Session 3: Case Work: Evaluating GLP-1 RAs in Patient-Centered Care for Type 2 Diabetes

Learning Objectives
1. Evaluate and apply current evidence regarding GLP-1 RA efficacy relative to other agents and across diabetes progression.
2. Evaluate and apply current evidence regarding safety of GLP-1 RAs, including recent data on specific label precautions (eg, thyroid cancer, pancreatitis, renal failure) and cardiovascular disease.
3. Evaluate and apply current evidence regarding tolerability and treatment satisfaction with GLP-1 RAs.
4. Evaluate and apply current evidence regarding nonglycemic effects of GLP-1 RAs (eg, effects on weight, blood pressure, lipid levels).

Faculty

Derek LeRoith, MD, PhD
Professor of Medicine
Director of Research
Division of Endocrinology, Diabetes, and Bone Disease
Mount Sinai School of Medicine
New York

Dr LeRoith is currently a professor of medicine and director of research of the division of endocrinology, diabetes, and bone disease at Mount Sinai School of Medicine in New York, New York.

Dr LeRoith received his medical and research training at University of Cape Town in Cape Town, South Africa, and completed his postgraduate training in London, United Kingdom. Subsequently, he was a member of the medical faculty at the Ben Gurion University Medical School in Israel.

Dr LeRoith worked at the National Institutes of Health (NIH) from 1979 until 2005 in the field of endocrinology and diabetes, and advanced to diabetes branch chief at the NIH in Bethesda, Maryland. His research interests include the role of insulin and insulin-like growth factors in normal physiology and disease states, including obesity, type 2 diabetes mellitus (T2DM), and cancer. His clinical focus primarily involves the pathophysiology and management of T2DM. Dr LeRoith has published over 500 research and review articles on these topics.

James LaSalle, DO, FAAFP
Medical Director
Excelsior Springs Clinic
Excelsior Springs, Missouri

Dr LaSalle is a fellow of the American Academy of Family Physicians. He received his medical degree from Kansas City University of Medicine and Biosciences (formerly the University of Health Sciences) in Kansas City, Missouri. Dr LaSalle holds membership in various state and national professional organizations. He is a member of the Excelsior Springs Clinic and is a practicing family physician.

Dr LaSalle is also an author and/or principal investigator of more than 150 clinical trials, placing him at the forefront of new clinical information and securing his role as a key opinion leader in his field. His research activities include extensive work in type 2 diabetes, hypertension, dyslipidemia, and the metabolic abnormalities commonly encountered with these disease states. Dr LaSalle's interests have focused on primary preventive cardiovascular medicine for much of his 30-year medical career.
Dr Shubrook is a family physician and diabetes specialist. He serves as the director of clinical research of the Diabetes Institute at Ohio University Heritage College of Osteopathic Medicine and director of diabetes fellowship for primary care physicians. His research focuses on childhood obesity, diabetes prevention, and early intervention. His favorite roles are as a husband to his wife and father to 2 daughters.

Faculty Financial Disclosure Statements

The presenting faculty report the following:

Derek LeRoith, MD, PhD, FACP, participates in advisory boards for AstraZeneca, Janssen Pharmaceuticals, and Merck & Co., Inc. He receives grant/research support from AstraZeneca, Janssen Pharmaceuticals, and Merck & Co., Inc.

James LaSalle, DO, FAAFP, is a consultant for Novo Nordisk Inc. He receives honoraria from Boehringer Ingelheim, Eli Lilly and Company, and Novo Nordisk Inc. Dr LaSalle is also on the speakers bureaus for Boehringer Ingelheim and Eli Lilly and Company.

Jay Shubrook, DO, FACOFP, FAAFP, receives grant/research support from Sanofi US.

Education Partner Financial Disclosure Statement

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Amy Carbonara, Director of Program Development, has nothing to disclose.

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Steve Weinman, RN, Executive Director, has nothing to disclose.

Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>glycated hemoglobin</td>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
<td>BPM</td>
<td>beats per minute</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
<td>BiD</td>
<td>twice daily</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>ACE</td>
<td>American College of Endocrinology</td>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>ADL</td>
<td>activities of daily living</td>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>AERS</td>
<td>adverse events reporting system</td>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>AGI</td>
<td>α-glucosidase inhibitor</td>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>ALBI</td>
<td>albiglutide</td>
<td>CrCl</td>
<td>creatinine clearance</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>AMP</td>
<td>adenosine monophosphate</td>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>ASP</td>
<td>insulin aspart</td>
<td>d</td>
<td>day</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>BL</td>
<td>baseline</td>
<td>DPP-4</td>
<td>dipeptidyl peptidase-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPP-4i</td>
<td>dipeptidyl peptidase-4 inhibitor</td>
</tr>
</tbody>
</table>
Suggested Reading List


Learning Objectives

Evaluate and apply current evidence regarding
- GLP-1 RA efficacy relative to other agents and across diabetes progression
- Safety of GLP-1 RAs, including recent data on specific label precautions (eg, thyroid cancer, pancreatitis, renal failure) and cardiovascular disease
- Nonglycemic effects of GLP-1 RAs (eg, effects on weight, blood pressure, lipid levels)
- Tolerability and treatment satisfaction with GLP-1 RAs

Introduction: Overview of GLP-1 RAs

Outline
- Mechanism/physiological action of GLP-1 RAs vs other antihyperglycemic agents
- Distinction between incretin-based therapies
  - GLP-1 RAs vs DPP-4 inhibitors
  - Head-to-head comparisons of GLP-1 RAs
Actions of GLP-1 RAs Complement Those of Commonly Used Antihyperglycemic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Effectiveness</th>
<th>Cellular Mechanism</th>
<th>Primary Physiological Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulins</td>
<td>Highest</td>
<td>Glucose disposal</td>
<td>Hepatic glucose production</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>High</td>
<td>Activate GLP-1 receptors</td>
<td>Insulin secretion (glucose-dependent)</td>
</tr>
<tr>
<td>SGLTs</td>
<td>High</td>
<td>Activate AMPK</td>
<td>Hepatic glucose production</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Intermediate</td>
<td>Activate PKA</td>
<td>Insulin sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GLP-1 secretion (glucose-dependent)</td>
</tr>
</tbody>
</table>

GLP-1 RAs: GLP-1 analogs; SGLTs: sulfonylureas; DPP-4 inhibitors: DPP-4 inhibitors; AMPK: AMP-activated protein kinase; PKA: protein kinase A.

Comparing Actions of DPP-4 Inhibitors and GLP-1 RAs

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

Marketed and Investigational GLP-1 RAs

<table>
<thead>
<tr>
<th>Duration of Action</th>
<th>Agent</th>
<th>Dosing or Anticipated Dosing</th>
<th>Base Peptide</th>
<th>US Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short</td>
<td>EXN BID</td>
<td>Twice daily</td>
<td>Exenatide-4</td>
<td>Marketed</td>
</tr>
<tr>
<td>Short</td>
<td>LIRI</td>
<td>Once daily</td>
<td>Exenatide-4</td>
<td>Regulatory filing</td>
</tr>
<tr>
<td>Long</td>
<td>LIRA</td>
<td>Once daily</td>
<td>GLP-1</td>
<td>Marketed</td>
</tr>
<tr>
<td>Long</td>
<td>EXN QW</td>
<td>Once weekly</td>
<td>Exenatide-4</td>
<td>Marketed</td>
</tr>
<tr>
<td>Long</td>
<td>ALBI</td>
<td>Once weekly</td>
<td>GLP-1</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Long</td>
<td>DULA</td>
<td>Once weekly</td>
<td>GLP-1</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Long</td>
<td>SEMA</td>
<td>Once weekly</td>
<td>GLP-1</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>

GLP-1 RAs: GLP-1 analogs; SGLTs: sulfonylureas; DPP-4 inhibitors: DPP-4 inhibitors; AMPK: AMP-activated protein kinase; PKA: protein kinase A.

Glycemic Control With Available GLP-1 RAs: Head-to-Head Trial Results

- **LEAD**: EXN BID (10 mcg), LIRI (1.8 mg), EXN QW (2.0 mg)
- **Duration**: LEAD-4, LIRI-14, EXN QW-24
- **Treatment**: SITA, EXN BID, EXN QW

Exenatide BID Reduces PPG More Than Exenatide QW and Liraglutide

- **Exenatide BID**: Baseline = 7 µM
  - Heart rate increase: None/small (1-2 bpm)
  - Body weight reduction: 1-5 kg
  - Nausea induction/attenuation: 20%-50% weeks-months

- **EXN BID**: Baseline = 1, LIRI = 41
  - Heart rate increase: Moderate (1-2.5 bpm)
  - Body weight reduction: 2-5 kg
  - Nausea induction/attenuation: 20%-45%/-4-8 weeks

- **DURATION-1**: Meal Tolerance Testing1
  - **Exenatide BID**: Baseline = 7 µM
    - 24 mg/dL
  - **Exenatide QW**: Baseline = 124 mg/dL
    - 95 mg/dL

- **LEAD-6**: SMBG2
  - Significantly greater PPG decreases with EXN BID vs LIRA
    - Breakfast estimated treatment difference: 24 mg/dL
    - Dinner estimated treatment difference: 18 mg/dL

GLP-1 RAs: GLP-1 analogs; SGLTs: sulfonylureas; DPP-4 inhibitors: DPP-4 inhibitors; AMPK: AMP-activated protein kinase; PKA: protein kinase A.
Summary

• Actions of GLP-1 RAs complement those of other antihyperglycemic agents commonly used in patients with T2DM
• DPP-4 inhibitors are not oral versions of GLP-1 RAs
• Short- and long-acting GLP-1 RAs differ in their effects on glycemic control
  – Greater PPG reduction with short-acting GLP-1 RAs
  – Greater A1C and FPG reduction with long-acting GLP-1 RAs
• Unique clinical characteristics of individual GLP-1 RAs may be leveraged for patient-centered care

GLP-1 RA Efficacy: Case 1

James R LaSalle, DO, FAAFP
Medical Director
Excelsior Springs Clinic
Excelsior Springs, Missouri

Case 1: Sandy

• Obese female (BMI 32 kg/m²)
• Age: 59 years
• T2DM for 9 years
• Medications
  – Metformin 2000 mg/d
  – Glimepiride 4 mg/d
  – Insulin glargine 46 U/d
• A1C 7.9%

GLP-1 RA Efficacy Across T2DM Progression

Outline

• Treatment recommendations
  – Prescribing information
  – Recent consensus statement (ADA/EASD and AACE/ACE)
• Evidence for use across T2DM progression
  – Prediabetes
  – Early (monotherapy)
  – Early (added to metformin as second-line agent)
  – Late T2DM (added to multiple oral antihyperglycemic agents)
  – Late T2DM (with insulin)

Label Recommendations Indicate GLP-1 RA Use Across T2DM Progression

<table>
<thead>
<tr>
<th>Indications and Usagea</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunct to diet and exercise (includes monotherapy)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Not recommended as first-line therapy for patients inadequately controlled on diet and exercise</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>With basal insulin (non-prandial)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

GLP-1 RA Efficacy Across T2DM Progression

Outline

• Treatment recommendations
  – Prescribing information
  – Recent consensus statement (ADA/EASD and AACE/ACE)
• Evidence for use across T2DM progression
  – Prediabetes
  – Early (monotherapy)
  – Early (added to metformin as second-line agent)
  – Late T2DM (added to multiple oral antihyperglycemic agents)
  – Late T2DM (with insulin)

Recent Treatment Algorithm

Recommendations for GLP-1 RAs in T2DM

ADA/EASD

• Combination
  – Second-line with metformin
  – In 3-drug combinations that do not include DPP-4 inhibitors
  – With basal insulin
• Among preferred agents for specific goals
  – Avoiding weight gain (GLP-1 RAs, DPP-4 inhibitors)
  – Avoiding hypoglycemia (GLP-1 RAs, DPP-4 inhibitors, TZDs)

AACE/ACE

• Monotherapy - first option in suggested usage hierarchy if metformin is not appropriateb
• Combination therapy
  – First option in suggested usage hierarchy for second-line combination with metformina
  – With basal insulin
• Cautiously consider in pre-DMc if
  – Glycemia not normalized with low risk agents (metformin, acarbose)
  – Multiple pre-DM criteria

a. Liraglutide and exenatide QW are not recommended as first-line agents for monotherapy, based on prescribing information.
b. Recommendation based on few adverse events or possible benefits.
c. FPG > 100 mg/dL and/or 2 hour PG > 140 mg/dL.
d. Not an FDA-approved indication.
http://www.accessdata.fda.gov/scripts/cder/DrugsatFDA.
Conversion From Prediabetes to Normal Glucose Tolerance With GLP-1 RAs

GLP-1 RAs are not FDA approved for treatment of prediabetes.

Efficacy of Marketed GLP-1 RAs Added to Metformin as Second-Line Agents

GLP-1 RAs Added to Basal Insulin

GLP-1 RAs Added to Multiple Oral Agents: Comparisons With Basal Insulin

Basal Insulin Added to GLP-1 RAs

Data from a retrospective database analysis with exenatide BID has demonstrated comparable benefit.

References:

Abbreviations:
GLAR, insulin glargine; EXN, exenatide; IDET, insulin detemir; LIRA, liraglutide; MET, metformin; OAD, oral antidiabetic agent; SU, sulfonylurea.

Results at 24 weeks
Results at 104 weeks

Exenatide twice daily (EXN BID)
Exenatide once weekly (EXN QW)
Liraglutide (LIRA)
Insulin glargine (GLAR)
GLP-1 RAs vs Prandial Insulin
Added to Basal Insulin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EXN BID</th>
<th>LIS TID</th>
<th>LIRA QD</th>
<th>ASP QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noninferior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>-2.5</td>
<td>2.1</td>
<td>-2.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Minor hypo, E/Y</td>
<td>2.1</td>
<td>5.0</td>
<td>1.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Noct hypo, E/Y</td>
<td>1.5</td>
<td>1.8</td>
<td>0.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>32</td>
<td>2</td>
<td>Nausea</td>
<td>LIRA&gt;ASP, first 2 wk</td>
</tr>
</tbody>
</table>

EXN, exenatide; LIS, insulin lispro; LIRA, liraglutide; QD, once daily; TID, three times daily.

Hypoglycemia With GLP-1 RAs: With and Without Sulfonylureas in Head-to-Head Trials

- Only 2 cases of major hypoglycemia (EXN BID + SU in LEAD-6)1-3
- Less minor hypoglycemia with LIRA vs EXN BID (1.93 vs 2.60 events per P-Y; \( P = .0131 \))1

EXN, exenatide; LIRA, liraglutide; P-Y, patient-year.

Patient-Centered Considerations: Sandy

- Patient is obese
  - Current ADA/EASD algorithm highlights GLP-1 RAs for use when avoidance of hypoglycemia or weight gain is a therapeutic goal
- Patient is not achieving glycemic control on MET + SU + insulin
  - Prescribing information and current treatment algorithms indicate GLP-1 RAs may be used across T2DM progression
  - GLP-1 RAs effectively improve glycemic control in combination with insulin
- Patient needs to improve A1C about 0.9% to reach appropriate glycemic control
  - GLP-1 RAs in combination with basal insulin may provide adequate glycemic control for the patient to reach her goal
- Patient may be at increased risk of hypoglycemia if agents are added to current regimen
  - GLP-1 RAs are associated with low risk of hypoglycemia
  - Consider reducing dose of SU and insulin

Recommendations for GLP-1 RA Use: Possible Hypoglycemia Risk

Prescribing Information Precautions: EXN BID, LIRA, EXN QW
- Increased risk of hypoglycemia with
c secretagogues/insulin
- Recommendation:
  - Consider lowering the dose of insulin secretagogue (eg, sulfonylurea) or insulin to reduce the risk of hypoglycemia

Hypoglycemic Risk of Antihyperglycemic Agents
Added to Metformin: A Network Meta-Analysis

Increased Risk vs Placebo
- AGI, ɑ-glucosidase inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.
- 39 randomized controlled trials.

Case 1: Faculty Discussion
Drs LeRoith, LaSalle, Shubrook
Case 2: Mike

- **Male**
- **Age:** 72 years
- **BMI:** 28 kg/m²
- **T2DM for 8 years**
- **Active, self-sufficient**
- **Medications**
  - Metformin 2000 mg/d
  - Glimepiride 4 mg/d
- **A1C:** 8.9%
- **Comorbidities/safety concerns**
  - Congestive heart failure
  - Mild to moderate renal insufficiency (eGFR 50 mL/min/1.73 m²)

GLP-1 RA Safety: Case 2

Jay Shubrook, DO, FACOFP, FAAFP
Associate Professor of Family Medicine
Director of Clinical Research
Director of Diabetes Fellowship
Department of Family Medicine
The Diabetes Institute
Ohio University Heritage College of Osteopathic Medicine
Athens, Ohio

GLP-1 RA Safety

Outline
- Cardiovascular safety
- Specific precautions
  - Acute renal failure/renal insufficiency
  - Pancreatitis
  - Medullary thyroid cancer
- Use in patients with comorbid conditions (eg, some elderly patients)

Post Hoc Analyses of GLP-1 RA Clinical Trial Data Reveal No Increased Risk of CV Events

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparators</th>
<th>Outcome</th>
<th>Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratner et al²</td>
<td>EXN BID (n = 2316) Non-EXN BID (n = 1629)³</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) Non-LIRA (n = 2381)³</td>
<td>CV death, stroke, MI</td>
<td>IR (95% CI) 0.73 (0.38-1.41)</td>
</tr>
</tbody>
</table>

Evidence Regarding Renal Impairment With GLP-1 RAs

- Evidence does not indicate direct renal toxicity with GLP-1 RAs¹-³
- Renal impairment impacts clearance of EXN but not LIRA¹⁴,⁵
- Renal impairment has been reported in patients taking GLP-1 RAs¹
  - Reversed in many cases with supportive treatment and discontinuation of potentially causative agents
  - Sometimes required hemodialysis or transplantation
- Some cases have occurred in patients who¹,⁶,⁷
  - Experienced nausea, vomiting, diarrhea, dehydration
  - Took medications known to affect renal function or hydration status
  - Had no known underlying renal disease

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

<table>
<thead>
<tr>
<th>Prescribing information Precautions</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not in severe RI (CrCl &lt; 30 mL/min) or ESRD</td>
<td>Use with caution in patients with RI (CrCl 30-50 mL/min)</td>
<td>Use with caution in patients with RI (CrCl 30-50 mL/min)</td>
<td></td>
</tr>
<tr>
<td>Use with caution in moderate RI (CrCl 30-50 mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recommendations

- Use with caution in patients with RI or renal transplantation, especially when initiating or escalating doses
- Hypovolemia due to nausea/vomiting may worsen renal function
- Do not use EXN BID or EXN QW in patients with severe RI or ESRD

ACS, acute coronary syndrome; CV, cardiovascular; EXN BID, exenatide twice daily; EXN QW, exenatide once weekly; LIRA, liraglutide; RI, renal impairment.

References

LIXI not FDA approved.

GLP-1 RA Safety: Case 2

Case 2: Mike

- **Male**
- **Age:** 72 years
- **BMI:** 28 kg/m²
- **T2DM for 8 years**
- **Active, self-sufficient**
- **Medications**
  - Metformin 2000 mg/d
  - Glimepiride 4 mg/d
- **A1C:** 8.9%
- **Comorbidities/safety concerns**
  - Congestive heart failure
  - Mild to moderate renal insufficiency (eGFR 50 mL/min/1.73 m²)
### Risk of Acute Pancreatitis With GLP-1 RAs

- Cases have been reported in patients taking GLP-1 RAs
- Risk is 1.5- to 2.5-fold higher in individuals with diabetes
- Mixed results regarding GLP-1 RA risk in database analyses
  - US Food and Drug Administration (3/4/13)
    - Ongoing investigation prompted by postmortem tissue study
  - Current recommendations
    - Patients who are taking GLP-1 RA should be monitored
  - European Medicines Agency (7/25/13)
    - Review of postmortem tissue study and other available data
    - Conclusions
      - No new data to indicate higher risk than previously identified
      - Current label information, monitoring efforts, and ongoing safety studies are sufficient

### Evidence Regarding Thyroid Cancer Risk With GLP-1 RAs

- Rodents, but not nonhuman primates, developed thyroid C-cell tumors when treated with GLP-1 RAs
- Unknown whether GLP-1 RAs cause C-cell tumors in humans; relevance of animal studies cannot be determined through trials because MTC is rare
  - Clinical trials
    - LIRA: 1.5 PTC cases per 1000 P-Ys vs 0.5 in controls, no confirmed MTC
    - EXN BID: 0.3 thyroid neoplasms per 100 P-Ys vs 0 in controls
    - Meta-analysis of published studies
      - No reported thyroid malignancies with EXN
      - No increased thyroid cancer risk with LIRA (OR 1.54 [95% CI 0.40-6.02])

### GLP-1 RAs in Patients With Comorbidities: Older Patients

**Diabetes Comorbidities**
- Renal disease: 3X higher ESRD prevalence in patients > 65 y with diabetes vs those without
- CVD: 43% of patients 65-74 y and 55% of patients > 75 y have CVD
- CHF: 2X higher CHF prevalence in patients > 65 y with diabetes vs those without

**Hepatic disease**
- Nearly 75% of patients ≥ 60 y have NAFLD

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

### Recommendations for GLP-1 RA Use: Possible Pancreatitis Risk

<table>
<thead>
<tr>
<th>Prescribing Information Precautions</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider other agents if history of pancreatitis</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

### Recommendations
- Educate patients and monitor for signs and symptoms
- Ask about medical history of pancreatitis
- Discontinue promptly if pancreatitis symptoms occur (eg, persistent severe abdominal pain that may or may not be accompanied by vomiting)
- If acute pancreatitis is confirmed, do not restart GLP-1 RA
- Report cases of pancreatitis to www.fda.gov/medwatch

### Recommendations for GLP-1 RA Use: Possible Thyroid Tumor Risk

<table>
<thead>
<tr>
<th>Prescribing Information Contraindications</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible thyroid tumor risk—do not use if history of MTC or MEN2</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Recommendations
- LIRA and EXN QW are contraindicated in patients with MEN2 or a personal or family history of MTC
- Counsel patients regarding MTC risk and symptoms of thyroid tumors
- Value of routine calcitonin and/or ultrasound monitoring is uncertain; such monitoring may lead to unnecessary procedures
- Patients with thyroid nodules or elevated serum calcitonin levels identified for other reasons should be sent to an endocrinologist
- To monitor potential associations, report MTC to state cancer registry, regardless of treatment

### Framework for Considering Glycemic Goals in Older Adults With Diabetes

**Patient Characteristics/Health Status**
- Healthy—few coexisting chronic illnesses, intact cognitive and functional status
  - Rationale: Longer remaining life expectancy
  - Reasonable A1C Goal:
    - < 7.5% or < 7.0%
- Complex/intermediate—multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild to moderate cognitive impairment
  - Rationale: Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk
  - Reasonable A1C Goal:
    - < 8.0%
- Very complex/poor health—long-term care or end-stage chronic illnesses or moderate to severe cognitive impairment or 2+ A1C dependencies
  - Rationale: Limited remaining life expectancy makes benefit uncertain
  - Reasonable A1C Goal:
    - < 8.5%

**ADL activities of daily living**
- Lower gastrointestinal distress, severe gastrointestinal or alimentary symptoms
- Day time glucosuria, dehydration, hyperglycemic hyperosmolar syndrome, and poor wound healing
- Other medical risk

**References**
GLP-1 RA Effects in Older and Younger Patients: Pooled Analyses of Phase 3 Trials

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>EXN BID a (10 mcg) 16 trials</th>
<th>EXN QW b (2.0 mg) 7 trials</th>
<th>LIRA c (1.8 mg) 6 trials</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 65 y</td>
<td>≥ 65 y</td>
<td>&lt; 65 y</td>
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<td>Hypoglycemia, major</td>
<td>16  19  6  8  14  15</td>
<td>16  19  6  8  14  15</td>
<td>16  19  6  8  14  15</td>
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<td>and minor, %</td>
<td></td>
<td></td>
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<tr>
<td>Nausea, %</td>
<td>38  41  15  11  21  25</td>
<td>38  41  15  11  21  25</td>
<td>38  41  15  11  21  25</td>
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<tr>
<td>Vomiting, %</td>
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<td>14  14  7  5  8  7</td>
<td>14  14  7  5  8  7</td>
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<tr>
<td>Diarrhea, %</td>
<td>11  10  11  12  13  13</td>
<td>11  10  11  12  13  13</td>
<td>11  10  11  12  13  13</td>
</tr>
</tbody>
</table>

Comparable, significant ∆ A1C from baseline for patients < 65 y and ≥ 65 y

Patient-Centered Considerations: Mike

- Patient is > 65 years old
  - GLP-1 RA efficacy, safety profiles are similar in older and younger patients
  - Be aware of geriatric syndromes that may affect ability to use GLP-1 RAs (eg, cognitive dysfunction, functional impairment, vision impairment, pain)
- Patient has renal impairment
  - GLP-1 RAs are not directly nephrotoxic, but should be used cautiously in patients with RI
  - EXN BID and EXN QW should not be used in patients with severe RI or ESRD
  - Hypovolemia may worsen renal function
- Patient has congestive heart failure
  - Analyses have demonstrated no increased risk of CV events with GLP-1 RAs
  - Long-term studies to better assess CV risk are in progress

Case 2: Faculty Discussion

Drs LeRoith, LaSalle, Shubbrook

Case 3: Marv

- Obese male (BMI 31 kg/m²)
- Age: 45 years
- T2DM for 3 years
- Medications
  - Metformin 2000 mg/d
  - Lisinopril 20 mg/d
- A1C: 8.1%
- Hypertension
  - BP 133/82 mm Hg
- Truck driver
- Back pain and vocation are barriers to regular exercise
- Also mentions discomfort in upper right abdomen

GLP-1 RA Nonglycemic Effects: Case 3

James R LaSalle, DO, FAAFP
Medical Director
Excelsior Springs Clinic
Excelsior Springs, Missouri

GLP-1 RA Nonglycemic Effects

Outline

- Overview of nonglycemic effects
  - Weight
  - Lipid levels
  - Blood pressure
- Implications for care beyond glycemic control
  - T2DM treatment goals other than hyperglycemia
  - NAFLD
Clinical Considerations for NAFLD/NASH

- Hepatic fat accumulation in the absence of other causes
  - Most prevalent liver disease in T2DM
  - May progress to NASH (liver damage with inflammation, necrosis, and fibrosis), cirrhosis, or hepatocellular carcinoma (HCC)
- Few clinical symptoms
- May or may not be associated with elevated ALT/AST
- May be detected using ultrasound (sensitivity not good)
- Currently no specific therapies
  - Recommend weight reduction, healthy diet, increased physical activity, avoidance of alcohol and unnecessary medications
  - Antioxidants (ie, vitamin E) and insulin sensitizers (ie, pioglitazone) may be effective\(^1\)

Effects of GLP-1 RAs on Hepatic Steatosis

- GLP-1 RAs are not FDA-approved for NAFLD/NASH
- Improved hepatic steatosis with GLP-1 RA treatment
  - Exenatide BID + pioglitazone – Significant hepatic fat reduction from 12.1% to 4.7% after 12 months (P < .05 vs pioglitazone alone)
  - Liraglutide – Hepatic fat reduced 15.9% after 6 months (P < .05 vs baseline)
  - GLP-1 RA (ie, exenatide BID, liraglutide) – 42% relative decrease in intrahepatic lipid (P < .00005 vs baseline)
- Improvements correlated with AST and ALT decreases, triglyceride and adiponectin changes, A1C decrease

* Assessed by magnetic resonance spectroscopy.


Patient-Centered Considerations: Marv

- Patient is obese
  - GLP-1 RAs do not promote weight gain and may encourage weight loss
- Patient needs to avoid hypoglycemia due to his profession
  - GLP-1 RAs are associated with low risk of hypoglycemia
- Patient needs to improve hypertension control
  - GLP-1 RAs may have beneficial effects on blood pressure and lipid levels
- Patient has nonspecific symptoms consistent with NAFLD
  - GLP-1 RA effects on weight are consistent with recommended management of NAFLD
  - Preliminary results suggest GLP-1 RAs may have beneficial effects in the management of NAFLD

Case 3: Faculty Discussion

Drs LeRoith, LaSalle, Shubrook

Case 4: Sarah

- Overweight female (BMI 28 kg/m²)
- Age: 52 years
- T2DM for 5 years
- A1C (before adding EXN BID): 7.6%
- Metformin 2000 mg/d
- Follow-up—EXN BID initiation
  - EXN BID at 10 mcg twice daily
  - Still reports nausea after 6 weeks, usually tolerable
  - Happy about weight loss (4 lbs)
  - Doesn’t like injecting 2× daily—occasionally misses evening dose

GLP-1 RA Treatment Satisfaction and Tolerability: Case 4

Jay Shubrook, DO, FACOFP, FAAFP
Associate Professor of Family Medicine
Director of Clinical Research
Director of Diabetes Fellowship
Department of Family Medicine
The Diabetes Institute
Ohio University Heritage College of Osteopathic Medicine
Athens, Ohio

GLP-1 RA Tolerability and Treatment Satisfaction

Outline
- Barriers, common adverse effects, and patient education
  - Injections
  - Nausea
  - Concerns regarding hypoglycemia
- Treatment satisfaction
  - Patient-reported outcomes (eg, treatment satisfaction, quality of life) from clinical trials
  - Resources (patient communication, patient assistance)
Patient Concerns Regarding Antihyperglycemic Treatments for T2DM

- Patients will pay extra to:
  - Decrease weight by 1 kg ($11/month)
  - Avoid hypoglycemia ($13/month)
  - Avoid 1-kg weight gain ($17/month)
  - Avoid injection ($24/month)
  - Improve A1C 1% ($26/month)
  - Avoid nausea ($35/month)

What Should the Patient Do to Reduce the Risk of Hypoglycemia?

- The risk of hypoglycemia is low with GLP-1 RAs, but you, your family, and your friends should be aware of hypoglycemia signs and symptoms.
- Have a plan to manage hypoglycemia—be ready to take 15-20 grams of sugars or carbohydrates if needed (e.g., ½ cup juice, 4-5 saltines)
- Be sure your healthcare professional knows all the medicines you are taking

Signs and Symptoms of Hypoglycemia:
- Headache
- Irritability
- Drowsiness
- Weakness
- Dizziness
- Fast heart beat
- Confusion
- Feeling jittery

Small 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
- Equivalent glycemic control for obese vs nonobese participants
- Significantly lower pain scores for 4 mm vs 5 mm and 8 mm needles
- ≥ 60% preferred 4mm over 5mm or 8mm

Self-Reported Hypoglycemia Negatively Affects Patient Health-Related Quality of Life

- Even mild hypoglycemia can significantly affect quality of life
- The magnitude of hypoglycemia impact increases with severity
- Hypoglycemia also associated with lower treatment satisfaction, poorer adherence, and greater resource utilization

<table>
<thead>
<tr>
<th>Study</th>
<th>Respondents (N)</th>
<th>Reported Hypoglycemia (%)</th>
<th>Severity (%)</th>
<th>HRQoL Decrement/a vs No Hypoglycemia</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Alvarez-Guisasola¹</td>
<td>1709</td>
<td>38</td>
<td>Mild</td>
<td>-2.68</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Severe</td>
<td>-16.09</td>
<td>&lt; .0001</td>
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<tr>
<td>Marrett²</td>
<td>1984</td>
<td>63</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Very severe</td>
<td>-0.21</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

GLP-1 RAs Are Administered by Subcutaneous Injection

- Exenatide BID
  - 5 mcg—orange, 10 mcg—yellow
  - Start with 5 mcg, increase to 10 mcg after 1 month
  - Inject within 60 min of 2 main meals

- Liraglutide
  - Adjust to deliver dose (0.6 mg, 1.2 mg, or 1.8 mg)
  - Start with 0.6 mg, increase after 1 week to 1.2 mg
  - May increase to 1.8 mg, if needed
  - Inject once daily, any time

- Exenatide QW
  - Inject immediately after suspension
  - Prior exenatide BID treatment not required
  - Inject missed dose only if next dose is ≥ 3 days away
  - Inject single 2-mg dose once weekly, any time

Smoothing the Transition to Injections

- Identify regimen with flexibility the patient needs/desires
  - EXN BID administer before 2 (largest) meals of day at least 6 hours apart
  - LRA, EXN QW—less frequent dosing
- Injection is relatively painless
  - Small, fine needle
  - Subcutaneous vs muscle
- Have patient see/use pen and needle before leaving office
- Refer patient to product resources for starting treatment

1. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA
3. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA
Managing Nausea Associated With GLP-1 RAs

- Draw on experience with other agents—7% to 26% of patients experience nausea/vomiting with metformin\(^1\).
- Discuss expectations\(^2\):
  - Nausea is likely to be mild and resolve in a few weeks
  - Nausea may actually be “fullness”
- Suggest behavioral changes\(^2\):
  - Meals—decrease portion sizes and reduce fat content
  - Keep a log to identify foods that cause nausea
- Titrate more slowly—wait until GI effects to ease before increasing dose\(^3\).
- Be aware of severe persistent abdominal pain, possibility of pancreatitis\(^3\).

Prescribing Information Precautions

<table>
<thead>
<tr>
<th>Prescribing Information Precautions</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe gastrointestinal disease (eg, gastroparesis)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Reports of Nausea Vary by Agent

Nausea may resolve more quickly with some agents\(^1\).

**Switch From EXN BID**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comparator</th>
<th>Significant Outcomes (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXN BID</td>
<td>GLAR (^a)</td>
<td>COMPARABLE improvement in HRQoL and treatment satisfaction</td>
</tr>
<tr>
<td>LIRA</td>
<td>GLIMP (^b)</td>
<td>BETTER HRQoL, weight assessment and concern, and emotional health</td>
</tr>
<tr>
<td>EXN BID</td>
<td>SITA (^a)</td>
<td>BETTER treatment satisfaction ((P &lt; .05) for all)</td>
</tr>
<tr>
<td>EXN BID</td>
<td>EXN QW (^a)</td>
<td>BETTER overall treatment satisfaction ((P &lt; .05))</td>
</tr>
<tr>
<td>EXN BID</td>
<td>PIO (^c)</td>
<td>BETTER improvement in weight-related quality of life ((P &lt; .05))</td>
</tr>
<tr>
<td>EXN BID</td>
<td>EXN QW (^d)</td>
<td>IMPROVED treatment satisfaction on switch from EXN BID</td>
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</tbody>
</table>

**Switch From SITA**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Comparator</th>
<th>Significant Outcomes (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITA</td>
<td>EXN BID (^a)</td>
<td>COMPARABLE improvement in weight-related quality of life, HRQoL, and treatment satisfaction</td>
</tr>
</tbody>
</table>

Patient-Centered Considerations: Sarah

- Patient is happy about weight loss
- Patient has persistent nausea
  - Nausea is tolerable
  - Provide education regarding meal sizes and fat content
- Patient has expressed dissatisfaction with dosing frequency
  - GLP-1 RAs with different dosing frequencies are available (twice daily, once daily, once weekly)

Other Resources

- General resources
- Patient assistance programs
  - Provide medication access for eligible patients and may improve adherence and outcomes\(^a\)
  - Specific information often available at product website
- Assessment tools for elderly patients\(^b\):
  - Unidentified cognitive deficits, functional status, nutritional needs: www.hospitalmedicine.org/geriresource/toolbox/howto.htm
  - Mini Nutritional Assessment: http://www.mna-elderly.com

**Diabetes Care** 2011;34:314-319.
**Diabetes Obes Metab** 2010;12:604-612.
**Health Qual Life Outcomes** 2006;4:80.
**Health Qual Life Outcomes** 2006;4:80.
**Health Qual Life Outcomes** 2006;4:80.
Case 4:
Faculty Discussion

Drs LeRoith, LaSalle, Shubrook

Question & Answer