Type 2 Diabetes Medication Update: Improving Control with Incretin Agents
Lucia M. Novak, MSN, ANP-BC, BC-ADM, CDTC
The Diabetes Institute
Walter Reed National Military Medical Center
Bethesda, MD

Faculty Disclosures
I have nothing to disclose

Objectives
On completion of this activity, participants should be able to:

- Distinguish the mechanism of action between the two classes of incretin agents and understand how this impacts glucose control.
- Understand the common side effects (SE) and potential adverse reactions (AR) of these agents.
- Determine how to choose the agent most appropriate for your individual patient.

The Incretin Effect
- Increased insulin release in response to oral glucose load when compared to IV administration of glucose
- Up to 60% of postprandial insulin secretion in healthy persons is attributable to the incretin effect
- Incretin hormones released from intestinal mucosa induce insulin secretion upon GI exposure to nutrients
  - GLP-1 (glucagon-like peptide-1)
  - GIP (glucose-dependent insulinoitropic peptide)

Incretin Effect
Increased β-cell Response to an Oral Glucose Load

Plasma Glucose (mg/dL)

Time (min)

Oral glucose (50 g) or isoglycemic infusion

Incretin Effect

C-peptide (nmol/L)

Time (min)

* * * * * *

Oral glucose (50 g)
or isoglycemic infusion

IV glucose

Oral glucose

α-cells

–60 0 60 120 180 240

Time (min)

Carb meal

Glucose

μU/mL

–60 0 60 120 180 240

Glucagon

pg/mL

–60 0 60 120 180 240

Glucagon

Reduces appetite

Liver:

Glucagon reduces output of sugar from liver

Stomach:

Helps slow stomach emptying

Reduces appetite

Pancreatic islet

β-cells:

Enhances insulin secretion

α-cells:

Enhances glucagon secretion

Photomicrograph courtesy of Michael Sarras, PhD, Rosalind Franklin University of Medicine and Science.


GLP-1 Secretion and Metabolism

DPP-4 enzyme

>80% GLP-1

Inactive

Rapid Inactivation

2-3 minutes

Renal Clearance

GLP-1 Actions

GLP-1

Plasma

Mixed Meal

Inappropriate Insulin and Glucagon Responses to Glucose in Patients With Type 2 Diabetes

Insulin

Glucagon

Normal

Diabetes

Normal

Diabetes


OK, SO NOW WHAT?
DPP-IV = dipeptidyl peptidase-IV

Among the pleiotropic effects of the incretins, there are beneficial effects on cardiometabolic risk factors and early signals indicating possible cardioprotection.

MOA of GLP-1 RA

PROLONGED EXPOSURE to GLP-1

GLP-1 Modulates Numerous Functions In Humans

Reduces appetite

Alpha cells: Post-prandial glucagon secretion

Beta cells: Enhances insulin secretion

Liver: Glucagon reduces output of sugar from liver

Stomach: Helps slow stomach emptying

GLP-1 stored in the L-cells of the ileum and colon, and released in response to neurohormonal signals and the presence of food in the gut.

Meta-Analysis: Blood Pressure Changes With GLP-1 RAs

Similar BP changes were reported between groups in head-to-head GLP-1 RA trials.


Data from Nauck MA, et al. Diabetologia. 1996;39:1546-1553; Data from Drucker DJ. Diabetes. 1998;47:159-169

Lipid Changes: Head-to-Head GLP-1 RA Trials


Meta-Analysis: Blood Pressure Changes With GLP-1 RAs

BP Change (mm Hg)

DBP -1.38 (-2.02 to -0.73)

SBP -3.27 (-5.49 to -1.66)

BP changes were reported between groups in head-to-head GLP-1 RA trials.

Meta-Analysis: Blood Pressure Changes

**GLP-RA Cardiovascular Safety in Clinical Trials**

- **Primary MACE endpoints:** CV mortality, stroke, myocardial infarction, acute coronary syndrome, and revascularization.

- **Trials**
  - EXSCEL
  - LEADER
  - EXN
  - LIRA
  - EXN LAR
  - LIRAGLUE
  - LIRAGLUE LAR
  - LIRAGLUE ECON

- **GLP-RA Cardiovascular Safety in Clinical Trials**

  - **Primary endpoint:** MACE: CV mortality, stroke, myocardial infarction, acute coronary syndrome, and revascularization.

- **HR (95% CI): 0.70 (0.63-0.79)**

- **Favors GLP-RA**

- **Favors Non-GLP-RA**

- **Trials in progress**
  - EXSCEL - GLP-RA CV risk (results expected in 2022)
  - LEADER - GLP-RA CV risk in patients with pre-existing CVD (results expected in 2022)

**POTENTIAL CARDIOPROTECTIVE EFFECTS: Independent of Changes on Glucose Control**

- Increased flow-mediated endothelial-dependent vasodilation in pts w/T2D with CAD
- Reduced infarct size and improved UVEF in pts post acute MI w/EF > 40%
- Improved LV contractile function and improved UVEF, improved exercise tolerance and improved QoL scores in patients w/T2D and NYHA class III and IV CHF
- Less likely to have CV-related events or CVD-related hospitalization in pts w/T2D
- Reduced MACE and all-cause mortality in pts w/T2D

**DPP-4 Inhibitors: (oral)**

- **Renal Adjustment Required**
  - Sitagliptin (Januvia ®)
    - 100 mg
    - 50 mg (<50 >30)
    - 25 mg (<30)
  - Saxagliptin (Onglyza ®)
    - 5 mg
    - 2.5 mg (<50)
  - Alogliptin (Nesina ®)
    - 25 mg
    - 12.5 mg (<60 >30)
    - 6.25 mg (<30)

- **No Renal Adjustment Required**
  - Linagliptin (Tradjenta ®)
    - 5 mg

**GLP1-RA (injections)**

- **Exendin-4 based (synthetic)**
  - Exenatide (Byetta ®)
    - 5 mcg & 10 mcg
    - Twice-daily dosing
  - Exenatide long-acting release (Bydureon ®)
    - 2 mg
    - Once-weekly dosing

- **Human rDNA Origin**
  - Liraglutide (Victoza ®)
  - Saxagliptin (Onglyza ®)

**GLP-1 RA and DPP-4 Inhibitors— Differences and Similarities**

<table>
<thead>
<tr>
<th></th>
<th>GLP-1 RA</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of stimulation of insulin secretion exclusively through GLP-1 effect</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Restoration of insulin secretion (7 phases)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Maintained counter-regulation by glucagon in hypoglycemia</td>
<td>Yes</td>
<td>Not tested</td>
</tr>
<tr>
<td>Inhibition of gastric emptying</td>
<td>Yes</td>
<td>Marginal</td>
</tr>
<tr>
<td>Effect on body weight</td>
<td>Weight loss</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea, vomiting, diarrhea</td>
<td>RA, sinusitis, rhinitis, rash, headache</td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous</td>
<td>Oral</td>
</tr>
</tbody>
</table>

**Glifos B. Eur Endocr Oa 2006:43-46.**
Incretin Therapy: Clinical Characteristics

**GLP-1 agonists**

- **Exenatide**: Subcutaneous, twice a day -0.4 to -0.9, 2.4
- **Exenatide ER**: Subcutaneous, once weekly -1.4 to -1.6, Continuous exposure
- **Liraglutide**: Subcutaneous, once a day -0.6 to -1.5, 13

**DPP-4 inhibitors**

- **Alogliptin**: Oral, once a day -0.5 to -0.6, <0.7
- **Linagliptin**: Oral, once a day -0.4 to -0.5, <0.7
- **Saxagliptin**: Oral, once a day -0.7 to -0.9, 2.5; 3.1 for AM
- **Sitagliptin**: Oral, once a day -0.6 to -0.8, 12.4


**Weight Effects and Hypoglycemia Risks of Agents Commonly Used to Treat Hyperglycemia in T2DM**

<table>
<thead>
<tr>
<th>Class</th>
<th>Weight Effect</th>
<th>Elevated Risk of Hypoglycemia?</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA</td>
<td>Loss</td>
<td>No</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Neutral</td>
<td>No</td>
</tr>
<tr>
<td>Biguanide (MET)</td>
<td>Neutral</td>
<td>No</td>
</tr>
<tr>
<td>TZD</td>
<td>Gain</td>
<td>No</td>
</tr>
<tr>
<td>SU</td>
<td>Gain</td>
<td>Yes</td>
</tr>
<tr>
<td>Insulin</td>
<td>Gain</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Greater A1C Effects with Longer-Acting GLP-1 RAs in Head-to-Head Clinical Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>LEAD-6</th>
<th>DURATION-1</th>
<th>DURATION-5</th>
<th>DURATION-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (N)</td>
<td>26</td>
<td>30</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Study length (week)</td>
<td></td>
<td>8.2</td>
<td>8.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.5</td>
<td>8.4</td>
<td>8.5</td>
<td>8.5</td>
</tr>
</tbody>
</table>

**Greater FPG Effects With Longer-Acting GLP-1 RAs in Head-to-Head Clinical Trials**

**Glycemic Control and Weight Change With Sitagliptin vs Liraglutide or Exenatide ER**

**Exenatide BID Reduces PPG More Than Exenatide ER and Liraglutide**

- **DURATION-1**: Self-measured plasma glucose profiles
- **DURATION-6**: Significantly greater postprandial decreases with EXN BID (breakfast and dinner)
- Estimated treatment differences
  - Breakfast: 24 mg/dL
  - Dinner: 18 mg/dL
GLP-1 RAs Improve Glycemic Control in Combination With Commonly Used Oral Agents

GLP-1 RAs Improve Glycemic Control in Combination With Commonly Used Oral Agents

Background Therapy

<table>
<thead>
<tr>
<th>Background Therapy</th>
<th>Δ A1C (%) With GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXN BID1,a 10 mcg BID 16-30 weeks</td>
<td>BLA1C: 2.4%-6.6%</td>
</tr>
<tr>
<td>LIRA1,b 1.8 mg QD 26-52 weeks</td>
<td>BLA1C: 0.2%-6.4%</td>
</tr>
<tr>
<td>EXN ER1,c 2 mg QW 26 weeks</td>
<td>BLA1C: 0.3%-8.4%</td>
</tr>
</tbody>
</table>

Monotherapy

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Δ A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET</td>
<td>-0.9</td>
</tr>
<tr>
<td>SU</td>
<td>-0.9</td>
</tr>
<tr>
<td>T2D + MET</td>
<td>-0.9 1,a</td>
</tr>
<tr>
<td>SU + MET</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

BL A1C, mean baseline A1C; MET, metformin; QD, once daily; QW, once weekly; ROSI, rosiglitazone; SU, sulfonylurea; TZD, thiazolidinedione.

Gastrointestinal Effects Are Common With GLP-1 RAs1-5

GLP-1 RA | Nausea (% of patients) | Vomiting (% of patients) | Diarrhea (% of patients) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXN BID,a 37</td>
<td>14</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>LIRA,a 10 - 40</td>
<td>4 - 17</td>
<td>8 - 19</td>
<td></td>
</tr>
<tr>
<td>EXN ER,a 9 - 35</td>
<td>2 - 15</td>
<td>5 - 13</td>
<td></td>
</tr>
<tr>
<td>MET,a,b 7 - 26</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

a Monotherapy or in combination with other agents.

b Includes values for several specific agents.
c Reported as nausea/vomiting or nausea.

Clinical Insights—Nausea

- Most episodes of nausea are of mild to moderate intensity
- Generally intermittent
- More frequent at treatment initiation
- Decrease over time

Advice for Managing Nausea Associated With GLP-1 RAs

- Discuss expectations:
  - Nausea is likely to be mild and resolve in a few weeks
  - Nausea may actually be “fullness”
- Suggest behavioral changes:
  - Decrease portion sizes
  - Reduce fat content of meals
  - Keep a log to identify foods that cause nausea
- Titrate more slowly – maintain at lower dose for a longer period

Tolerability of DPP-4 Inhibitors

- Generally very well tolerated
- Weight neutral
- Nasopharyngitis, headache, URI, cough

SOUNDS TOO GOOD TO BE TRUE ...
... IS IT?
The EXN BID data do not seem to clearly reflect lower rates with longer-acting GLP-1 RAs. Compared with MacConell data, ranges cited by Russell-Jones for EXN BID seem more consistent (36-57% nausea, 10-17% vomiting, 8-17% diarrhea) BUT that study includes only about 6-7 trials, and the MacConell analysis includes 19, so I’d rather cite it...

Add a statement regarding lower nausea with longer-acting agents in head-to-head trials, or leave as-is and save that information for later? (It's included in Talk 3.)

Kim McFarland, 7/7/2012
Advice for Managing Nausea Associated With GLP-1 RAs (cont.)

- Be aware of severe gastrointestinal disease
  - GLP-1 RAs slow gastric emptying and are associated with GI AEs\(^1\)\(^-\)\(^3\)
  - GLP-1 RAs have not been studied in patients with severe GI disease\(^1\)\(^-\)\(^3\)
  - Avoid exenatide in patients with history of severe gastrointestinal disease (eg, gastroparesis)\(^1\)\(^-\)\(^3\)
- Be aware of severe persistent abdominal pain, which could indicate pancreatitis\(^3\)

Reports of GLP-1 RA and Pancreatitis

<table>
<thead>
<tr>
<th>Exenatide</th>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 cases in clinical trials</td>
<td>7 cases in clinical trials</td>
</tr>
<tr>
<td>36 postmarketing reports</td>
<td>1 postmarketing report</td>
</tr>
<tr>
<td>- 30 cases reported to FDA from launch to October 2007; 27 patients had 1 or more risk factors for pancreatitis</td>
<td>- Patient with a history of pancreatitis received exenatide for 4 years, then switched to liraglutide</td>
</tr>
<tr>
<td>- After issuing the Information for Healthcare Professionals in October 2007, the FDA received reports of 6 cases of hemorrhagic or necrotizing pancreatitis between October 2007 and August 2008</td>
<td></td>
</tr>
</tbody>
</table>

Pancreatitis risk has been added to product drug labels around the world


Clinical Insights—Pancreatitis

- Ask appropriate questions about past medical history
- GLP-1 agonist and other potentially suspect drugs should be discontinued promptly if pancreatitis is suspected
- GLP-1 agonist should not be restarted if pancreatitis is confirmed
- Consider antidiabetic therapies other than GLP-1 agonists in patients with a history of pancreatitis

Risk of pancreatitis is greater in patients with T2D than in patients without diabetes

Factors that contribute to increased risk in patients with T2DM remain unclear

GLP-1 Receptor Agonists and Thyroid Tumors

- Thyroid c-cell tumors observed in rodents but not in nonhuman primates\(^1\)
- Liraglutide
  - No medullary thyroid carcinoma; 5 cases of papillary thyroid cancer in clinical trials\(^1\)\(^-\)\(^2\)
  - Approvability supported regarding papillary thyroid cancer risk (FDA Advisory Committees)\(^1\)
  - No effect on thyroid C-cell function\(^4\)
  - Label carries a black box warning of thyroid cancer risk
- Exenatide
  - No thyroid cancer in clinical trials\(^2\)
  - 9 cases of thyroid cancer in postmarketing experience\(^2\)
  - No effect on thyroid C-cell function\(^4\)

GLP-1 Receptor Agonists and Thyroid Tumors

- Thyroid c-cell tumors observed in rodents but not in nonhuman primates\(^1\)
- Liraglutide
  - No medullary thyroid carcinoma; 5 cases of papillary thyroid cancer in clinical trials\(^1\)\(^-\)\(^2\)
  - Approvability supported regarding papillary thyroid cancer risk (FDA Advisory Committees)\(^1\)
  - No effect on thyroid C-cell function\(^4\)
  - Label carries a black box warning of thyroid cancer risk
- Exenatide
  - No thyroid cancer in clinical trials\(^2\)
  - 9 cases of thyroid cancer in postmarketing experience\(^2\)
  - No effect on thyroid C-cell function\(^4\)
Clinical Insights—Thyroid Tumors

- Ask the patient appropriate questions about past medical history
- Query the patient about personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2

Drug–Drug Interactions With GLP-1 Agonists

- Does delayed gastric emptying result in clinically relevant interactions?
  - None identified
    - Oral contraceptives
    - Digoxin
    - Lisinopril
    - Warfarin

Clinician Considerations Regarding Risk of Acute Renal Impairment With GLP-1 RAs

- Renal impairment (RI) has been reported in patients taking GLP-1 RAs, sometimes requiring hemodialysis or transplantation1-3
- RI was reversed in many cases with supportive treatment and discontinuation of potentially causative agents1-3
- Evidence does not indicate that GLP-1 RAs are directly toxic to kidney cells1-5
- Nausea associated with GLP-1RA tends to be mild to moderate and will diminish with time.
- In head-to-head trials with exenatide BID, liraglutide and exenatide ER provided
  - Greater glycemic control benefits
  - Similar weight loss benefits

Summary

- GLP-1 RAs are appropriate options for improving glycemic control across the spectrum of T2D progression, including
  - Intensification of metformin monotherapy
    - Use in combination with basal insulin therapy (except Bydureon)
  - Additional benefits of GLP-1 RAs include
    - Low risk of hypoglycemia
    - Potential weight loss

GLP-1 Receptor Agonist Use in Patients With Renal Impairment

<table>
<thead>
<tr>
<th>Renal Status</th>
<th>Exenatide BID†</th>
<th>Exenatide ER†</th>
<th>Liraglutide†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild impairment</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td></td>
<td>or recommendation</td>
<td></td>
<td>Use caution when initiating or escalating doses*</td>
</tr>
<tr>
<td>Moderate impairment</td>
<td>Use caution when initiating or escalating doses*</td>
<td>Use with caution*</td>
<td>Use caution when initiating or escalating doses*</td>
</tr>
<tr>
<td>(CrCl 30-50 mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe impairment</td>
<td>Should not be used</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>(CrCl &lt; 30 mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>Use with caution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal transplant</td>
<td>Use with caution</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Byetta (exenatide) [prescribing information].
2. Bydureon (exenatide extended-release for injectable suspension) [prescribing information].
3. Victoza (liraglutide) [prescribing information].

HOW DO I FIGURE THIS OUT?
Target Sites of Action

- Sulfonylureas
- Glinides
- GLP-1 RA
- DPP-4 inhibitors
- Metformin
- TZDs
- SGLT2

Diabetes.

Contribution of FPG and PPG to A1C in T2DM

Diurnal Glycemic Variation (mmol/L) in T2DM According to A1c Level

Glycemic Control Algorithm

Glucose Targets—T2DM vs non-T2DM

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Target</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>70–130 mg/dL</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Peak postprandial capillary glucose</td>
<td>&lt;180 mg/dL</td>
<td>&lt;140 mg/dL</td>
</tr>
<tr>
<td>(tested 1–2 h after the start of a meal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C</td>
<td>&lt;7% (ADA)</td>
<td>≤6.5% (AACE)</td>
</tr>
</tbody>
</table>
Went with this version that was generated for ADA. Will need to reformat when new template is available.

Removed footnotes because they are not included in the ADA/EASD slides

Animated per conversation with EM.

Please retain animation when formatting.

Kim McFarland, 7/7/2012
### Classes of Antihyperglycemic Agents Available for Treatment of T2D

<table>
<thead>
<tr>
<th>Class</th>
<th>A1C Reduction</th>
<th>Fasting or PPG</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>Dosing (times/day)</th>
<th>Outcome Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>1.5–2.5%</td>
<td>Fasting</td>
<td>No</td>
<td>Neutral</td>
<td>2</td>
<td>UKPDS, DIGAMI, (DCCT)</td>
</tr>
<tr>
<td>Insulin, long-acting</td>
<td>1.5–2.5%</td>
<td>Fasting</td>
<td>Yes</td>
<td>Gain</td>
<td>1, injected</td>
<td>UKPDS, UKPDS, DIGAMI, UKPDS, DCCT</td>
</tr>
<tr>
<td>Insulin, rapid-acting</td>
<td>1.5–2.5%</td>
<td>PPG</td>
<td>Yes</td>
<td>Gain</td>
<td>1–4, injected</td>
<td>UKPDS, DIGAMI, UKPDS, DCCT, (DCCT)</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>1.5%</td>
<td>Fasting</td>
<td>Yes</td>
<td>Gain</td>
<td>1</td>
<td>UKPDS</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.5–1.6%</td>
<td>Fasting</td>
<td>No</td>
<td>Neutral</td>
<td>2</td>
<td>PROactive, RECORD pending</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>1–1.5%</td>
<td>Both</td>
<td>Yes</td>
<td>Gain</td>
<td>3</td>
<td>None</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>0.5–0.8%</td>
<td>PPG</td>
<td>No</td>
<td>Neutral</td>
<td>3</td>
<td>NAVIGATOR Pending</td>
</tr>
<tr>
<td>α-glucosidase inhibitor</td>
<td>0.5–1.0%</td>
<td>PPG</td>
<td>No</td>
<td>Neutral</td>
<td>3</td>
<td>AACE pending</td>
</tr>
<tr>
<td>Glyburide</td>
<td>0.5–1.0%</td>
<td>PPG</td>
<td>No</td>
<td>Gain</td>
<td>3, injected</td>
<td>None</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>0.5–1.0%</td>
<td>PPG</td>
<td>No</td>
<td>Gain</td>
<td>3</td>
<td>TECOS pending</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.6–0.8%</td>
<td>Both</td>
<td>No</td>
<td>Neutral</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Amylin-mimetics</td>
<td>0.5–1.0%</td>
<td>PPG</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>NAVIGATOR Pending</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>0.5–1.0%</td>
<td>PPG</td>
<td>No</td>
<td>Gain</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>0.5–1.0%</td>
<td>PPG</td>
<td>No</td>
<td>Neutral</td>
<td>3</td>
<td>TECOS pending</td>
</tr>
<tr>
<td>Basal insulin analogs</td>
<td>130–229</td>
<td>Both</td>
<td>No</td>
<td>Neutral</td>
<td>2</td>
<td>None</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>192–318</td>
<td>Both</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>TECOS pending</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>230–242</td>
<td>Both</td>
<td>No</td>
<td>Neutral</td>
<td>1–2</td>
<td>None</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>230–242</td>
<td>Both</td>
<td>No</td>
<td>Neutral</td>
<td>1–2</td>
<td>None</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>192–318</td>
<td>Both</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>TECOS pending</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>315–455</td>
<td>Both</td>
<td>No</td>
<td>Neutral</td>
<td>1</td>
<td>TECOS pending</td>
</tr>
</tbody>
</table>

### Retail Prices for Commonly Used Antidiabetic Agents—July 2012

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Approximate Cost for 30-day Supply ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>7-170</td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>17-510</td>
</tr>
<tr>
<td>NPH insulin</td>
<td>54-71</td>
</tr>
<tr>
<td>Basal insulin analogs</td>
<td>130-229</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>192-318</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>230-242</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>315-455</td>
</tr>
</tbody>
</table>

* Co-payments vary by insurance provider

### ADA/EASD Position Statement: Approach to Goal Setting

- **Patient attitude and expected treatment efforts:**
  - **More stringent:**
    - More motivation, adherence, excellent self-care capacities
  - **Less stringent:**
    - Less motivated, adherent, poor self-care capacities

- **Risk potentially associated with hyperglycemia, other adverse events:**
  - **High:**
    - Newly diagnosed
  - **Low:**
    - Long-standing

- **Disease duration:**
  - **Short:**
    - Absent
  - **Long:**
    - Absent

- **Life expectancy:**
  - **High:**
    - Absent
  - **Low:**
    - Absent

- **Important considerations:**
  - **Present:**
    - Normal
  - **Absent:**
    - Normal

- **Established vascular complications:**
  - **Present:**
    - Present
  - **Absent:**
    - Present

- **Resources, support system:**
  - **Readily available:**
    - Present
  - **Limited:**
    - Present


### Patients With T2DM Who Should Use GLP-1 Agonists

- According to the ADA, patients should use lifestyle changes, metformin, and a GLP-1 agonist as Tier 2 therapy
- According to the AACE, GLP-1 agonists can be recommended for any patients with T2DM regardless of A1C level
- GLP-1 agonists are especially useful in patients who need to lose weight, have fasting or postprandial hyperglycemia, are worried about hypoglycemia, or have failed on oral agents

### Case 1: Rachel

- 71 yo Caucasian woman
- 5’4”, 160 lbs, BMI 27.5
- T2D x 3 years; HTN, HLD; no other concerning history
- LABS:
  - A1C 7.4%
  - Scr 1.5 mg/dL; GFR: 39 mL/min
- Current DM mgmt:
  - Metformin 1000 mg/day
- SMBG:
  - FBG: ~108 mg/dL
  - 2 Hr PP: ~156 mg/dL
- “NO INJECTIONS”
Case 1: Rachel (continued)

• CONSIDERATIONS:
  — Renal function poor

• WHAT DO YOU DO?
  — GLP1-RA?
  — DPP-4 inhibitor?

Case 2: Maria (continued)

• CONSIDERATIONS:
  — 1) Post meal BG high
  — 2) GAINING WEIGHT
  — 3) Good renal function
  — 4) already on an injectable medication

• WHAT DO YOU DO?
  — GLP1-RA?
  — DPP-4 inhibitor?

Case 1: Rachel (continued)

• PLAN:
  — 1) TLC
  — 2) Stop metformin
  — 3) START DPP-4 inhibitor appropriately dosed
    • Safe in renal impairment
    • No hypoglycemia
    • Weight neutral
  — 4) Close f/u, may need adjunct therapy

Case 2: Maria (continued)

• PLAN:
  — 1) TLC
  — 2) ADD short acting GLP1-RA
    • Better addresses post meal, her FBG good
    • Low risk hypoglycemia
    • Potential weight loss
  — 3) May need to reduce basal insulin as glucose control improves
  — 3 month f/u
    — A1c: 6.6% (-1.2%), no hypoglycemia
    — WEIGHT: LOSS of 2 lbs

Case 2: Maria

• 52 yo Hispanic woman
• 5’7”, 190 lbs, BMI: 29.8 (gained at least 11 lbs in last 3 months)
• T2D x6 years, No HTN; No HLD; no other concerning history
• Labs:
  — A1c: 7.8%
  — Scr: .99 mg/dL; GFR: 88 mL/min
• Current DM mgmt:
  — Basal Insulin 30 units every night
  — Metformin 1000 mg twice daily
• SMBG:
  — FBG: ~106 mg/dL
  — 2 hr PP: ~215 mg/dL
• “WEIGHT GAIN, FRUSTRATED”

Case 3: George

• 39 yo AA man
• 5’10”, 225 lbs, BMI: 32.1
• T2D x 3 months, +HTN; +HLD; no other concerning history
• Labs:
  — A1c: 8.3%
  — Scr: 0.95 mg/dL; GFR: 93 mL/min
• Current DM mgmt:
  — Metformin 1000 mg twice daily
• SMBG:
  — FBG: ~140 mg/dL
  — 2 hr PP: ~190 mg/dL
• “TOO HEAVY, CAN'T KEEP UP WITH KIDS, UPSET STOMACH AND INTERMITTENT DIARRHEA SINCE INCREASING METFORMIN AND MISSES EVENING DOSE AT LEAST ONCE A WEEK”
Case 3: George (continued)

• CONSIDERATIONS:
  – 1) Both Fasting and Post meal BG high
  – 2) WEIGHT affecting QOL
  – 3) Good renal function
  – 4) Problem tolerating current metformin
  – 5) Missing meds that are > 1x daily

• WHAT DO YOU DO?
  – GLP1-RA?
  – DPP-4 inhibitor?

Case 3: George (continued)

• PLAN:
  – 1) TLC
  – 2) ADD Long acting GLP1-RA
     • Also addresses FINS
     • Low risk hypoglycemia
     • Potential weight loss
     • Once daily or once weekly
  – 3) CHANGE metformin to metformin extended release
     • Better tolerated, can take once daily
• 3 month f/u
  – A1c: 7.8% (-5%), no hypoglycemia
  – WEIGHT: no loss/gain
  – Taking all meds, no problem

• 6 month f/u
  – A1c: 6.0% (-1.8%), no hypoglycemia
  – WEIGHT: LOSS of 19 lbs
  – Taking all meds, no problem

Summary

• The incretin effect is important in both early and longer-duration T2D
• By preventing inactivation of the incretin hormone GLP-1, incretin agents are effective, appropriate therapies for most patients with T2D.
• DPP-4 inhibitors:
  • are associated with significant and clinically relevant decreases of A1c
  • have a favorable safety profile and a low incidence of hypoglycemia and are weight neutral.
• GLP-1 RA:
  • have important effects in multiple organ systems, including improving the health of alpha and beta cells, reducing gastric emptying, increasing satiety:
  • may help with weight loss
  • other effects include reducing BP and lipids
• There are signals of incretin-mediated cardioprotective effects
• Can be combined with all other forms of current oral antidiabetes therapy