Session 2: Incorporating GLP-1 Receptor Agonist Therapy in T2DM Management: Achieving a Comfort Zone in 2014

Learning Objectives

1. Implement treatment regimens for patients with type 2 diabetes in accordance with recently updated treatment recommendations
2. Review the clinical evidence for the use of incretin-based therapies in type 2 diabetes management

Faculty

Jack L. Leahy, MD
Professor of Medicine
Chief, Division of Endocrinology, Diabetes and Metabolism
University of Vermont
Burlington, Vermont

Dr Jack Leahy is a professor in the department of medicine and codirector of the division of endocrinology, diabetes and metabolism at the University of Vermont. After receiving his BS from the University of Toronto and his MD from the Medical College of Virginia, Dr Leahy completed his medical and endocrine training at the Medical College of Virginia and then joined the faculty of Harvard Medical School in 1984 and Tufts University School of Medicine in 1992. Dr Leahy has been at the University of Vermont since 1996 where his primary clinical interest is diabetes. He also runs a basic research laboratory that is focused on identifying the molecular mechanisms behind the islet beta cell failure in type 2 diabetes. He has published more than 90 articles and chapters on the pathogenesis and management of the disease.

Javier Morales, MD
St. Francis Hospital
Vice President
Principal Clinical Trials Investigator
Advanced Internal Medicine Group, PC
Great Neck, New York

Dr Javier Morales is in private practice with the Advanced Internal Medicine Group, Great Neck, New York. After graduating from the University of Medicine and Dentistry of New Jersey (UMDNJ)-New Jersey Medical School, he continued his medical training with residencies at Memorial Sloan-Kettering Cancer Center and North Shore University Hospital, where he served as chief medical resident. He sits on multiple committees at St. Francis Hospital in Roslyn, New York, has contributed to several publications and has served as principal investigator for numerous studies and clinical trials. He is also clinical instructor for several nurse practitioner and physician assistant programs in addition to the internal medicine residency program at North Shore University Hospital and Winthrop University Hospital.

Jeff Unger, MD
American Board of Family Medicine
Director, Metabolic Studies
Catalina Research Institute
Chino, California

Dr Jeff Unger is currently director of metabolic studies at the Catalina Research Institute in Chino, California. The research center incorporates primary care with clinical research in areas related to diabetes, sexual dysfunction, diabetic neuropathy, diabetic nephropathy, hyperlipidemia, hypertension, pain, obesity, and mental illness.

A board certified family physician and a fellow of the American Association of Clinical Endocrinologists, Dr Unger is an international primary care thought leader in the field of diabetes. He has educated patients and clinicians around the world regarding intensive diabetes management through both speeches and his textbook Diabetes Management in Primary Care. An avid writer, Dr Unger has published more than 160 peer reviewed articles on headaches and diabetes. He also serves on the editorial boards of several medical journals.
Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Jack L. Leahy, MD, serves as an advisor for Merck, Novo Nordisk, Sanofi.

Javier Morales, MD, serves as an advisor for BI, Bristol Myers Squibb, Novo Nordisk, Pfizer, Sanofi-Aventis and Warner Chilcott; and participates in speakers’ bureau for Novo Nordisk, Sanofi-Aventis and Warner Chilcott.

Jeff Unger, MD, participates in speakers’ bureau for Janssen Pharmaceuticals, Novo Nordisk and Valeritas. Serves as an advisor or consultant for Dance Pharmaceuticals, Halozyne, Johnson and Johnson, Novo Nordisk, Sanofi-Aventis and Valeritas; receives grants for clinical research from BI, GSK, Johnson and Johnson, Lilly, Novo Nordisk, Pfizer and Sanofi-Aventis; and receives payment for clinical trials program from Catalina Research Institute.

Education Partner Financial Disclosure Statement
The content collaborators at Vindico Medical Education have reported the following:

Ronald A. Codario, MD, FACP, RPVI, FNLA, CCMEP, medical director, has no relevant financial relationships to disclose.

Chris Rosenberg, director of medical education, has no relevant financial relationships to disclose.

Suggested Reading List


Ryder RE. The potential risks of pancreatitis and pancreatic cancer with GLP-1-based therapies are far outweighed by the proven and potential (cardiovascular) benefits. *Diabet Med*. 2013;30(10):1148-1155.


Incorporating GLP-1 Receptor Agonist Therapy in T2DM Management: Achieving a Comfort Zone in 2014

Drug List

- Acarbose
- Alogliptin
- Bromocriptine QR
- Colesevelam
- Exenatide
- Exenatide ER
- Exenatide LAR/QW
- Glimepride
- Insulin Detemir
- Insulin Glargine
- Linagliptin
- Liraglutide
- Losartan
- Metformin
- Orlistat
- Saxagliptin
- Sitagliptin
- Vildagliptin

Learning Objectives

- Implement treatment regimens for patients with type 2 diabetes in accordance with recently updated treatment recommendations
- Review the clinical evidence for the use of incretin-based therapies in type 2 diabetes management

Introduction

Javier Morales, MD
St. Francis Hospital
Vice President
Principal Clinical Trials Investigator
Advanced Internal Medicine Group, PC
Great Neck, NY

Goals and Objectives

1. Utilize a case-based, practical approach to allow you to effectively employ incretin-based therapies in your patients with T2DM
2. Interactive cases will illustrate:
   a. How to use the latest guidelines
   b. When and how to use incretin-based therapies alone and in combination with other antidiabetes agents
   c. What you need to know about safety issues

Safe, Timely, and Effective Use of Guidelines for Treating Primary Care Patients to Their Metabolic Targets

Jeff Unger, MD, FACE
Medical Director
Unger Primary Care Medical Center
Chino, CA
Why Bother Attending Yet Another Diabetes Lecture?

America is Changing!

- 26 million Americans have diabetes and an additional 79 million Americans have prediabetes resulting in $299 billion in healthcare expenditures
- By 2030, more than 55 million Americans will have diabetes
- In 2050, 1 in 3 adults will have T2DM

90% of all diabetes management occurs within the primary care setting


Case 1: Barbara

- 56-year-old Latina woman presents to your office for continued follow-up for T2DM and hypertension.
- Currently taking: metformin 1000 mg BID, glimepiride 4 mg daily, insulin detemir 15 units daily and losartan 100 mg daily.
- Patient has been adherent to medication therapy and has gained weight despite counseling and lifestyle changes, stating: "Doctor, I am having a terrible time controlling my appetite."

BMI: 34 kg/m²
Waist: 40 inches
BP: 146/92 mm Hg (bilaterally)
Random glucose: 207 mg/dL
A1C: 8.2%
eGFR: >60 mL/min/1.73 m²
Total cholesterol: 224 mg/dL
HDL-C: 41 mg/dL
TG: 225 mg/dL
LDL-C: 138 mg/dL

The Ominous Octet:
Its NOT Just About “The Sugar!”

Setting Glycemic Targets for Patients with T2DM: ADA/EASD Position Statement Recommendations

- For most patients, A1C <7.0% is appropriate
- Individualization is the key
  - Tighter targets for younger, healthier patients
  - Less stringent targets for older patients; those with comorbidities, known CAD, hypoglycemia unawareness, short life expectancy; and/or those who live alone
- Safety and efficacy trump cost
- Minimize risk of hypoglycemia


SGLT2 Inhibitors

- Oral agents – canagliflozin, dapagliflozin
- Efficacy:
  - Moderate A1C improvement (average A1C reductions 0.6-0.9%)
  - Reduce systolic and diastolic blood pressure
  - Weight loss (2-4 kg)
- Safety:
  - No added hypoglycemia unless used with secretagogues and/or insulin
  - Both increase LDL-C; canagliflozin can also increase non-HDL-C
  - Dapagliflozin not indicated for eGFR < 60 mL/min/1.73 m²
  - Canagliflozin not indicated for eGFR < 30 mL/min/1.73 m²

Where to Initiate Incretin-based Therapies: Important Distinctions

1. GLP-1 RAs – slow gastric emptying, increase satiety, promote weight reduction, improve cardiovascular risk factors, may improve beta cell mass and function (animal models only), now listed in new AACE guidelines as a treatment option in patients with prediabetes (currently off-label)

2. DPP-4 inhibitors – weight neutral, taken orally, generally well tolerated


DPP-4 Inhibitors

- Efficacy:
  - Moderate A1C improvement
  - Higher potency when combined with metformin
  - Weight neutral
  - Improved cardiovascular risk profile

- Safety:
  - No added hypoglycemia unless used with sulfonylurea
  - No gastrointestinal side effects

- Dosing adjustments for renal dysfunction EXCEPT linagliptin


Comparison of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
<th>Alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>25, 50, 100 mg once daily</td>
<td>2.5, 5.0 mg once daily</td>
<td>5 mg once daily</td>
<td>8.25, 12.5, 25 mg daily</td>
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<tr>
<td>Half-life (t1/2)</td>
<td>12.4 h</td>
<td>2.2 to 3.8 h</td>
<td>&gt; 113 h</td>
<td>21 h</td>
</tr>
<tr>
<td>24h DPP-4 inhibition</td>
<td>&lt; 80%</td>
<td>5% mg = 55%</td>
<td>&gt; 90%</td>
<td>&gt; 78%</td>
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<tr>
<td>Elimination</td>
<td>Kidney (mostly unchanged)</td>
<td>Liver and kidney active metabolites</td>
<td>Liver, &lt;5% renal</td>
<td>Kidney (mostly unchanged)</td>
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<tr>
<td>Dose adjustments for renal impairment</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
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<tr>
<td>Drug interaction potential</td>
<td>Low</td>
<td>Strong CYP3A4/5 inhibitors</td>
<td>Strong CYP3A4/5 inhibitors</td>
<td>Low</td>
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</tbody>
</table>


Sitagliptin Saxagliptin Linagliptin Alogliptin

Dosage 25, 50, 100 mg once daily 2.5, 5.0 mg once daily 5 mg once daily 8.25, 12.5, 25 mg daily

Half-life (t1/2) 12.4 h 2.2 to 3.8 h > 113 h 21 h

24h DPP-4 inhibition < 80% 5% mg = 55% > 90% > 78%

Elimination Kidney (mostly unchanged) Liver and kidney active metabolites Liver, <5% renal Kidney (mostly unchanged)

Dose adjustments for renal impairment Yes Yes None Yes

Drug interaction potential Low Strong CYP3A4/5 inhibitors Strong CYP3A4/5 inhibitors Low


Hypoglycemia Risk in Diabetes Patients Treated with DPP-4 Inhibitors*

<table>
<thead>
<tr>
<th></th>
<th>Mono</th>
<th>w/ MET</th>
<th>w/ PIO</th>
<th>w/ SUL</th>
<th>w/ Insulin</th>
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<tbody>
<tr>
<td>GLP-1 RA</td>
<td>SITA (100 mg)</td>
<td>SAXA (5.0 mg)</td>
<td>LINI (5.0 mg)</td>
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<td></td>
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<tr>
<td>1.2</td>
<td>5.6</td>
<td>7.5</td>
<td>14.6</td>
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<tr>
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<td>1.6</td>
<td>15.7</td>
<td>19.8</td>
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<td>31.4</td>
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<td>31.4</td>
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</table>

1. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA

Comparison of DPP-4 Inhibitors

- Efficacy:
  - Moderate A1C improvement
  - Higher potency when combined with metformin
  - Weight neutral
  - Improved cardiovascular risk profile
- Safety:
  - No added hypoglycemia unless used with sulfonylurea
  - No gastrointestinal side effects
- Dosing adjustments for renal dysfunction EXCEPT linagliptin


The GLP-1 RA Class: Pharmacokinetic Properties

GLP-1 RA

Short-acting (<24 hours) Exenatide BID

Long-acting (224 hours) Liraglutide OD Dulaglutide OW Albiglutide DW Semaglutide OW


Differences in the Mechanisms of Action of DPP-4 Inhibitors and GLP-1 RAs

- GLP-1 RAs
  - Subcutaneous administration
  - Add exogenous GLP-1 activity
  - Increase GLP-1 activity ≥ 9-fold
  - Greater A1C and weight effects than DPP-4 inhibitors
  - DPP-4 inhibitors
  - Oral administration
  - Block DPP-4 degradation of GLP-1
  - Increase endogenous GLP-1 levels = 2-Acid

Differences in Pharmacokinetic Properties

GLP-1 Baseline = 7 pM

Exenatide BID, saxagliptin OD, sitagliptin OD.

Comparison of Short-acting Versus Long-acting GLP-1 RAs

<table>
<thead>
<tr>
<th>Effects</th>
<th>Short-acting GLP-1 RAs</th>
<th>Long-acting GLP-1 RAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose levels</td>
<td>Modest reduction</td>
<td>Strong reduction</td>
</tr>
<tr>
<td>Postprandial hyperglycemia</td>
<td>Strong reduction</td>
<td>Modest reduction</td>
</tr>
<tr>
<td>Fasting insulin secretion</td>
<td>Modest stimulation</td>
<td>Strong stimulation</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Gastric emptying rate</td>
<td>Deceleration</td>
<td>Transient</td>
</tr>
<tr>
<td>Induction of nausea</td>
<td>20-50%, attenuates slowly (weeks to many months)</td>
<td>20-40%, attenuates quickly (~4-8 weeks)</td>
</tr>
<tr>
<td>Body weight reduction</td>
<td>1-5 kg</td>
<td>2-5 kg</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Heart rate</td>
<td>No effect or small increase (0-2 bpm)</td>
<td>Moderate increase (2-5 bpm)</td>
</tr>
</tbody>
</table>

Effects Short-acting GLP-1 RAs
- Fasting blood glucose levels: Modest reduction
- Postprandial hyperglycemia: Strong reduction
- Fasting insulin secretion: Modest stimulation
- Glucagon secretion: Reduction
- Gastric emptying rate: Deceleration
- Induction of nausea: 20-50%, attenuates slowly (weeks to many months)
- Body weight reduction: 1-5 kg
- Blood pressure: Reduction
- Heart rate: No effect or small increase (0-2 bpm)

Effects Long-acting GLP-1 RAs
- Fasting blood glucose levels: Strong reduction
- Postprandial hyperglycemia: Modest reduction
- Fasting insulin secretion: Strong stimulation
- Glucagon secretion: Reduction
- Gastric emptying rate: Transient
- Induction of nausea: 20-40%, attenuates quickly (~4-8 weeks)
- Body weight reduction: 2-5 kg
- Blood pressure: Reduction
- Heart rate: Moderate increase (2-5 bpm)

Effects
- Body weight reduction: 1-5 kg (Short-acting) vs. 2-5 kg (Long-acting)
- Blood pressure: Reduction (both)
- Heart rate: No effect or small increase (Short-acting) vs. Moderate increase (Long-acting)

Long-acting GLP-1 RAs:
- ≥24 hours

Short-acting GLP-1 RAs:
- <24 hours

**p<0.0001 vs. liraglutide 1.8 mg; **p<0.001 vs. liraglutide 1.8 mg; ***p<0.0001 vs. liraglutide 1.2 mg

Short- and Long-acting GLP-1 RAs Have Different Effects on Plasma Glucose

**GLP-1 RA**

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Addition of Insulin Detemir to Metformin + Liraglutide: A1C

Case 1

After discussing various treatment options, you initiate treatment with a GLP-1 RA, adding liraglutide to her existing therapy, continuing with dietary counseling and exercise and advising her to self-monitor blood glucose daily before breakfast and 2 hours after supper.

She returns in 12 weeks with the following data:

- A1C: 7.1%
- TG: 145 mg/dL
- Preprandial glucose: 108 to 114 mg/dL
- Total chol: 164 mg/dL
- Postprandial glucose: 139 to 149 mg/dL
- HDL-C: 44 mg/dL
- LDL-C: 91 mg/dL
- Weight: down 5 lbs
**Therapeutic Rationale**

Advantages of GLP-1 RA compared to other possible therapies in this patient:
1. Weight reduction (weight gain with insulin; weight neutral with DPP-4 inhibitor)
2. Reduced postprandial lipemia and hypertriglyceridemia (increased LDL-C and non-HDL-C with SGLT2 inhibitors)
3. Low risk of hypoglycemia (increased risk with secretagogues and insulin)
4. Blood pressure reduction (SGLT2 inhibitors also lower blood pressure – no direct effects with other agents)
5. Increased satiety (not seen with other agents) – the patient needs help curbing her appetite

**How to Initiate GLP-1 RA Therapy**

- **Liraglutide** – once daily initially 0.6 mg/day for 1 week and then 1.2 mg/day; may increase to 1.8 mg daily
  - If >3 days have elapsed since last dose, reinitiate at 0.6 mg/day and then titrate
- **Exenatide** – initially 5 mcg twice daily within 60 minutes of AM or PM meals; may increase to 10 mcg twice daily after 1 month
- **Exenatide extended release (ER)** – 2 mg once every 7 days

**GLP-1 RAs**

- Subcutaneous injectable – exenatide, liraglutide, exenatide ER
- **Efficacy:**
  - Greater reduction in A1C than DPP-4 inhibitors
  - Potential for weight loss
  - Improved cardiovascular risk profile
- **Safety:**
  - Gastrointestinal side effects – nausea/vomiting, diarrhea
  - No added hypoglycemia unless used with sulfonylurea
  - C-cell hyperplasia and medullary cancer in rodents
  - Pancreatitis – not seen in large data base analyses

**Properties of GLP-1 RAs**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Exenatide Twice Daily</th>
<th>Liraglutide Once Daily</th>
<th>Exenatide ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Synthetic exendin-4</td>
<td>Human GLP-1 analog</td>
<td>Exenatide extended release</td>
</tr>
<tr>
<td>Half-life</td>
<td>2-4 h</td>
<td>12-14 h</td>
<td>&gt; 1 wk</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>I I</td>
<td>I I I I</td>
<td>I I</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>I I I I</td>
<td>I I I I</td>
<td>I I I I I</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>+0.9</td>
<td>+1.1-1.6</td>
<td>+1.7</td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>Approximate decrease of 0.5 kg</td>
<td>Varies across class and with study duration</td>
<td></td>
</tr>
<tr>
<td>Common adverse effects</td>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Take Home Pearls for Clinical Practice GLP-1 RAs**

1. Increase glucose-dependent insulin secretion
2. Decrease glucose-dependent glucagon secretion
3. Slow gastric emptying
4. Increase satiety (decreasing appetite)
5. Promote weight reduction
6. Positively affect cardiovascular risk factors
7. Decrease fasting and postprandial glucose with short-acting agonists primarily affecting postprandial glucose
8. Carry low risk of hypoglycemia

**The Whys and Hows of Incretin-based Therapy**

Jack L. Leahy  
Endocrinology, Diabetes and Metabolism  
University of Vermont
Case 2: Irene

- 43-year-old woman presents for help managing her T2DM of 4 years duration.
- “I’m afraid. My sugars keep rising – now always 200s. I’m gaining weight. My doctor says I may need more BP and lipid medicines. I’m frustrated and overwhelmed. I want to feel healthy and in control.”
- Taking: metformin 1000 mg BID, and losartan 100 mg daily.

BMI: 32 kg/m²
Waist: 39 inches
BP: 139/80 mm Hg (bilaterally)
Random glucose: 221 mg/dL
A1C: 8.5%
eGFR: >60 mL/min/1.73 m²
Total cholesterol: 170 mg/dL
HDL-C: 36 mg/dL
TG: 206 mg/dL
LDL-C: 93 mg/dL

Look AHEAD Trial

- 5145 overweight or obese subjects with T2DM randomized to intensive lifestyle modifications focused on weight reduction versus diabetes education
- Primary outcome CV events – expected 13.5 years
- Stopped after 9.6 years:
  - Greater weight loss (6% versus 3.5% loss of BW at end)
  - Greater reduction in A1C and CV risk factors
- No difference in CV events

American Diabetes Association

A1C Recommendations

Less Stringent
(7.5-8%)
(ADA < 7%)

More Stringent
(as close to 6% as possible)

- Long diabetes duration
- Short life expectancy
- Complications, comorbidities
- History of severe hypoglycemia
- Short diabetes duration
- Long life expectancy
- No CVD

Blood Pressure Guidelines with Type 2 Diabetes

- American Diabetes Association:
  - Treat to <140/80 mm Hg.
  - Lower systolic targets (<130) may be appropriate for certain individuals.
  - Drug therapy should include ACE inhibitor or ARB.
- AACE:
  - Treat to <130/80 mm Hg
- JNC 8:
  - 18-60 years old, treat to <140/90 mm Hg

Lipid Guidelines with T2DM

- American Diabetes Association:
  - LDL goal is <100 mg/dL; <70 mg/dL established CAD.
  - Statin therapy for established CAD or > 40 years old with established CAD risk factors (family history CAD, smoking, hypertension, hyperlipidemia, albuminuria).
- AACE:
  - Treatment goal with diabetes <100 mg/dL; <70 mg/dL for DM + another CV risk factor.
- AHA/ACC:
  - Statin therapy for all T2DM 40-75 years old.

Relative A1C Lowering and Hypoglycemia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Efficacy (ΔA1C)</th>
<th>Hypoglycemia</th>
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<tbody>
<tr>
<td>Sulfonylureas</td>
<td>0.85%</td>
<td>HIGH</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.42%</td>
<td>LOW</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>0.61%</td>
<td>LOW</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.5%-0.8%</td>
<td>LOW</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>0.52-0.94%</td>
<td>LOW</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>1.0%-1.9%</td>
<td>LOW</td>
</tr>
<tr>
<td>Insulin</td>
<td>unlimited</td>
<td>HIGH</td>
</tr>
</tbody>
</table>

[References]

AAD, Diabetes Care 2014;37 Suppl 1:S14-S80.
Relative Weight Effects

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Weight Neutral</th>
<th>Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant</td>
<td>Modest</td>
<td></td>
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</table>

- Pioglitazone
- Glimepiride
- Glipizide
- Insulin

- SUs
- Glyburide
- Nateglinide

- Metformin
- DPP-4 Inhibitors
- α-glucosidase Inhibitors
- Coleselam
- Bromocriptine

- GLP-1 RAs
- SGLT2 Inhibitors
- Pramlintide
- Bariatric Surgery


"What Is Incretin Therapy?"

- Incretins are gut-derived hormones:
  - Secretd in response to nutrients that potentiate insulin secretion and suppress glucagon secretion
  - Act in a glucose-dependent fashion
  - The signal between food ingestion and postmeal glucose lipid control
- Two predominant incretins:
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP)
- Rapidly inactivated by dipeptidyl peptidase 4 (DPP-4)

Treatment Strategies Involving the Incretin System

- DPP-4 inhibitors:
  - Oral. Molecule selectivity inhibits activity of DPP-4
  - Sitagliptin, saxagliptin, linagliptin, alogliptin in United States
  - Vildagliptin in other countries
  - Lack "high" GLP-1 effects
- GLP-1 RAs:
  - Subcutaneous injection
  - Exenatide, liraglutide, exenatide ER
  - Others in development

Liraglutide vs. Sitagliptin, Both in Combination with Metformin: 1-Year Comparison

- A1C Reduction from Baseline (8.4%–8.5%) to 52 Weeks
- Weight Effects (kg)

Garber AJ. *Diabetes Care*. 2011;34 Suppl 2:S279-S284;
Dicker D. *Diabetes Care*. 2011;34 Suppl 2:S276-S278.


**Risk factor** | **Exenatide** 10 mcg twice daily (3.5 years) | **Liraglutide** 1.2 mg once daily (26 weeks) | **Exenatide ER** 2.0 mg once weekly (1 year)
---|---|---|---
Systolic BP (mm Hg) | -3.5* | -6.7* | -6.2*
Diastolic BP (mm Hg) | -3.3* | -2.3 | -2.6*
Total cholesterol (mg/dL) | -10.8* | -8.1 | 7.9*
LDL cholesterol (mg/dL) | -11.8* | -10.8* | -2.2
HDL cholesterol (mg/dL) | 8.5* | -1.2 | NR
Triglycerides (mg/dL) | -44.4* | -14.7* | -40.0*
Free fatty acids (mmol/L) | NR | -1.2 | NR

*P<0.05 vs baseline; †P<0.05 vs placebo.

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**Take Home Points**

1. Incretin-based therapies are effective to treat fasting and postprandial glucose with a low risk of hypoglycemia.
2. GLP-1 RA therapy can facilitate weight loss, suppress appetite and have beneficial effects on surrogate markers of cardiovascular risk (blood pressure and lipids).
3. Short-acting GLP-1 RA (exenatide) effectively treats postprandial glucose excursions.
4. Long-acting GLP-1 RAs (liraglutide and exenatide ER) effectively treat fasting and postprandial glucose.

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**Case 3: Miguel**

- Hispanic man
- Age: 72 years
- Medications
  - Metformin 2000 mg/d
  - Glimepiride 4 mg/d
  - Simvastatin 20 mg/d
- BMI: 28 kg/m²
- A1C: 8.5%
- FBS: 140 mg/dL
- PPG: 200-220 mg/dL
- Triglycerides: 450 mg/dL
- LDL-C: 110 mg/dL
- HDL-C: 38 mg/dL
- Comorbidities/safety concerns
  - Congestive heart failure
  - Mild to moderate renal insufficiency (eGFR 50 mL/min/1.73 m²)

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**GLP-1 RA Safety**

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Vice President
Principal Clinical Trials Investigator
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GLP-1 RA Safety

Outline

• Cardiovascular safety
• Specific precautions
  – Acute renal failure/renal insufficiency
  – Nausea
  – Medullary thyroid cancer
  – Pancreatitis and pancreatic cancer
• Use in patients with comorbid conditions (ie, some older patients)
• Injection techniques

GLP-1 RA Cardiovascular Safety:
Post Hoc Analyses of Pooled Clinical Trial Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>Outcome</th>
<th>Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratner et al1</td>
<td>EXN BID (n = 2316)</td>
<td>CV death, stroke, MI, ACS, revascularization</td>
<td>RR (95% CI) 0.70 (0.38-1.31)</td>
</tr>
<tr>
<td>Marso et al2</td>
<td>LIRA (n = 4257)</td>
<td>CV death, stroke, MI</td>
<td>IR (95% CI) 0.73 (0.36-1.41)</td>
</tr>
</tbody>
</table>

• Long-term trials to further evaluate the impact of GLP-1 RAs on the occurrence of CV events are in progress:3
  – LIRA (LEADER—NCT01179048): results anticipated in 2016
  – EXN ER (EXSCEL—NCT01144338): results anticipated in 2017
  – LIXI (ELIXA—NCT01147250): results anticipated in 2014

Evidence Regarding Renal Impairment with GLP-1 RAs

• No evidence of direct renal toxicity associated with GLP-1 RAs:1-3
  – Clearance of exenatide is impacted by renal impairment; clearance of liraglutide is not:1,4,5
  – Hypovolemia due to nausea/vomiting may worsen renal function:1
• Renal impairment has been reported in patients taking GLP-1 RAs:1
  – Impairment was reversible in many cases with the discontinuation of the suspected causative agents and implementation of supportive treatment
  – Hemodialysis or transplantation were required in some cases
• Some cases occurred in patients who:1,6-9
  – Experienced nausea, vomiting, diarrhea, dehydration
  – Took medications known to affect renal function or hydration status
  – Had no known underlying renal disease

Possible Renal Impairment Risk for GLP-1 RA Use: Clinical Recommendations

<table>
<thead>
<tr>
<th>Prescribing Information Precautions</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>Not in severe RI (CrCl &lt; 30 mL/min) or ESRD</td>
<td>Use with caution</td>
<td>Not in severe RI (CrCl &lt; 30 mL/min) or ESRD</td>
</tr>
</tbody>
</table>

• Recommendations
  – Caution is indicated when used in patients with renal impairment or renal transplantation, especially when initiating or escalating doses
  – Renal function may be impaired by hypovolemia due to nausea/vomiting
  – EXN BID or EXN ER should not be used in patients with severe RI or ESRD

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Nausea: Exenatide ER Versus Exenatide BID and Exenatide ER Versus Liraglutide


Nausea with Liraglutide Versus Sitagliptin or Exenatide BID


GLP-1 RA Safety

Outline
• Cardiovascular safety
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Possible Thyroid Tumor Risk: Clinical Concerns with GLP-1 RA Use

Prescribing Information Contraindications

<table>
<thead>
<tr>
<th>Exenatide ER (EXN ER)</th>
<th>Liraglutide (LIRA)</th>
<th>Exenatide BID (EXN BID)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Possible thyroid tumor risk</strong></td>
<td><strong>Do not use if history of MTC or MEN2</strong></td>
<td><strong>X</strong></td>
</tr>
</tbody>
</table>

- **Recommendations**
  - LIRA and EXN ER are contraindicated in patients with MEN2 or a personal or family history of MTC1
  - Patients should be counseled regarding MTC risk and symptoms of thyroid tumors1
  - Uncertain if there is a value to routine calcitonin and/or ultrasound monitoring; such monitoring may lead to unnecessary procedures1
  - Patients with thyroid nodules or elevated serum calcitonin levels identified for other reasons should be sent to an endocrinologist1
  - To monitor potential associations, report MTC to state cancer registry, regardless of treatment http://www.naaccr.org/Membership/MembershipDirectory.aspx1,2


GLP-1 RA Safety

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Recommendations for Incretin-based Therapies: Potential Pancreatitis Risk

Diabetes increases risk of pancreatitis 1.5- to 3-fold higher1-6

**GLP-1 RAs**

- **Precautions**
  - Cases have been reported
  - If patient has pancreatitis history, do not use exenatide, exenatide ER or liraglutide

- **Recommendations**
  - Educate patients, monitor for signs/symptoms
  - Ask about pancreatitis history
  - Discontinue immediately if pancreatitis symptoms occur

- If acute pancreatitis is confirmed, do not restart GLP-1 RA

- Report cases of pancreatitis to www.fda.gov/medwatch

**DPP-4 Inhibitors**

- **Precautions**
  - Cases have been reported
  - Unknown if pancreatitis history increases risk with DPP-4 inhibitor use

- **Recommendations**
  - Observe for signs/symptoms at initiation
  - If pancreatitis is suspected:
    - Promptly discontinue use
    - Initiate appropriate management

Pancreatic Safety of Incretin-based Drugs – FDA and EMA Assessment

• FDA reevaluated more than 250 toxicology studies, totaling nearly 18,000 healthy animals (15,480 rodents and 2475 nonrodents). Microscopic examinations from these toxicology studies yielded no findings of overt pancreatic toxic effects or pancreatitis.

• EMA conducted a similar review for the European Union. Drug-induced pancreatic tumors were absent in rats and mice that had been treated for up to 2 years (their life span) with incretin-based drugs, even at doses that greatly exceed the level of human clinical exposure.


GLP-1 RA Safety

Outline

• Cardiovascular safety
• Specific precautions
  – Acute renal failure/renal insufficiency
  – Nausea/GI intolerance
  – Medullary thyroid cancer
  – Pancreatitis and pancreatic cancer
• Use in patients with comorbid conditions (eg, older patients; concomitant medications)

GLP-1 RAs in Older Patients with Comorbidities

"Classic" Diabetes Comorbidities1-3

- Renal disease: 4% higher ESRD prevalence in patients > 65 y with diabetes vs those without1
- CVD: 43% of patients 65-74 y and 55% of patients > 75 y have CVD2
- Hepatic disease: Nearly 75% of patients ≥ 60 y have NAFLD3

Geriatric Syndromes4

- Cognitive dysfunction
- Functional impairment
- Falls and fractures
- Polypharmacy
- Depression
- Vision and hearing impairment
- Pain from neuropathy or other causes
- Urinary incontinence


Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin

Risk of Hypoglycemia Increased in Patients Taking Sulfonylurea in Combination with GLP-1 RAs

- LIRA (1.8 mg QD)
- EXN (10 mcg BID)
- EXN ER (2.0 mg)

Without Sulfonylurea

With Sulfonylurea

GLP-1 RAs in Older Patients with Comorbidities

Without Sulfonylurea

With Sulfonylurea

GLP-1 RA Safety

Outline

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Summary: Label Recommendations for GLP-1 RA Use in Patients with T2DM

Indications and usage

- Adjunct to diet and exercise
- Not first-line therapy
- Approved with basal insulin (not prandial)
- Do not use if history of MTC or MEN2
- History of pancreatitis
- Renal impairment
- Increased risk of hypoglycemia with secretagogues/insulin
- Hypersensitivity
- Severe gastrointestinal disease

http://www.pdr.net/drugpages/productlabeling.aspx?mpcode=57558000

AGI, α-glucosidase inhibitor; DPP-4i, DPP-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SU, sulfonylurea; TZD, thiazolidinedione.

17.8
10.5
8.9
4.8
1.1
0.9
0.5
0.4

Increased Risk vs Placebo

No Increased Risk vs Placebo

Odds Ratio

Bisphosphonate
Oxandrolone
Sulfonylurea
GLP-1 RA
TZD
AGI


Without Sulfonylurea With Sulfonylurea

a Minor hypoglycemia = self-treatable, with plasma glucose < 55 mg/dL; major hypoglycemia = requiring third party assistance.

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MEN2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma

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Take Home Points

1. Individualize treatments according to patient needs
2. Know the guidelines
3. Counsel patients regarding risks and benefits of various therapies
4. Treating patients with diabetes not only means achieving glycemic, lipid and blood pressure goals, but reducing cardiovascular risk, progression of disease and beta cell deterioration
5. Choose those medications that will achieve these goals, provide your patients with the best quality of life and increase their compliance to therapy

Question & Answer