Incorporating GLP-1 Receptor Agonist Therapy in T2DM Management: ACHIEVING A COMFORT ZONE IN 2014

Thursday, November 20, 2014
Jacob K. Javits Convention Center • New York, NY
9:45 am – 11:15 am

Educational Partner
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

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, 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.

Jeffrey S. Freeman, DO, FACOI
Professor and Chairman
Division of Endocrinology and Metabolism
Department of Internal Medicine
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

Dr. Jeffrey Freeman is professor and chairman of the division of endocrinology and metabolism in the department of internal medicine at the Philadelphia College of Osteopathic Medicine. Dr. Freeman earned his medical degree at the College of Osteopathic Medicine and Surgery, Des Moines, Iowa. He served an internship at the Pontiac Osteopathic Hospital and a residency at the University of Medicine and Dentistry of New Jersey (UMDNJ) Stratford Division and completed a fellowship in endocrinology and metabolism at the UMDNJ/Veterans Hospital in East Orange. Dr. Freeman's clinical interest focuses on diabetes therapy and its complications. He has been an investigator in trials of pramlintide, peroxisome proliferator activated receptor dual agonists, dipeptidyl peptidase 4 inhibitors, and glucose sensing. He has served as assistant editor of Diabetes Forecast and has published numerous peer reviewed articles.
John J. Russell, MD  
Clinical Professor of Family and Community Medicine  
Temple University School of Medicine  
Philadelphia, PA  
Associate Director, Family Medicine Residency Program  
Abington Memorial Hospital  
Abington, Pennsylvania

Dr. John Russell is the director of the family medicine residency program at Abington Memorial Hospital, Jenkintown, Pennsylvania; where, for the last 6 years, he has been chairman of the pharmacy and therapeutics committee at Abington and is president of the Abington Hospital medical staff. Dr. Russell is a graduate of Temple University and the Pennsylvania State University College of Medicine. He completed his family medicine training at Abington Memorial Hospital, serving as chief resident, and joined the faculty in 1993. Dr. Russell has served as contributing editor for several primary publications and has been a reviewer and contributor to *American Family Physician*. He has worked on the palm based guidelines for the American Diabetes Association (ADA) and The Infectious Disease Society of America. Dr. Russell has completed several recent video CME projects for American Academy of Family Physicians (AAFP) on diabetes and atrial fibrillation available on their website. Until recently, he recorded a twice monthly journal review podcast, Clinical Update for AAFP. Dr. Russell now records a monthly podcast on diabetes for the ADA The Diabetes Core Update. He is coauthor of the text, “Dermatology Skills in Primary Care”. Dr. Russell lectures extensively to primary care physicians on a national level and has won several resident teaching awards. He was named a “Top Doctor” in family medicine by *Philadelphia* magazine as well as *US News and World Report*. His special interests include pediatrics, dermatology, cardiology, pharmacology, medical history, and bioethics.

Faculty Financial Disclosure Statements  
The presenting faculty reported the following:  
Dr. Javier Morales serves as an advisor for Boehringer Ingelheim, Bristol-Myers Squibb, Novo Nordisk, Pfizer, Sanofi-Aventis and Warner Chilcott; and parparticipates in speakers bureau for Novo Nordisk, Sanofi-Aventis and Warner Chilcott.

Dr. Jeffrey S. Freeman has no relevant financial relationships to disclose

Dr. John Russell serves as an advisor for Takeda and Valeant; and participates in speakers bureau for Sanofi.

Education Partner Financial Disclosure Statement  
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Suggested Reading List  


Session 2


SESSION 2
9:45am – 11:15am

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

SPEAKERS
Javier Morales, MD
Jeffery Freeman, DO, FACOI
John Russell, MD

Presenter Disclosure Information
The following relationships exist related to this presentation:
► Javier Morales, MD, serves as an advisor for Boehringer Ingelheim, Bristol-Myers Squibb, Novo Nordisk, Pfizer, Sanofi-Aventis and Warner Chilcott. He also participates in speakers bureau for Novo Nordisk, Sanofi-Aventis and Warner Chilcott.
► Jeffrey S. Freeman, DO, FACOI, has no relevant financial relationships to disclose.
► John J. Russell, MD, serves as an advisor for Takeda and Valeant. He also participates in speakers bureau for Sanofi.

Presenter Disclosure Information
Off-Label/Investigational Discussion
► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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

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

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
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

Drug List

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

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

John J. Russell, MD
Chairman, Pharmacy and Therapeutics Committee
Director, Family Medicine Residency Program
Abington Memorial Hospital
Abington, PA

Why Bother Attending Yet Another Diabetes Lecture?

America is Changing!

- 29 million Americans have diabetes and an additional 92 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: | 179 mg/dL |
| HDL-C:     | 41 mg/dL |
| TG:        | 225 mg/dL |
| LDL-C:     | 93 mg/dL |

 Persistent uncontrolled T2DM is associated with:
1. Continued insulin resistance
2. Decreased satiety
3. Reduced meal-related incretin release
4. Enhanced hepatic glucose production
5. Enhanced glucagon release
6. Deterioration of beta cell function and mass
7. Acceleration of gastric emptying
The Ominous Octet: Its NOT Just About “The Sugar!”

- Impaired Insulin Secretion
- Decreased Insulin Effect
- Increased Glucagon Secretion
- Decreased Glucose Uptake
- Increased Glucose Reabsorption
- Neurotransmitter Dysfunction
- Increased Lipolysis

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

Look AHEAD Trial

- 5,145 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

Mechanisms of Action of Current Diabetes Medications

- Insulin
- Sulfonylureas
- Meglitinides (TZD)
- GLP-1 RA
- DPP-4 inhibitors
- Insulin
- TZDs
- SGLT2 inhibitors
- Metformin
- Insulin
- TZDs
- GLP-1 RA
- Bromocriptine
- GLP-1 RA
- Insulin
- TZDs

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). Only available via sc injection.
2. DPP-4 inhibitors – weight neutral, taken orally, generally well tolerated

- AACE/ACE Algorithm for Glycemic Control
- Lifestyle Modification
- GLP-1 RA
- DPP-4 inhibitor
- TZD
- SGLT2 inhibitor
- SU/LN
- No Symptoms
- Symptoms
- Dual Therapy
- Triple Therapy
- Insulin ± Other Agents
- If A1C >6.5% in 3 months, add second drug (dual therapy)
- If not at goal in 3 months, proceed to triple therapy
  - Possible benefits or few adverse events
  - Use with caution

- A1C ≥ 7.5%
- A1C > 9.0%
- Monotherapy
- Dual Therapy
- Metformin
- GLP-1 RA
- DPP-4 inhibitor
- TZD
- SGLT2 inhibitor
- SU/LN
- Bromocriptine QR
- AG inhibitor

AG, α-glucosidase; GLN, glinide; QR, quick release; SGLT2, sodium glucose cotransporter 2; SU, sulfonylurea; TZD, thiazolidinedione.


SGLT2 Inhibitors

• Oral agents — canagliflozin, dapagliflozin, empagliflozin
• 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/1.73m²
• Canagliflozin not indicated for eGFR < 30mL/min/1.73m²

Heap G. Decision Resources. Drugwatch Blog. January 2014

Relative A1C Lowering and Hypoglycemia

<table>
<thead>
<tr>
<th>Agent</th>
<th>Efficacy (ΔA1C)</th>
<th>Hypoglycemia</th>
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</thead>
<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>
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</table>


Relative Weight Effects

<table>
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<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>
</tr>
<tr>
<td>Pioglitazone</td>
<td>SUs</td>
<td>Metformin</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>GLP-1 RAs</td>
<td>SGLT2</td>
</tr>
<tr>
<td>Glipizide</td>
<td></td>
<td>Inhibitors</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td>Pramlintide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bariatric Surgery</td>
</tr>
</tbody>
</table>


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 orARB.
• AACE:
  – Treat to <130/80 mm Hg
• JNC 8:
  – 18-60 years old, treat to <140/90 mm Hg

ADA, Diabetes Care 2014;37 Suppl 1:S14-S80.
James PA, et al. JAMA. 2014;311:5-7-520.

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.

ADA, Diabetes Care 2014;37 Suppl 1:S14-S80.

Summary: Guidelines for Diabetes Care

• ADA/EASD and AACE recommend individualized A1c targets
• ADA/EASD emphasize patient-centered approach to antihyperglycemic therapy
• BP targets vary, but most recommend < 140 mm Hg systolic
• Lipid guidelines are in state of flux, but most agree that people > 40 with diabetes should be on a statin
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

“What Is Incretin Therapy?”

- Incretins are gut-derived hormones:
  - Secreted 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 and lipid control
- Two predominant incretins:
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP)
- Rapidly inactivated by dipeptidyl peptidase 4 (DPP-4)

Increased insulin
Lowered glucagon
Enhanced insulin sensitivity
Promoted satiety
Slowed motility
Increased CV dynamics
Anabolic

The Incretin Effect Is Reduced in Type 2 Diabetes Patients

- 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, albiglutide
  - Higher blood levels result in increased satiety
  - Others in development

Treatment Strategies Involving the Incretin System
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-fold

EXN BID, exenatide twice daily; SITA, sitagliptin.

a Cross-over study, 2-week segments (N = 61).

GLP-1
Baseline = 7 pM

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>Glucagon-like peptide-1 receptor agonists</th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
<th>Alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></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>
</tr>
<tr>
<td><strong>Half-life (t1/2)</strong></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><strong>24h DPP-4 inhibition</strong></td>
<td>&lt; 80%</td>
<td>5 mg: &lt; 55%</td>
<td>&gt; 90%</td>
<td>&gt; 78%</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Kidney (mostly unchanged)</td>
<td>Liver and kidney active metabolite</td>
<td>Liver, &lt;5% renal</td>
<td>Kidney (mostly unchanged)</td>
</tr>
<tr>
<td><strong>Dose adjustments for renal impairment</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Drug interaction potential</strong></td>
<td>Low</td>
<td>Strong CYP3A4/5 inhibitors</td>
<td>Strong CYP3A4/5 inhibitors</td>
<td>Low</td>
</tr>
</tbody>
</table>


GLP-1 RAs

- **Subcutaneous injectable** – exenatide, liraglutide, exenatide ER, albiglutide, dulaglutide
- **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


Albiglutide

- FDA approved April 2014
- Once weekly injectable GLP-1 RA
- Half-life of 4-7 days
- Indicated once weekly as monotherapy or combination therapy with metformin, glimepiride, pioglitazone or insulin.
- Not indicated for patients with T1DM
- Black box warning for thyroid C-cell tumors due to rodent data
- FDA is requiring post marketing studies to evaluate a medullary thyroid cancer registry of at least 15 years
- Associated with a REMS (risk evaluation and mitigation strategy)

Dulaglutide

- FDA approved September 2014
- Once weekly injectable GLP-1 RA
- Indicated once weekly as monotherapy or combination therapy with metformin, sulfonylureas, TZDs or prandial insulin.
- Not indicated for patients with T1DM
- Not recommended as first-line therapy due to safety concerns
- Black box warning for thyroid C-cell tumors due to rodent data
- Should not be used in patients with a personal or family history of medullary thyroid cancer or in patients with multiple endocrine neoplasia syndrome type 2.
- Should not be used in patients with pancreatitis
- FDA is requiring post marketing studies to evaluate a medullary thyroid cancer registry of at least 15 years
- Associated with a REMS (risk evaluation and mitigation strategy)

Dungan KM, et al. 
Lancet. 2014 Jul 10; Wysham C, et al. 
Diabetes Care. 2014;37(8):2168-76

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 hyperglycaemia</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>Transparent</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>

Bpm: beats per minute; GLP-1 RA, glucagon-like peptide 1 receptor agonist; LAR, long-acting release

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 (hours)</td>
<td>2-4 h</td>
<td>12-14 h</td>
<td>&gt; 1 wk</td>
</tr>
<tr>
<td>Fasting blood glucose (%)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Postprandial plasma glucose (%)</td>
<td>↑↑</td>
<td>↑↑</td>
<td>↑↑</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>Naugse</td>
<td></td>
</tr>
</tbody>
</table>


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

- Fasting blood glucose levels
- Postprandial hyperglycemia
- Fasting insulin secretion
- Glucagon secretion
- Gastric emptying rate
- Induction of nausea
- Body weight reduction
- Blood pressure
- Heart rate

Properties of GLP-1 RAs

Lancet. 2010;375:1447-1456
Lancet. 2010;376:431-439

Liraglutide or Exenatide ER vs. Sitagliptin (All Added to Metformin)

- A1C Change (%)
- BLAIC (%)
- LIRAs results sustained over 1 year

Lancet. 2010;375:1447-1456
Lancet. 2010;376:431-439

Exenatide ER versus Twice-Daily Exenatide for 30 Weeks

- A1C change (%)
- FPG change (mg/dL)
- Weight change (kg)
- Change in weight (%) patients

Lancet. 2010;376:431-439
Lancet. 2010;376:431-439
26-Week Comparison of Liraglutide and Exenatide Twice Daily

<table>
<thead>
<tr>
<th>Baseline A1C</th>
<th>8.2%</th>
<th>8.1%</th>
</tr>
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<tbody>
<tr>
<td>Change in A1C</td>
<td>-1.1</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

**Effect of Albiglutide on A1C**

<table>
<thead>
<tr>
<th>Harmony 7</th>
<th>Albiglutide vs Liraglutide, Both Forced Uptitration</th>
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<tbody>
<tr>
<td>A1C %</td>
<td>0.6%</td>
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<table>
<thead>
<tr>
<th>Harmony 6</th>
<th>Albiglutide vs Lispro, Both With Titrated Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C %</td>
<td>-0.8</td>
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</table>

<table>
<thead>
<tr>
<th>Harmony 5</th>
<th>Albiglutide vs Liraglutide, Both With Titrated Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C %</td>
<td>-0.79</td>
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</table>

**Effect of Albiglutide on Weight**

<table>
<thead>
<tr>
<th>Harmony 7</th>
<th>Albiglutide vs Liraglutide, Both Forced Uptitration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change (kg)</td>
<td>-1.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Harmony 6</th>
<th>Albiglutide vs Lispro, Both With Titrated Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change (kg)</td>
<td>-0.8</td>
</tr>
</tbody>
</table>

**Effect of GLP-1 RAs on CVD Risk Factors**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Exenatide</th>
<th>Liraglutide</th>
<th>Exenatide ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>-3.5</td>
<td>-4.7</td>
<td>-4.2</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>-3.1</td>
<td>-2.3</td>
<td>-2.8</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>-10.9</td>
<td>-6.1</td>
<td>-7.9</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>-11.0</td>
<td>-10.8</td>
<td>-2.2</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>8.6</td>
<td>-1.2</td>
<td>NR</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>-44.4</td>
<td>-14.7</td>
<td>-46.9</td>
</tr>
<tr>
<td>Free fatty acids (mM/L)</td>
<td>NR</td>
<td>-1.1</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Case 2**

After reviewing her past medical and family history, while also discussing various treatment options, you initiate treatment with a GLP-1 RA, adding liraglutide to her existing therapy, started a statin and referred her for dietary counseling and exercise. 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
• Albiglutide 30 mg once every 7 days

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

GLP-1 RA Safety

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

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)

Safety of Incretin Based Therapies: Focus on GLP-1 RA

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 al</td>
<td>EXN BID (n = 2316) Non-EXN BID (n = 1629)</td>
<td>CV death, stroke, MI, ACS, revascularization</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.70 (0.38-1.31)</td>
</tr>
<tr>
<td>Marso et al</td>
<td>LIRA (n = 4257)</td>
<td>CV death, stroke, MI</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.73 (0.38-1.41)</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.
  - LIRA (LEADER—NCT01179048): results anticipated in 2016
  - LIXI (ELIXA—NCT01147250): results anticipated in 2014
  - DIUWA (REWIND-NCT01394952): results anticipated 2019
  - SEMA (SUSTAINNG—NCT01720446): results anticipated 2016

Evidence Regarding Renal Impairment with GLP-1 RAs

- No evidence of direct renal toxicity associated with GLP-1 RAs.
  - Clearance of exenatide is impacted by renal impairment; clearance of liraglutide is not.
  - Hypovolemia due to nausea/vomiting may worsen renal function.
- Renal impairment has been reported in patients taking GLP-1 RAs.
  - 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:
  - 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>
<th>ALBIGLUTIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not in severe RI (CrCl &lt; 30 mL/min)</td>
<td>Use with caution</td>
<td></td>
<td>Use with caution</td>
<td></td>
</tr>
<tr>
<td>or ESRD</td>
<td></td>
<td></td>
<td></td>
<td></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.

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

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

- Significant lower vs EXN BID
GLP-1 RA Safety

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- Injection techniques

Possible Thyroid Tumor Risk:
Clinical Concerns with GLP-1 RA Use

Prescribing Information

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible thyroid tumor risk</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
- Recommendations
  - LIRA and EXN ER are contraindicated in patients with MEN2 or a personal or family history of MTC
  - Patients should be counseled regarding MTC risk and symptoms of thyroid tumors
  - Uncertain if there is a value to routine calcitonin and/or ultrasound monitoring; such monitoring may lead to unnecessary procedures
  - Patients with history of nodules or elevated serum calcitonin levels may benefit from regular monitoring
  - To monitor potential associations, report MTC to state cancer registry, regardless of treatment

Recommendations

- LIRA and EXN ER are contraindicated in patients with MEN2 or a personal or family history of MTC
- Patients should be counseled regarding MTC risk and symptoms of thyroid tumors
- Uncertain if there is a value to routine calcitonin and/or ultrasound monitoring; such monitoring may lead to unnecessary procedures
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GLP-1 RA Safety

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  - Nausea
  - Medullary thyroid cancer
  - Pancreatitis and pancreatic cancer
- Use in patients with comorbid conditions (ie, some older patients)
- Injection techniques

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

- FDA reevaluated more than 250 toxicity studies, totaling nearly 18,000 healthy animals (15,480 rodents and 2475 nonrodents). Microscopic examinations from these toxicity 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)
• Injection techniques

GLP-1 RA Safety

GLP-1 RAs in Older Patients with Comorbidities

“Classic” Diabetes Comorbidities1-3

Renal disease:
• >3X higher ESRD prevalence in patients > 65 y with diabetes vs those without1
• 43% of patients 65-74 y and 55% of patients > 75 y have CVD1

CV: Hypertension
• 2X higher CHF prevalence in patients > 65 y with diabetes vs those without1

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

“Classic” Diabetes Comorbidities1-3

Geriatric Syndromes4

Increased Risk vs Placebo
No Increased Risk vs Placebo

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

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

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
Smaller Pen Needle Size Is Effective and Preferred

- 4 mm × 32 G vs 5 mm × 31 G or 8 mm × 31 G
- 164 study participants
  - Mean BMI: 31.0 kg/m²
  - BMI range: 20 to 49 kg/m²
  - 52% with BMI > 30 kg/m²
- No difference in glycemic control or safety among needle sizes
- Significantly lower pain scores for 4 mm vs 5 mm and 8 mm needles
- Equivalent glycemic control for obese vs nonobese participants


Smoothing the Transition to Injections

Rapid Response Kit

- Identify regimen with flexibility the patient needs/desires
  - EXN BID administer before 2 (largest) meals of day
  - LIRA, EXN QW—less frequent dosing
- Injection is relatively painless
  - Small, fine needle
  - Fatty tissue vs muscle
- "See one, do one, teach one."3
  - Have patient see/use pen and needle before leaving office
  - Refer patient to product-specific resources for starting treatment

1. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.
Photo courtesy of Scott V Joy.

Case 3: Miguel

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

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