CASE WORK:
EVALUATING GLP-1 RECEPTOR AGONISTS IN PATIENT-CENTERED CARE FOR TYPE 2 DIABETES

ATLANTA, GEORGIA • NOVEMBER 13, 2013
Session 1: Case Work: Evaluating GLP-1 Receptor Agonists in Patient-Centered Care for Type 2 Diabetes

Learning Objectives
1. Evaluate and apply current evidence regarding GLP1 Receptor Agonist (RA) efficacy relative to other agents and across diabetes progression
2. Evaluate and apply current evidence regarding safety of GLP1 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 GLP1 RAs
4. Evaluate and apply current evidence regarding nonglycemic effects of GLP1 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, New York

Dr Derek LeRoith is currently a professor of medicine and director of research of the division of endocrinology, diabetes and bone diseases 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 James 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 Frank Lavernia has been a practicing diabetologist in South Florida for over 30 years. He is the founder and director of the North Broward Diabetes Center in Pompano Beach, Florida. He is also an adjunct faculty member of the National Diabetes Education Initiative, Vascular Biology Working Group, and for the Coalition for the Advancement of Cardiovascular Health. Presently, he lectures nationally on lipid and hypertension disorders, obesity, prediabetes, diabetes, and their complications. He has previously presented for Pri-Med, the American College of Physicians, the National Association for Continuing Education, the Primary Care Network, and the annual meeting of the American Diabetes Association (ADA). He has published multiple articles in a variety of national medical journals and online publications. He has also appeared on the Discovery Channel and on National Public Radio. Most recently, he participated as faculty for several CME videos for the ADA. Dr Lavernia is a member of the ADA, the American Association of Clinical Endocrinology, and the National Hispanic Medical Association.

**Faculty Financial Disclosure Statements**

The presenting faculty reports the following:

Derek LeRoith, MD, PhD reports that he 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.

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Steve Weinman, RN, Executive Director, has no financial relationships to disclose.

**Acronym List**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>A1C</td>
<td>glycated hemoglobin</td>
<td>AST</td>
<td>aspartate aminotransferase</td>
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<td>AACE</td>
<td>American Association of Clinical Endocrinologists</td>
<td>BL</td>
<td>baseline</td>
</tr>
<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>ADA</td>
<td>American Diabetes Association</td>
<td>BPM</td>
<td>beats per minute</td>
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<tr>
<td>ACE</td>
<td>American College of Endocrinology</td>
<td>BID</td>
<td>twice daily</td>
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<tr>
<td>ADL</td>
<td>activities of daily living</td>
<td>BMI</td>
<td>body mass index</td>
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<td>AERS</td>
<td>adverse events reporting system</td>
<td>CHD</td>
<td>coronary heart disease</td>
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<td>AGI</td>
<td>α glucosidase inhibitor</td>
<td>CHF</td>
<td>congestive heart failure</td>
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<tr>
<td>ALBI</td>
<td>albiglutide</td>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
<td>CKD</td>
<td>chronic kidney disease</td>
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<tr>
<td>AMP</td>
<td>adenosine monophosphate</td>
<td>CrCl</td>
<td>creatinine clearance</td>
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<td>ASP</td>
<td>insulin aspart</td>
<td>CV</td>
<td>cardiovascular</td>
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<td></td>
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<td>CVD</td>
<td>cardiovascular disease</td>
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<td>Term</td>
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<tr>
<td>DM</td>
<td>diabetes mellitus</td>
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<td>DPP4</td>
<td>dipeptidyl peptidase-4</td>
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<tr>
<td>DPP4i</td>
<td>dipeptidyl peptidase-4 inhibitor</td>
<td></td>
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<td>DULAGLUTIDE</td>
<td>dulaglutide</td>
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<tr>
<td>DURATION</td>
<td>Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention With Exenatide Once Weekly</td>
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<tr>
<td>EASD</td>
<td>European Association for the Study of Diabetes</td>
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<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>EP</td>
<td>events per patient year</td>
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<td>ESRD</td>
<td>end-stage renal disease</td>
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<td>EXN</td>
<td>exenatide</td>
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<td>EXSCEL</td>
<td>Exenatide Study of Cardiovascular Event Lowering Trial: A Trial to Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly in Patients With Type 2 Diabetes Mellitus</td>
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<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>FFA</td>
<td>free fatty acid</td>
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<tr>
<td>FPG</td>
<td>fasting plasma glucose</td>
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<td>GIP</td>
<td>glucose-dependent insulinotropic polypeptide</td>
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<tr>
<td>GLAR</td>
<td>insulin glargine</td>
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<td>GLIM</td>
<td>glimepiride</td>
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<tr>
<td>GLP1</td>
<td>glucagon like peptide 1</td>
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<td>GLP1 RA</td>
<td>glucagon like peptide 1 receptor agonist</td>
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<tr>
<td>h</td>
<td>hour</td>
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<td>HCC</td>
<td>hepatocellular carcinoma</td>
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<tr>
<td>HDLC</td>
<td>high density lipoprotein cholesterol</td>
<td></td>
<td></td>
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<tr>
<td>HF</td>
<td>heart failure</td>
<td></td>
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<tr>
<td>HRQoL</td>
<td>health related quality of life</td>
<td></td>
<td></td>
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<tr>
<td>IDET</td>
<td>insulin detemir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
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</tr>
<tr>
<td>INS</td>
<td>insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td>incidence ratio</td>
<td></td>
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</tr>
<tr>
<td>KATP</td>
<td>ATP sensitive potassium channels</td>
<td></td>
<td></td>
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<tr>
<td>LDLC</td>
<td>low density lipoprotein cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEADER</td>
<td>Liraglutide Effect and Action in Diabetes</td>
<td></td>
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</tr>
<tr>
<td>LIRA</td>
<td>liraglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIS</td>
<td>insulin lispro</td>
<td></td>
<td></td>
</tr>
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<td>LIXI</td>
<td>lixisenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN2</td>
<td>multiple endocrine neoplasia type 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td>metformin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
<td></td>
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<tr>
<td>MTC</td>
<td>medullary thyroid carcinoma</td>
<td></td>
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<tr>
<td>NAFLD</td>
<td>nonalcoholic fatty liver disease</td>
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<td>NASH</td>
<td>nonalcoholic steatohepatitis</td>
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</tr>
<tr>
<td>NDEP</td>
<td>National Diabetes Education Program</td>
<td></td>
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</tr>
<tr>
<td>Noct</td>
<td>nocturnal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR</td>
<td>not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVD</td>
<td>nausea, vomiting, diarrhea</td>
<td></td>
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<tr>
<td>OAD</td>
<td>oral antidiabetic agent</td>
<td></td>
<td></td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
<td></td>
<td></td>
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<tr>
<td>ORL</td>
<td>orlistat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO</td>
<td>placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PG</td>
<td>plasma glucose</td>
<td></td>
<td></td>
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<tr>
<td>PIO</td>
<td>pioglitazone</td>
<td></td>
<td></td>
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<tr>
<td>PP</td>
<td>postprandial</td>
<td></td>
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<tr>
<td>PPAR</td>
<td>peroxisome proliferator-activated receptor</td>
<td></td>
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<tr>
<td>PPG</td>
<td>postprandial plasma glucose</td>
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<tr>
<td>PTC</td>
<td>papillary thyroid carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-Y</td>
<td>patient year</td>
<td></td>
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</tr>
<tr>
<td>PYE</td>
<td>patient years of exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QD</td>
<td>daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QW</td>
<td>once-weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
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<tr>
<td>RI</td>
<td>renal insufficiency</td>
<td></td>
<td></td>
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<tr>
<td>RR</td>
<td>risk ratio</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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<tr>
<td>SEMA</td>
<td>semaglutide</td>
<td></td>
<td></td>
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<tr>
<td>SITAGLITIN</td>
<td>sitagliptin</td>
<td></td>
<td></td>
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<tr>
<td>SU</td>
<td>sulfonylurea</td>
<td></td>
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</tr>
<tr>
<td>T2DM</td>
<td>type 2 diabetes mellitus</td>
<td></td>
<td></td>
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<tr>
<td>TRIG</td>
<td>triglyceride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TZD</td>
<td>thiazolidinedione</td>
<td></td>
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<tr>
<td>U</td>
<td>unit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USD</td>
<td>United States dollar</td>
<td></td>
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</tr>
<tr>
<td>Wt</td>
<td>weight</td>
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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 (e.g., thyroid cancer, pancreatitis, renal failure) and cardiovascular disease
- Nonglycemic effects of GLP-1 RAs (e.g., 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

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.
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

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% (eAG 180 mg/dL)

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 Usage†</th>
<th>EXN BID</th>
<th>LIRA</th>
<th>EXN QW</th>
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<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>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>With basal insulin (not prandial)</td>
<td>X</td>
<td>X</td>
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† GLP-1 RAs are not FDA approved for treatment of prediabetes.
**Efficacy of Marketed GLP-1 RAs as Monotherapy**

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Study Length (Number)</th>
<th>GLP-1 RA Comparator(s)</th>
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<tbody>
<tr>
<td>EXN BID</td>
<td>24 wk (N = 232)</td>
<td>MET + SU (n = 355)</td>
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<td></td>
<td>7.8%-7.9%</td>
<td>10 mg: -0.9</td>
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<tr>
<td>LIRA</td>
<td>52 wk (N = 746)</td>
<td>GLIM: -0.5</td>
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<tr>
<td>ASP QD</td>
<td>26 wk (N = 820)</td>
<td>MET: -1.5</td>
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**Efficacy of Marketed GLP-1 RAs Added to Metformin as Second-Line Agents**

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>Study Length (Number)</th>
<th>GLP-1 RA Comparator(s)</th>
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</thead>
<tbody>
<tr>
<td>EXN BID</td>
<td>30 wk (N = 336)</td>
<td>PBO: +0.1</td>
</tr>
<tr>
<td>LIRA</td>
<td>26 wk (N = 1087)</td>
<td>PBO: +0.1</td>
</tr>
<tr>
<td>ASP QD</td>
<td>26 wk (N = 658)</td>
<td>SITA: -0.9</td>
</tr>
</tbody>
</table>

**Efficacy of Marketed GLP-1 RAs Added to Multiple Oral Agents: Comparisons With Basal Insulin**

- **GLAR**
- **EXN BID**
- **LIRA**
- **EXN QW**
- **IDET**
- **MET + SU**
- **2-3 OADs**
- **MET + GLIM**
- **MET + SU**
- **MET + SU**

**GLP-1 RAs Added to Basal Insulin**

- **LIRA 1.8 mg + IDET vs Control**
  - 26-wk clinical trial
  - Baseline A1C
  - ΔA1C (%)
  - P = .001

**GLP-1 RAs Added to Basal Insulin**

- **LIRA 1.8 mg + IDET vs Control**
  - 26-wk clinical trial
  - Baseline A1C
  - ΔA1C (%)
  - P = .001

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

**Basal Insulin Added to GLP-1 RAs**

- **LIRA 1.8 mg + IDET vs Control**
  - 26-wk clinical trial
  - Baseline A1C
  - ΔA1C (%)
  - P = .001

**GLP-1 RAs vs Prandial Insulin Added to Basal Insulin**

- **Added to GLAR (30 wk, N = 637)**
  - Baseline A1C
  - ΔA1C (%)
  - P = .0024

- **Added to IDEG (26 wk, N = 177)**
  - Baseline A1C
  - ΔA1C (%)
  - P = .0024
Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin: A Network Meta-Analysisa


AGI, α-glucosidase inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

a 39 randomized controlled trials.

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.

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

Recommendations for GLP-1 RA Use: Possible Hypoglycemia Risk

Prescribing Information Precautions EXN BID LIRA EXN QW
Increased risk of hypoglycemia with secretagogues/insulin X X X

Recommendation:
– Consider lowering the dose of insulin secretagogue (eg, sulfonylurea) or insulin to reduce the risk of hypoglycemia

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

Case 1: Faculty Discussion

Drs LeRoith, LaSalle, Lavernia

GLP-1 RA Safety: Case 2

James R LaSalle, DO, FAAFP
Medical Director
Excelsior Springs Clinic
Excelsior Springs, Missouri
### Post Hoc Analyses of GLP-1 RA Clinical Trial

**Study**

<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)</td>
<td>CV death, stroke, MI, ACS, revascularization</td>
<td>RR (95% CI) 0.70 (0.38-1.31)</td>
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<td>Non-EXN BID (n = 1639)</td>
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<tr>
<td>Marso et al</td>
<td>LIRA (n = 4037)</td>
<td>CV death, stroke, MI</td>
<td>RR (95% CI) 0.73 (0.38-1.41)</td>
</tr>
<tr>
<td></td>
<td>Non-LIRA (n = 2381)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Recommendations**

- 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
  - EXN QW (EXSCEL—NCT01144338): results anticipated in 2017

---

### Precautions


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### Evidence Regarding Renal Impairment With GLP-1 RAs

- Evidence does not indicate direct renal toxicity with GLP-1 RAs.
- Renal impairment impacts clearance of EXN but not LIRA.
- Renal impairment has been reported in patients taking GLP-1 RAs.
  - Reversed in many cases with supportive treatment and discontinuation of potentially causative agents.
  - Sometimes required hemodialysis or transplantation.
- Most cases in patients who had nausea, vomiting, diarrhea, dehydration.
- Some cases in patients who took medications known to affect renal function or hydration status or who had no known renal disease.

---

### Acute Pancreatitis (AP) Risk With GLP-1 RAs

- Diabetes is associated with higher AP risk (1.5- to 2.5-fold).
- Cases have been reported in patients taking GLP-1 RAs.
- Mixed results regarding GLP-1 RA risk in database analyses.
- Recent statements.
  - US Food and Drug Administration (3/14/13):
    - Ongoing investigation prompted by postmortem tissue study.
    - Current recommendations.
    - Review of postmortem tissue study and other available data.
    - Conclusions.

---

### 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>Not in severe RI (CrCl &lt; 30 mL/min) or ESRD</td>
<td>Use with caution in patients with RI</td>
<td>Not in severe RI (CrCl &lt; 30 mL/min) or ESRD</td>
</tr>
<tr>
<td></td>
<td>Use with caution in moderate RI (CrCl 30-50 mL/min)</td>
<td></td>
<td>Use with caution in moderate RI (CrCl 30-50 mL/min)</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.
Recommendations for GLP-1 RA Use: Possible Pancreatitis Risk

Prescribing Information Precautions EXN BID LIRA EXN QW
Consider other agents if history of pancreatitis X X X X

Recommendations
- Educate patients and monitor for signs and symptoms
- Ask about medical history of pancreatitis
- Discontinue promptly if pancreatitis symptoms occur (e.g., 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

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. 6
- Relevance of animal studies in humans is unknown and cannot be determined through trials because MTC is rare. 3,4
- Clinical trials - reported as vs controls1,2
  - LIRA: 1.5 vs 0.5 PTC cases per 1000 P-Y; 1.3 vs 1.0 CCH cases per 1000 P-Y; no confirmed MTC with LIRA
  - EXN: 0.3 vs 0 thyroid neoplasms4 per 100 P-Y (3 vs 0 per 1000 P-Y)
- Meta-analysis of published studies5
  - No reported thyroid malignancies with EXN
  - No increased thyroid cancer risk with LIRA (OR 1.54 [95% CI 0.40-6.02])

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

Prescribing Information Contraindications EXN BID LIRA EXN QW
Possible thyroid tumor risk do not use if history of MTC or MEN2

Recommendations
- LIRA and EXN QW are contraindicated in patients with MEN2 or a personal or family history of MTC1
- Counsel patients regarding MTC risk and symptoms of thyroid tumors3
- Value of routine calcitonin and ultrasound monitoring is uncertain; 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, -

GLP-1 RAs in Patients With Comorbidities: Older Patients

Diabetes Comorbidities1-3
- Renal disease:
  - 3X 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
    - 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

A Framework for Considering Glycemic Goals in Older Adults With Diabetes

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

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

- Comparable, significant A1C from baseline for patients < 65 y and ≥ 65 y
- Adverse events generally comparable in type and frequency

Clinical Outcome EXN BID (10 mcg) 16 trials EXN QW (2.0 mg) 7 trials LIRA (1.8 mg) 6 trials
< 65 y 65 y 65 y 65 y
Hypoglycemia, major and minor, % 10% 10% 10% 10% 10%< 65 y 10% 10%
Nausea, % 38 41 15 11 21 25
Vomiting, % 14 14 7 5 9 7
Diarrhea, % 11 10 11 12 13 13

1. Lira RA, exenatide SR 2.0 mg, LiraQW 2.0 mg, EXN once weekly; LIRA, liraglutide.
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, Lavernia

GLP-1 RA Nonglycemic Effects: Case 3

Frank Lavernia, MD
Founder and Director
North Broward Diabetes Center
North Broward Medical Center
Pompano Beach, Florida

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% (eAG 186 mg/dL)
- 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

Outline

- Overview of nonglycemic effects
  - Weight
  - Lipid levels
  - Blood pressure

- Implications for care beyond glycemic control
  - T2DM treatment goals other than hyperglycemia
  - NAFLD

T2DM Treatment Selection Can Impact Body Weight

<table>
<thead>
<tr>
<th>Monotherapies</th>
<th>MET Combination Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ Weight (24-mo median, kg)</td>
<td>∆ Weight (24-mo median, kg)</td>
</tr>
<tr>
<td>-10.0</td>
<td>-10.0</td>
</tr>
<tr>
<td>-5.0</td>
<td>-5.0</td>
</tr>
<tr>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

All P < .001 vs baseline EXCEPT P = .6 vs baseline for DPP-4 inhibitor monotherapy

MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione.

a Analysis of UK General Practice Research Database.
GLP-1 RA Weight Effects in Patients With T2DM

**Meta-Analysis**

(69 Published RCTs)\(^1,\)\(^a\)

<table>
<thead>
<tr>
<th>Δ Weight (kg)</th>
<th>LIRA (1.8 mg)</th>
<th>EXN BID (0.6 mg)</th>
<th>EXN QW (0.3 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2.03</td>
<td>-2.29</td>
<td>-2.41</td>
<td></td>
</tr>
</tbody>
</table>


- Generally similar between in head-to-head GLP-1 RA trials
  - EXN BID vs LIRA\(^2\)
  - EXN BID vs EXN QW\(^1,\)\(^a\)
  - Exception: LIRA (3.6 kg) vs EXN QW (2.7 kg, \(P = .0005\))\(^1\)
  - Weight loss in > 75% of head-to-head trial participants\(^1,\)\(^a\)
  - Weight loss significant in the absence of GI AEs, but greater with GI AEs\(^1,\)\(^a\)

Liraglutide Effects on Systolic Blood Pressure With or Without Antihypertensive (AH) Agents

**Meta-analysis of 6 × 26-week clinical trials (N = 3967)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Incremental Change</th>
<th>Potential Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight/obesity(^1)</td>
<td>6% weight loss over 4 years</td>
<td>- A1C (8.4%) - SBP (5 mm Hg) - HDL-C (14 mg/dL) - TRIG (26 mg/dL)</td>
</tr>
<tr>
<td>Hypertension(^2)</td>
<td>10 mm Hg decrease in SBP</td>
<td>- Risks: - Diastolic-related death (17%) - All-cause mortality (12%) - MI (12%) - Stroke (12%) - HF (15%)</td>
</tr>
<tr>
<td>Dyslipidemia(^3,)(^a)</td>
<td>40 mg/dL decrease in LDL-C</td>
<td>10% ↓ in acute mortality</td>
</tr>
<tr>
<td>Effects of GLP-1 RAs on Hepatic Steatosis(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 RAs are not FDA-approved for NAFLD/NASH(^1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved hepatic steatosis with GLP-1 RA treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Exenatide BID + pioglitazone(^2) - Significant hepatic fat reduction from 12.1% to 4.7% after 12 months ((P &lt; .05) vs pioglitazone alone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Liraglutide(^1) - Hepatic fat reduced 15.9% after 6 months ((P &lt; .05) vs baseline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 RA (ie, exenatide BID, liraglutide)(^1) - 42% relative decrease in intrahepatic lipid ((P &lt; .0005) vs baseline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvements correlated with AST and ALT decreases(^4,)(^a), triglyceride and adiponectin changes(^2,)(^a), A1C decrease(^4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Considerations for NAFLD/NASH

- Hepatic fat accumulation in the absence of other causes\(^1\)
  - Most prevalent liver disease in T2DM (\(> 2\%\) vs no T2DM)\(^1\,\)\(^a\)
  - May progress to NASH (liver damage with inflammation, necrosis, and fibrosis), cirrhosis, or hepatocellular carcinoma (HCC)\(^1\)
- Few clinical symptoms\(^1\)
  - 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 unneeded medications\(^a\)
  - Antioxidants (ie, vitamin E) and insulin sensitizers (ie, pioglitazone) may be effective\(^1\,\)\(^a\)

Blood Pressure and Lipid Changes With GLP-1 RAs: Meta-Analysis of RCTs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>-3.57 mm Hg</td>
<td>-5.49 to -1.66</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-1.38 mm Hg</td>
<td>-2.02 to -0.73</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-3.9 mg/dL</td>
<td>-6.19 to -1.55</td>
</tr>
</tbody>
</table>

- Weight changes in patients treated for 12 weeks.
- May or may not be associated with elevated ALT/AST
- May progress to NASH (liver damage with inflammation, necrosis, and fibrosis)
- Weight loss significant in the absence of GI AEs, but greater with GI AEs
- Generally similar between in head-to-head GLP-1 RA trials

Potential Benefits of Incremental Changes in CV Risk Factors

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Effects of GLP-1 RAs on Hepatic Steatosis\(^a\)

- GLP-1 RAs are not FDA-approved for NAFLD/NASH\(^1\)
- Improved hepatic steatosis with GLP-1 RA treatment
  - Exenatide BID + pioglitazone\(^2\) - Significant hepatic fat reduction from 12.1% to 4.7% after 12 months (\(P < .05\) vs pioglitazone alone)
  - Liraglutide\(^1\) - Hepatic fat reduced 15.9% after 6 months (\(P < .05\) vs baseline)
- GLP-1 RA (ie, exenatide BID, liraglutide)\(^1\) - 42% relative decrease in intrahepatic lipid (\(P < .0005\) vs baseline)
- Improvements correlated with AST and ALT decreases\(^4,\)\(^a\), triglyceride and adiponectin changes\(^2,\)\(^a\), A1C decrease\(^4\)
**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 LeRoiith, LaSalle, Lavernia

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**GLP-1 RA Treatment Satisfaction and Tolerability: Case 4**

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

**Case 4: Sarah**

- Overweight female (BMI 28 kg/m²)
- Age: 52 years
- T2DM for 5 years
- A1C (before adding EXN BID) 7.6% (eAG 171 mg/dL)¹
  - Metformin 2000 mg/d
- Follow-up—EXN BID initiation
  - EXN BID at 10 mcg twice daily
  - Still reports nausea after 8 weeks, usually tolerable
  - Happy about weight loss (4lb/2kg)
  - Doesn't like injecting 2× daily—occasionally misses evening dose

---

**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)


### Exenatide QW
- Significant decreased with all degrees of hypoglycemia
- Severe hypoglycemia has greater impact

### Exenatide BID
- Significantly greater mean annual costs ($1510-$2550)

### Morbidity and Mortality
- Higher accident risk (e.g., driving, falls)
- 9% mortality with severe events

### Impact of Hypoglycemia on Individuals With T2DM

**Work Productivity**
- 3% 11 h/mo of lost time with nonsevere, nocturnal hypoglycemia

**Quality of Life**
- Significantly decreased with all degrees of hypoglycemia
- Severe hypoglycemia has greater impact

**Treatment and Resource Use**
- Significantly greater mean annual costs

**Morbidity and Mortality**
- Higher accident risk (e.g., driving, falls)
- 9% mortality with severe events

---

### 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., 1 cup juice, 4-5 saltines).
- Be sure your healthcare professional knows all the medicines you are taking.

### GLP-1 RAs Are Administered by Subcutaneous Injection

<table>
<thead>
<tr>
<th>Exenatide BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 5 mcg—orange, 10 mcg—yellow</td>
</tr>
<tr>
<td>- Start with 5 mcg, increase to 10 mcg after 1 month</td>
</tr>
<tr>
<td>- Inject within 60 min of 2 main meals</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adjust to deliver dose (0.6 mg, 1.2 mg, or 1.8 mg)</td>
</tr>
<tr>
<td>- Start with 0.6 mg, increase after 1 week to 1.2 mg</td>
</tr>
<tr>
<td>- May increase to 1.8 mg, if needed</td>
</tr>
<tr>
<td>- Inject once daily, any time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exenatide QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Do not substitute needles or other delivery system components</td>
</tr>
<tr>
<td>- Inject immediately after suspension</td>
</tr>
<tr>
<td>- Prior exenatide BID treatment not required</td>
</tr>
<tr>
<td>- Inject missed dose only if next dose is ≥ 3 days away</td>
</tr>
<tr>
<td>- Inject single 2-mg dose once weekly, any time</td>
</tr>
</tbody>
</table>

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### Reports of Nausea Vary by Agent

<table>
<thead>
<tr>
<th>Agent</th>
<th>Nausea %</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIRA 1.0 mg OD</td>
<td>26</td>
</tr>
<tr>
<td>EXN 10 mcg BID</td>
<td>21</td>
</tr>
</tbody>
</table>

---

### 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
  - LIRA, 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

---

### 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
- 60% preferred 4 mm over 5 mm or 8 mm

---

### 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
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- No difference in glycemic control or safety among needle sizes
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  - Subcutaneous vs muscle
- Have patient see/use pen and needle before leaving office
- Refer patient to product resources for starting treatment
Managing Nausea Associated With GLP-1 RAs

- Draw on experience with other agents—7% to 26% of patients experience nausea/vomiting with metformin.
- Discuss expectations:
  - Nausea is likely to be mild and resolve in a few weeks
  - Nausea may actually be “fullness”
- Suggest behavioral changes:
  - 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.
- Be aware of severe persistent abdominal pain, possibility of pancreatitis.

<table>
<thead>
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<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></td>
<td></td>
</tr>
</tbody>
</table>

Prescribing Information Precautions

Severe gastrointestinal disease (eg, gastroparesis) X X

Patient-Assistance Programs

- Patient has expressed dissatisfaction with dosing
  - Provide education regarding meal sizes and fat content
  - Consider decreasing GLP-1 RA dose

Patient-Centered Considerations: Sarah

- Patient is happy about weight loss
  - Available GLP-1 RAs generally promote similar weight loss
- Patient has persistent nausea
  - Nausea is tolerable
  - Provide education regarding meal sizes and fat content
  - Consider decreasing GLP-1 RA dose
- 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
  - http://bloodsugarbasics.com

- Patient assistance programs
  - Provide medication access for eligible patients and may improve adherence and outcomes
  - Specific information often available at product website

- Assessment tools for elderly patients
  - Unidentified cognitive deficits, functional status, nutritional needs:
    - www.hospitalmedicine.org/get/resource/toolbox/howto.htm
  - Mini-Nutritional Assessment: http://www.mna-elderly.com