Incretin Therapies: Clinical Updates for Type 2 Diabetes

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Disclosures/Conflict of Interest

• Drs. Jessica Kerr and Jennifer Rosselli have received community and patient health education grants from Novo Nordisk during years 2014 and 2015.

• Dr. Jessica Kerr has provided CPE credits for unrestricted educational grants sponsored by Sanofi.

Objectives

• At the conclusion of this program, the pharmacist/technicians will be able to:
  • Describe glycemic effects of incretin-based therapies.
  • Compare and contrast the efficacy and safety concerns of individual incretin medications.
  • Describe the role of incretin-based medicines in diabetes management.
  • Explain injection administration clinical pearls for GLP-1 receptor agonists.

Pre-Session Assessment #1

Which of the following is a mechanism of action for GLP-1 receptor agonists?
SELECT ALL THAT APPLY
A. decrease insulin secretion
B. enhance glucagon secretion
C. increase amylin secretion
D. slow gastric emptying
E. both B and D are mechanisms of action for GLP-1 receptor agonists

Pre-Session Assessment #2

DPP-4 inhibitors have been clinically assessed for cardiovascular outcomes. Which of the following DPP-4 inhibitors has been associated with a clinical concern of heart failure?

A. alogliptin
B. omagliptin
C. sitagliptin
D. saxagliptin

Pre-Session Assessment #3

A 42 y/o WM with a 10-year history of diabetes has an A1C of 8.4% and BMI of 32 kg/m² on metformin 1500 mg BID, glipizide ER 20 mg daily, and citalopram 20 mg daily. He has declined to start insulin per last PCM note.

PMH: depression. estCrCl > 90 ml/min. Family history: CVA, DM

Which of the following is an ideal add-on therapy to better control his diabetes?
A. exenatide 5 mcg BID x 4 weeks, then 10 mcg BID
B. liraglutide 0.6 mg daily x 1 week, then 1.2 mg daily
C. linagliptin 5 mg daily
D. sitagliptin 50 mg daily

Pre-Session Assessment #2

DPP-4 inhibitors have been clinically assessed for cardiovascular outcomes. Which of the following DPP-4 inhibitors has been associated with a clinical concern of heart failure?

A. alogliptin
B. omagliptin
C. sitagliptin
D. saxagliptin
**Pathophysiology of T2DM**

<table>
<thead>
<tr>
<th>Increased</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>glucagon secretion</td>
<td>insulin secretion</td>
</tr>
<tr>
<td>hepatic glucose production</td>
<td>glucose uptake</td>
</tr>
<tr>
<td>lipolysis</td>
<td>incretin function</td>
</tr>
<tr>
<td>glucose reabsorption</td>
<td></td>
</tr>
</tbody>
</table>

**Incretin System**

- Incretins are naturally occurring glucoregulatory hormones.
- Glucose-dependent release by the gut
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP)
- Incretin hormones are rapidly degraded by dipeptidyl peptidase 4 (DPP-4)

**Physiologic Affects of the Incretin System**

- Food intake
  - Release of incretin hormones
  - Insulin release
  - Glucagon suppression
  - Decreases GI motility
  - Reduces appetite
  - Slows glucose absorption
  - Increases cardiac output

**DPP-4 Inhibitors**

- Alogliptin (Nesina®)
- Linagliptin (Tradjenta®)
- Saxagliptin (Onglyza®)
- Sitagliptin (Januvia®)
- Vildagliptin (Galvus®)*

*Approved for use in Europe

**Current DPP-4 Inhibitors**

- Alogliptin (Nesina®)
- Linagliptin (Tradjenta®)
- Saxagliptin (Onglyza®)
- Sitagliptin (Januvia®)
- Vildagliptin (Galvus®)*

*Approved for use in Europe
Overview of DPP-4 Inhibitors

• Supplied as oral formulations
• Currently, once daily administration, without regards to meals
• A1C reduction 0.2-1.15%
• Minimal weight loss to weight neutral
• Low incidence of hypoglycemia
• Studied as combination and monotherapy

Comparison of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Dose</th>
<th>Dose Adjustment</th>
<th>Unique Warnings</th>
<th>A1C Change (%</th>
<th>FPG Change (mg/dl)</th>
<th>2h PPG Change (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>6.25 mg, 12.5 mg, 25 mg</td>
<td>25 mg/d</td>
<td>Renal impairment Crl = 30 ml/min/1.73 m²</td>
<td>Hepatic failure</td>
<td>-0.5 to -1.0</td>
<td>-8 to 16</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5 mg</td>
<td>5 mg/d</td>
<td>None (Decreased effectiveness with P-glycoprotein or CYP 3A4 inhibitors)</td>
<td></td>
<td>0.0 to 0.6</td>
<td>-5 to -19</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5 mg, 5 mg</td>
<td>2.5 mg/d</td>
<td>Renal impairment Crl &lt; 50 ml/min/1.73 m²</td>
<td>Increased edema with TZDs</td>
<td>-0.4 to -0.9</td>
<td>-7 to -22</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg</td>
<td>100 mg/d</td>
<td>Renal impairment Crl &lt; 30 ml/min/1.73 m²</td>
<td>Acute renal failure</td>
<td>-0.3 to -1.35</td>
<td>-10 to -30</td>
</tr>
</tbody>
</table>

Safety Concerns of DPP-4 Inhibitors

• Most common ADRs: upper respiratory infection, nasopharyngitis, headache
• Hypersensitivity reactions: angioedema, anaphylaxis, Steven’s-Johnson syndrome
• Acute pancreatitis
• Arthralgias: severe and disabling have been reported

DPP-4 Inhibitor Cardiovascular (CV) Outcomes Studies

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Primary Outcomes</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53</td>
<td>CV death, nonfatal CVA or nonfatal MI</td>
<td>n = 5380</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>ACS or HF</td>
<td>n = 13,442</td>
</tr>
<tr>
<td>TECOS</td>
<td>CV death, nonfatal CVA or nonfatal MI</td>
<td>n = 16,422</td>
</tr>
</tbody>
</table>

Baseline Characteristics from DPP-4 Inhibitor Cardiovascular Outcomes Studies

<table>
<thead>
<tr>
<th>Trait</th>
<th>SAVOR-TIMI 53</th>
<th>EXAMINE</th>
<th>TECOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>75</td>
<td>61</td>
<td>66</td>
</tr>
<tr>
<td>Mean duration diabetes, years</td>
<td>10.3</td>
<td>7.3</td>
<td>10</td>
</tr>
<tr>
<td>Mean baseline A1c, %</td>
<td>8.0</td>
<td>8.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>71</td>
<td>Not reported</td>
<td>77</td>
</tr>
<tr>
<td>Active smokers, %</td>
<td>Not reported</td>
<td>24</td>
<td>33</td>
</tr>
<tr>
<td>Previous heart failure, %</td>
<td>22</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Mean duration of follow up, years</td>
<td>2.2</td>
<td>1.5</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Incidence of Hospitalization for Heart Failure in DPP-4 Inhibitor Cardiovascular Outcomes Studies

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Study Drug</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI 53</td>
<td>3.9%</td>
<td>2.8%</td>
<td>1.27</td>
<td>1.14-2.37</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>3.9%</td>
<td>3.7%</td>
<td>1.19</td>
<td>0.89-1.58</td>
</tr>
<tr>
<td>TECOS</td>
<td>3.9%</td>
<td>3.3%</td>
<td>1.19</td>
<td>0.89-1.58</td>
</tr>
</tbody>
</table>
Ongoing Trials to Evaluate CV Outcomes

- Linagliptin: CARMELINA, CAROLINA (both to be completed in 2018)

Grab a Partner

Mr. Starch is a 49 y/o who was recently discharged from the hospital for his 1st episode of acute pancreatitis. You two are pharmacists at his home pharmacy where presents to refill his routine diabetes medications (metformin, saxagliptin, and glimepiride). Mr. Starch tells you that he remembers the doctor at the hospital telling him to stop taking one of his medications, but he isn’t sure which one that is and he has misplaced the papers they gave him.

What questions do you have for Mr. Starch?
What additional information would you like to have?
What is your recommendation even if you don’t get answers to the above questions?

Summary of DPP-4 Inhibitors

- Can be used in combination with orals or basal insulin
- Similar A1c reduction (up to ~1%) between individual drugs
  - Linagliptin lowest A1c reduction (max 0.6%)
- No head-to-head trials
- Renal dosing with all, except for linagliptin
- Pancreatitis warnings
- No long term outcomes
- Choice likely dependent on formulary/cost

GLP-1 Agonists

Incretin Mimetic

Food intake → Small Intestines: Release of Incretin Hormones → Brain, GI Tract, Heart, Pancreas
- Insulin release
- Glucagon suppression
- Decreases GI motility
- Reduces appetite
- Slows glucose absorption
- Increases cardiac output

Exogenous GLP-1

Current GLP-1 Agonists

- Exenatide (Byetta®) 2005
- Liraglutide (Victoza®) 2010
- Exenatide extended-release (Bydureon®) 2012
- Albiglutide (Tanzeum®) 2014
- Dulaglutide (Trulicity®) 2014
### Overview of GLP-1 Agonists

- Supplied as subcutaneous injections
- Twice daily, once daily, or once weekly administration depending on medication
- Product preparation required of patient varies by medication
- ASC reduction varies by medication (-0.5% to -1.9%)
- Weight loss of 1.5-3 kg on average
- Low incidence of hypoglycemia
- Studied as monotherapy and in combination

### Comparison of GLP-1 Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unique Warnings</th>
<th>Dose Adjustment</th>
<th>FPG Change (%)</th>
<th>2h PPG Change (%)</th>
<th>Weight Change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Increased INH with warfarin</td>
<td>Renal impairment Avoid if GGT &gt; 300 units</td>
<td>-0.5 to -1.2</td>
<td>-1.5 to -2.1</td>
<td>0.3 to -2.5</td>
</tr>
<tr>
<td></td>
<td>Administer oral contraception 3 hours prior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>None</td>
<td>Renal impairment Avoid if GGT &gt; 300 units</td>
<td>-0.8 to -1.5</td>
<td>-1.5 to -2.1</td>
<td>-2.2 to -2.6</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>Injection site reactions</td>
<td>Renal impairment Avoid if GGT &gt; 300 units</td>
<td>-0.8 to -1.5</td>
<td>-1.5 to -2.1</td>
<td>-2.2 to -2.6</td>
</tr>
<tr>
<td></td>
<td>(subcutaneous nodules, cellulitis, abscess, necrosis) Monitor for increased INH with warfarin. Not studied in combination with insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide</td>
<td>None</td>
<td>Renal impairment Avoid if GGT &gt; 300 units</td>
<td>-0.8 to -1.5</td>
<td>-1.5 to -2.1</td>
<td>-2.2 to -2.6</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Not studied in combo with basal insulin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Safety Concerns

- Most common ADRs: nausea, vomiting, diarrhea, headache, injection site reaction
- Hypersensitivity reactions: angioedema, anaphylaxis, rash, pruritis
- Acute pancreatitis
- Severe gastrointestinal disease (ex. gastroparesis)
- Hypoglycemia risk increased when used with insulin or sulfonylurea
- Renal impairment

### GLP-1 Agonists and Thyroid Carcinoma

- All GLP-1 agonists except for exenatide IR have black box warning for thyroid carcinoma
- Contraindicated with a personal or family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2)
- Thyroid C-cell tumors observed in animal studies
- Cases of MTC in humans treated with liraglutide have been reported in post marketing period
- Counsel patients regarding risks and symptoms of MTC
- Refer to endocrinologist if thyroid nodules are present

### GLP-1 Agonist Head-to-Head Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>A1C Change (%)</th>
<th>Weight Change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pratley et al. (AWARD-1)</td>
<td>Liraglutide 30 mg, up to 35 mg weekly</td>
<td>-2.2*</td>
<td>-3.61*</td>
</tr>
<tr>
<td>Wysham et al. (AWARD-3)</td>
<td>Dulaglutide 1.5 mg weekly</td>
<td>-1.3</td>
<td>-2.9</td>
</tr>
<tr>
<td>Dungan et al. (DURATION-6)</td>
<td>Dulaglutide 1.5 mg daily</td>
<td>-1.24</td>
<td>-2.9</td>
</tr>
<tr>
<td>Basa et al. (LEAD-6)</td>
<td>Liraglutide 1.8 mg daily</td>
<td>-1.52*</td>
<td>-3.4</td>
</tr>
<tr>
<td>Buse et al. (DURATION-1)</td>
<td>Exenatide ER 2 mg weekly</td>
<td>-0.95*</td>
<td>-2.68</td>
</tr>
<tr>
<td>Buse et al. (RHYTHM-2)</td>
<td>Dulaglutide 1.5 mg weekly</td>
<td>-1.3</td>
<td>-2.9</td>
</tr>
<tr>
<td>Buse et al. (DURATION-5)</td>
<td>Dulaglutide 1.5 mg weekly</td>
<td>-1.3</td>
<td>-2.9</td>
</tr>
<tr>
<td>Buse et al. (DURATION-4)</td>
<td>Exenatide ER 2 mg weekly</td>
<td>-1.18</td>
<td>-3.7</td>
</tr>
<tr>
<td>Buse et al. (LEAD-5)</td>
<td>Liraglutide 1.8 mg daily</td>
<td>-1.52*</td>
<td>-3.4</td>
</tr>
</tbody>
</table>

*Statistically significant

### Summary of GLP-1 Agonists

<table>
<thead>
<tr>
<th>Medication</th>
<th>Injection Schedule</th>
<th>Dosing Regimen</th>
<th>Product Preparation and Administration</th>
<th>Storage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Multi-dose pen</td>
<td>5 mg BID 5 days, every 6 hours</td>
<td>Administer within 60 min prior to 2 biggest meals (6 hours apart)</td>
<td>Refrigerate until opened. Good for 31 days once opened.</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Daily</td>
<td>0.6 mg every 2 weeks, then 1.2 mg daily every 2 weeks</td>
<td>Administer regardless of meal timing</td>
<td>Refrigerate until opened. Good for 31 days once opened.</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>Single-dose pen</td>
<td>2 mg once weekly</td>
<td>Administer immediately after reconstitution. Rotate injection sites</td>
<td>Refrigerate until opened. Discard after 4 weeks of room temperature.</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Single-dose pen</td>
<td>0.75 mg once weekly</td>
<td>Wait 15-30 minutes for reconstituted solution to mix. Use within 8 hours of reconstitution</td>
<td>Refrigerate until opened. Discard after 4 weeks of room temperature.</td>
</tr>
</tbody>
</table>
GLP-1 Agonists Cardiovascular Outcomes Studies

Monami et al.

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials included</td>
<td>37</td>
</tr>
<tr>
<td>Subjects, No.</td>
<td>N=15,398</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Albiglutide, Exenatide, Exenatide LAR, Liraglutide, Taspoglutide</td>
</tr>
<tr>
<td>Duration of included trials (mean)</td>
<td>42 weeks</td>
</tr>
<tr>
<td>Results</td>
<td>Odds Ratio (95% CI) 0.78 (0.54 to 1.13)</td>
</tr>
</tbody>
</table>

Bentley-Lewis et al.

<table>
<thead>
<tr>
<th>Trial design</th>
<th>Randomized, placebo-controlled, parallel-group, multinational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Lixisenatide 5-10 mg/day</td>
</tr>
<tr>
<td>Subjects</td>
<td>N=6,068, T2DM and discharge in recent 180 days for ACS</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td>Mean age 65 years, 69% male, 75% white, duration of T2DM 9 years, BMI 30 kg/m², HbA1C 7.7%, history of HF 12%</td>
</tr>
<tr>
<td>Mean follow-up</td>
<td>2 years</td>
</tr>
<tr>
<td>Results [Hazard Ratio (95% CI)]</td>
<td>• Primary outcome: CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina 1.017 (0.886 to 1.168) • Secondary outcome: HF 0.96 (0.75 to 1.23)</td>
</tr>
</tbody>
</table>


Ongoing Trials to Evaluate Major CV Outcomes

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Primary Outcome Measure</th>
<th>Estimated Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>CV death, non-fatal MI, non-fatal stroke, Death, HF hospitalization, change in pro-B-type natriuretic peptide</td>
<td>2016, 2016</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>CV death, non-fatal MI, or non-fatal stroke</td>
<td>2018</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>CV death, MI, or stroke</td>
<td>2019</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>CV death, non-fatal MI, or non-fatal stroke</td>
<td>2019</td>
</tr>
</tbody>
</table>

Help Mrs. Sugar

Mrs. Sugar calls for your advice. She is scheduled to take her weekly dulaglutide tomorrow and she just found her medication in the kitchen cabinet with 2 remaining pens. She picked up the medication September 12th and assumes they have been out of the fridge since then. Which of the following is correct?

a. She should discard all remaining pens and obtain a new supply today prior to administration.
b. She may use the remaining 2 pens for tomorrow and next Saturday’s injections.
c. She may use 1 pen tomorrow but will need a new supply prior to next Saturday.
d. She may use 1 pen tomorrow and 1 pen next Saturday if she refrigerates it between now and then.

Summary of GLP-1 Agonists

- Can be used in combination with orals or insulin (exenatide ER not studied with insulin)
- Dulaglutide, exenatide ER, and liraglutide result in largest A1c lowering
- Similar cancer and pancreatitis profiles (no cancer warning for exenatide IR)
- No long term CV outcomes with available medications
- Choice likely dependent on formulary, cost, and patient preferences

Pancreatic Concerns with Incretin-based Therapies
Pancreatic Pathology and Incretin Therapies

- Population-based, rodent, and human autopsy studies caused concern that incretin-based therapy may be associated with pancreatic changes.
- Since March 2013, FDA has been evaluating this information.
- Cases of pancreatitis in humans have been associated with DPP-4 inhibitors and GLP-1 agonists.

If Pancreatitis Occurs While Taking Incretin Therapy

- Discontinue the DPP-4 inhibitor or GLP-1 agonist.
- Do not restart incretin medications.
- Consider other antidiabetic therapies if patient has a history of pancreatitis.

Pancreatic Pathology and Incretin Therapies

- June 2013 joint statement from ADA/EASD/IDF: no concern for pancreatic disease with incretins after review of data.
- July 2013 European Medicines Agency: present data do not confirm increased pancreatic risk with incretin-based therapy.

Summary of GLP-1 Agonists

- Can be used in combination with orals or basal insulin (exenatide ER not studied with insulin).
- Liraglutide has better A1c lowering in head-to-head studies (not clinically significant).
- Similar cancer and pancreatitis profiles (no cancer warning for Byetta).
- No long term CV outcomes with available medications.
- Choice likely dependent on formulary, cost, and patient preference for dosing.

Role of Incretin Therapies in Type 2 Diabetes

- Take a patient-centered approach.
- Always encourage weight control, healthy eating, and physical activity.
- ADA: metformin initial monotherapy, add-on with incretin-based therapy, sulfonylurea, thiazolidinedione, or insulin.
- AACE: depending on A1C, monotherapy, dual, or triple therapy is recommended with incretin-based therapy as an option at any tier.
- FDA does not recommend GLP-1 agonists as 1st line therapy because of the risk of pancreatitis and potential risk of MTC.
Help Mrs. Candy

Mrs. Candy is a 56 y/o with type 2 diabetes and is struggling to gain glycemic control. Recent A1C was 9%.

Current meds: metformin 1000 mg BID, glipizide 10 mg BID, insulin glargine 50 units HS.

PMH: Hyperlipidemia (LDL 116, TG 290, HDL 30), HTN (current BP 130/80), T2DM x 10 yrs, CrCl 48 ml/min. Family history includes unknown thyroid cancer in brother. Denies EtOH, tobacco, or illicit drug use.

Which of the following is the most appropriate addition to her regimen?

A. alogliptin 12.5 mg daily
B. dulaglutide 0.75 mg weekly
C. exenatide 5 mcg BID
D. saxagliptin 5 mg daily

Key Points

- Incretin-based therapies primarily increase glucose-dependent insulin secretion and suppress glucagon release.
- DPP-4 inhibitors are well tolerated, weight neutral, and have modest effects on A1C.
- GLP-1 agonists may cause GI upset initially, promote weight loss, and may result in significant A1C reduction.
- Acute pancreatitis has been associated with use of incretin-based medications in humans. Thyroid cancer is a black box warning for most GLP-1 agonists.

Post-Session Assessment #1

Which of the following is a mechanism of action for GLP-1 receptor agonists?

SELECT ALL THAT APPLY

A. decrease insulin secretion
B. enhance glucagon secretion
C. increase amylin secretion
D. slow gastric emptying
E. Both B and D are mechanisms of action for GLP-1 receptor agonists.

Post-Session Assessment #2

DPP-4 inhibitors have been clinically assessed for cardiovascular outcomes. Which of the following DPP-4 inhibitors has been associated with a clinical concern of heart failure?

A. alogliptin
B. omarglaptin
C. sitagliptin
D. saxagliptin

Post-Session Assessment #3

A 48 y/o WM with a 10-year history of diabetes has an A1C of 8.4%, BMI of 32 kg/m² on metformin 1000 mg BID, glipizide ER 20 mg daily, and citalopram 20 mg daily. He has declined to start insulin per last PCM note.

PMH: depression. estCrCl > 90 ml/min. Family history: CVA, DM

Which of the following is an ideal add-on therapy to better control his diabetes?

A. exenatide 5 mcg BID x 4 weeks, then 10 mcg BID
B. liraglutide 0.6 mg daily x 1 week, then 1.2 mg daily
C. linagliptin 5 mg daily
D. sitagliptin 50 mg daily

Key Points

- Incretin-based therapies primarily increase glucose-dependent insulin secretion and suppress glucagon release.
- DPP-4 inhibitors are well tolerated, weight neutral, and have modest effects on A1C.
- GLP-1 agonists may cause GI upset initially, promote weight loss, and may result in significant A1C reduction.
- Acute pancreatitis has been associated with use of incretin-based medications in humans. Thyroid cancer is a black box warning for most GLP-1 agonists.

References

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