobin A1c

**Bolus**
- Required insulin dose reduction ranged from 15%-63% in studies
- Decrease bolus dose by 35%

Required insulin dose reduction ranged from 30%-40% in studies
- Decrease basal dose by 10%


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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>

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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>
</tr>
</thead>
<tbody>
<tr>
<td>Inagaki 2012</td>
<td>0/215</td>
<td>0/212</td>
<td>Not estimable</td>
<td>0.34 (0.05 to 2.36)</td>
</tr>
<tr>
<td>Kadowaki 2009</td>
<td>0/111</td>
<td>0/40</td>
<td>Not estimable</td>
<td>0.36 (0.05 to 2.58)</td>
</tr>
<tr>
<td>Kaku 2010</td>
<td>0/176</td>
<td>0/88</td>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Kikuchi 2010</td>
<td>0/102</td>
<td>0/100</td>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Kothny 2012</td>
<td>0/216</td>
<td>0/153</td>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Hollander 2011</td>
<td>0/151</td>
<td>0/150</td>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Buse 2011</td>
<td>0/137</td>
<td>0/122</td>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Charra 2011</td>
<td>0/501</td>
<td>0/267</td>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Dialmant 2010</td>
<td>1/333</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>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Gallwitz 2012a</td>
<td>1/776</td>
<td>0/775</td>
<td>2.9</td>
<td>7.38 (0.15 to 371.92)</td>
</tr>
<tr>
<td>Gallwitz 2012b</td>
<td>1/511</td>
<td>1/508</td>
<td>5.8</td>
<td>0.99 (0.06 to 15.92)</td>
</tr>
<tr>
<td>Gather 2009</td>
<td>2/697</td>
<td>0/248</td>
<td>5.2</td>
<td>6.69 (0.24 to 185.11)</td>
</tr>
<tr>
<td>Grunberger 2012</td>
<td>0/132</td>
<td>1/32</td>
<td>1.8</td>
<td>0.01 (0.00 to 0.84)</td>
</tr>
<tr>
<td>Haak 2012</td>
<td>0/428</td>
<td>0/363</td>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Henry 2012</td>
<td>0/223</td>
<td>0/101</td>
<td>Not estimable</td>
<td>0.38 (0.06 to 2.37)</td>
</tr>
<tr>
<td>Hollander 2011</td>
<td>1/381</td>
<td>0/184</td>
<td>2.6</td>
<td>4.41 (0.07 to 288.65)</td>
</tr>
</tbody>
</table>

BMJ 2014 Apr 15;348

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# Pancreatitis Risk

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>N1</th>
<th>N2</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naukck 2009</td>
<td></td>
<td>0/248</td>
<td>0/49</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Naukck 2013a</td>
<td></td>
<td>0/715</td>
<td>0/322</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Naukck 2015</td>
<td></td>
<td>1/728</td>
<td>1/356</td>
<td>5.2 (0.42 to 66.96)</td>
</tr>
<tr>
<td>NCTD0083381 2009</td>
<td></td>
<td>0/382</td>
<td>1/267</td>
<td>2.9 (0.13 to 6.66)</td>
</tr>
<tr>
<td>NCTD0094770 2009</td>
<td></td>
<td>1/588</td>
<td>0/584</td>
<td>2.9 (0.15 to 63.87)</td>
</tr>
<tr>
<td>NCTD0103357 2009</td>
<td></td>
<td>1/551</td>
<td>0/364</td>
<td>2.8 (0.10 to 88.61)</td>
</tr>
<tr>
<td>NCTD0127015 2009</td>
<td></td>
<td>0/978</td>
<td>1/328</td>
<td>2.2 (0.02 to 1.71)</td>
</tr>
<tr>
<td>NCTD0128172 2011</td>
<td></td>
<td>1/710</td>
<td>0/352</td>
<td>2.9 (0.11 to 87.29)</td>
</tr>
<tr>
<td>NCTD0195512 2013</td>
<td></td>
<td>1/891</td>
<td>0/163</td>
<td>2.2 (0.04 to 151.76)</td>
</tr>
<tr>
<td>NCTD0482799 2009</td>
<td></td>
<td>1/625</td>
<td>0/621</td>
<td>2.9 (0.15 to 370.02)</td>
</tr>
<tr>
<td>NCTD0575589 2010</td>
<td></td>
<td>0/428</td>
<td>1/430</td>
<td>2.9 (0.14 to 6.86)</td>
</tr>
<tr>
<td>NCTD0614939 2011</td>
<td></td>
<td>0/85</td>
<td>1/85</td>
<td>2.9 (0.14 to 6.82)</td>
</tr>
<tr>
<td>NCTD0722371 2011</td>
<td></td>
<td>0/922</td>
<td>1/695</td>
<td>2.9 (0.10 to 5.10)</td>
</tr>
<tr>
<td>NCTD0757588 2011</td>
<td></td>
<td>0/104</td>
<td>1/151</td>
<td>2.6 (0.05 to 13.16)</td>
</tr>
<tr>
<td>NCTD0954447 2012</td>
<td></td>
<td>3/631</td>
<td>1/630</td>
<td>11.7 (2.72 to 49.36)</td>
</tr>
<tr>
<td>NCTD1138122 2013</td>
<td></td>
<td>0/159</td>
<td>1/377</td>
<td>2.9 (0.13 to 6.80)</td>
</tr>
<tr>
<td>NCTD1204294 2012</td>
<td></td>
<td>0/228</td>
<td>0/124</td>
<td>Not estimable</td>
</tr>
<tr>
<td>NCTD1289119 2013</td>
<td></td>
<td>0/252</td>
<td>1/253</td>
<td>2.9 (0.14 to 6.85)</td>
</tr>
<tr>
<td>Pan 2012</td>
<td></td>
<td>0/284</td>
<td>0/284</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Prattley 2013</td>
<td></td>
<td>1/694</td>
<td>0/257</td>
<td>2.6 (0.07 to 264.65)</td>
</tr>
<tr>
<td>Ratner 2010</td>
<td></td>
<td>0/433</td>
<td>0/109</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Raz 2012</td>
<td></td>
<td>0/245</td>
<td>0/123</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Rosenstock 2009a</td>
<td></td>
<td>0/305</td>
<td>0/51</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Rosenstock 2009b</td>
<td></td>
<td>2/260</td>
<td>0/129</td>
<td>5.2 (0.24 to 154.42)</td>
</tr>
<tr>
<td>Ross 2012</td>
<td></td>
<td>0/447</td>
<td>0/44</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Russell-Jones 2009</td>
<td></td>
<td>0/230</td>
<td>0/346</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Russell-Jones 2012</td>
<td></td>
<td>1/411</td>
<td>0/409</td>
<td>2.9 (0.15 to 37.05)</td>
</tr>
<tr>
<td>Selno 2010</td>
<td></td>
<td>0/268</td>
<td>0/132</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Selno 2012a</td>
<td></td>
<td>0/188</td>
<td>0/100</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Selno 2012b</td>
<td></td>
<td>0/154</td>
<td>0/157</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Unrubay 2011</td>
<td></td>
<td>2/196</td>
<td>0/66</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Yang 2011</td>
<td></td>
<td>0/697</td>
<td>0/331</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Zimman 2009</td>
<td></td>
<td>0/356</td>
<td>0/177</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>23/20127</td>
<td>14/13100</td>
<td>1.11 (0.57 to 2.17)</td>
</tr>
</tbody>
</table>

*Test for heterogeneity: χ²=32.40, df=27, P=0.22, I²=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:**

  ![Diagram showing normal glucose handling and in diabetes mellitus](http://courses.washington.edu/conj/bess/polyuria/polyuria.htm)

  - In normal glucose handling:
    - 100% reabsorption of glucose
    - Normoglycemia
    - Filtration of glucose

  - In diabetes mellitus:
    - Filtered load exceeds reabsorption capacity
    - Hyperglycemia
    - High filtered load of glucose
    - Glucose in urine
    - Polyuria

  - SGLT-2 co transporter
  - Glucose

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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>

\[Contraindicated\] GFR < 30 mL/min
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 ¹
  - 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 ²
  - Subsequent meta-analysis showed no further significant increase in cardiovascular adverse events during extended use ³

• **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 ⁴

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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*

It’s Becoming a Stretch

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

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# 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 ↓ glucose production ↓ glucose absorption</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></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%

Yes* 

Add Basal **Insulin**
- Most effective

Add **Sulfonylurea**
- Least expensive

Add **Glitazone**
- No hypoglycemia

A1C ≥ 7%

No 

Yes* 

No 

A1C ≥ 7%

Yes* 

No 

A1C ≥ 7%

Yes* 

Add Basal **Insulin**

Add **Sulfonylurea**

Add Basal or Intensify **Insulin**

**Intensive insulin + Metformin +/- Glitazone**

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My Algorithm for **MOST**

1st Line
Metformin

2nd Line
Sulfonylurea (not glyburide)

3rd Line
Basal Insulin

4th Line
GLP-1 Agonist

4th Line
Bolus Insulin

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

3rd Line
Basal insulin
GLP-1 agonist

4th Line
Bolus Insulin

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

*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