

- Faculty

Lawrence Blonde, MD, FACP, FACE
Director, Ochsner Diabetes Clinical Research Unit
Department of Endocrinology, Diabetes,
and Metabolic Diseases
Associate Internal Medicine Residency Program Director
Ochsner Medical Center
New Orleans, Louisiana

- Disclosure Statement

The Network for Continuing Medical Education requires that CME faculty disclose, during the planning of an activity, the existence of any personal financial or other relationships they or their spouses/partners have with the commercial supporter of the activity or with the manufacturer of any commercial product or service discussed in the activity.

- Faculty Disclosure

Lawrence Blonde MD, FACP, FACE, has received honoraria from AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Daiichi Sankyo, Inc., GlaxoSmithKline, Halozyme Therapeutics, Johnson & Johnson, LifeScan, Inc., Mannkind Corporation, Merck & Co., Inc., Novo Nordisk Inc., Roche Laboratories Inc., sanofi-aventis, and VeroScience; and has received research support from Amgen Inc., Eli Lilly and Company, Merck & Co., Inc., Novo Nordisk Inc., Roche Laboratories Inc., and sanofi-aventis.

- Learning Objectives

After taking part in this activity, participants should be able to:

- Identify clinician and patient barriers to achieving glycemic targets in patients with type 2 diabetes
- Recognize the role of the incretin hormones, including GLP-1, gastric inhibitory polypeptide, and dipeptidyl peptidase IV, in the pathophysiology of type 2 diabetes
- Interpret the efficacy, safety, and tolerability data of available and emerging incretin therapies
- Integrate incretin-related therapies into treatment paradigms for type 2 diabetes

- Prevalence of Diabetes

Is Increasing in the US, 2007

- Prevalence and Risk of Diabetes Complications
- Natural History of Type 2 Diabetes^{1,2}
- Progressive Loss of β -Cell Function in Type 2 Diabetes: UKPDS 16
- Why Does the β -Cell Fail?
- AACE/ACE Diabetes Algorithm for Glycemic Control
- The Efficacy of Oral Antihyperglycemic Agents Declines With Time¹⁻³
- Sulfonylureas and metformin
 - Initial declines in A1C
 - Subsequent progressive increases in A1C of ~0.2% to 0.3% per year, even when doses were increased
- Thiazolidinediones
 - Also associated with progressive increases in A1C after the first year, although somewhat slower
- All associated with progressive declines in β -cell function after first year
- Dose increases and combination therapies are routinely needed
- Clinical Challenges in Type 2 Diabetes
- Long-term Efficacy of Monotherapy: ADOPT
- Unmet Needs With Conventional Antihyperglycemic Therapies^{1,2}
- Most therapies are associated with weight gain
- Insulin and insulin secretagogue therapies are associated with significant risk for hypoglycemia
- Other AEs with some therapies include GI side effects and edema
- Most therapies fail to adequately control postprandial hyperglycemia
- Wide glycemic fluctuations persist despite treatment with most therapies

- Most therapies fail to maintain long-term glycemic control
- The Incretins GLP-1 and GIP
- GLP-1 Levels Are Decreased in Patients With IGT and Type 2 Diabetes
- The Incretin Effect Is Diminished in Type 2 Diabetes
- Glucose-Dependent Actions of GLP-1 in Type 2 Diabetes
- Subcutaneous GLP-1 Slows Gastric Emptying in Type 2 Diabetes
- GLP-1 and Food Intake
- Summary: GLP-1 Reduces Food Intake and Body Weight in Type 2 Diabetes¹⁻³
- Binds and activates neurons in key homeostatic regions of the brain
- Slows gastric emptying
- Reduces body weight and body fat
- These effects are independent of nausea
- Weight loss is sustained, not temporary
- The change in body fat improves patient compliance and acceptance
- Overall, incretin therapy provides a rational approach to the treatment of obese patients with type 2 diabetes

GLP-1 Receptor Agonists

- Structure of Native GLP-1 and 2 GLP-1 Analogs
- Exenatide Decreases Postprandial Glucose and Glucagon Secretion
- Exenatide Reduces Fasting Hyperglycemia

- Phase III Clinical Trials:
Exenatide Lowers A1C at 30 Weeks
- Phase III Clinical Trials: Exenatide Reduces Fasting Plasma Glucose at 30 Weeks
- Exenatide Added to TZDs in
Suboptimally Controlled Type 2 Diabetes
- Exenatide Reduces A1C and
Weight Over 3 Years
- Changes in Glycemia and Weight in
3 Studies of Exenatide vs Insulin
- Improvement in CV Risk Factors After
3.5 Years of Exenatide Treatment^a
- Liraglutide Monotherapy Improves
A1C and FPG Over 52 Weeks
- Liraglutide in Combination With
Metformin and Thiazolidinedione
- Liraglutide in Combination With
Metformin and Thiazolidinedione (*cont*)
- Liraglutide vs Insulin Glargine
In Combination With Metformin and Sulfonylurea
- Liraglutide vs Exenatide
In Combination With Metformin and Sulfonylurea
- Liraglutide vs Exenatide
In Combination With Metformin and Sulfonylurea
- Liraglutide and Thyroid Tumors
- Thyroid C-cell tumors observed in rodent models¹

- Clinical and postmarketing data
 - LEAD-6 (liraglutide vs exenatide)²
 - Small, similar decreases in mean calcitonin levels were observed in both groups
 - Liraglutide clinical trials^{1,3}
 - No medullary thyroid carcinoma
 - Papillary thyroid carcinoma: 5 cases in liraglutide groups vs 1 case in comparator groups
 - Approvable on the basis of low risk of carcinoma in humans
 - Exenatide³
 - No thyroid cancer in clinical trials
 - 3 cases of papillary and 6 cases of unspecified thyroid cancer in postmarketing experience

- Incretin Mimetic Drugs and Pancreatitis Risk

- FDA issued an alert to healthcare professionals regarding exenatide¹

- Reported cases

- Exenatide: postmarketing cases reported, including cases of hemorrhagic/necrotizing pancreatitis that resulted in patient deaths¹
- Liraglutide: cases reported during clinical trials, no pancreatitis-related deaths^{2,3,4}

- Recent analysis of an insurance database revealed no increased risk for exenatide or sitagliptin compared with patients treated with metformin or glyburide⁵

- Pancreatitis: Recommendations for Healthcare Professionals

- Observe patients for symptoms of acute pancreatitis (persistent severe abdominal pain that may be accompanied by vomiting)^{1,2}
- Exenatide or liraglutide, and other potentially suspect drugs, should be promptly discontinued if pancreatitis is suspected^{1,2}
- Exenatide or liraglutide should not be restarted if pancreatitis confirmed^{1,2}
- Consider antihyperglycemic therapies other than exenatide in patients with a history of pancreatitis¹
- Liraglutide should be used with caution in patients with a history of pancreatitis²

- Incretin Mimetic Drugs:
General Safety Issues
- The most common adverse events associated with GLP-1 mimetics are gastrointestinal adverse events (nausea and vomiting)^{1,2}
 - Nausea is mostly mild-to-moderate, and is most common at initiation of therapy; it tends to decrease with continuing treatment
- Hypoglycemia with GLP-1 mimetics is usually of mild-moderate intensity^{1,2}
 - When co-administered with metformin alone, GLP-1 mimetics are not associated with an increased risk of hypoglycemia
 - When co-administered with an sulfonylurea, GLP-1 mimetics are associated with an increased incidence of hypoglycemia compared with sulfonylurea alone
 - Generally manageable by reduction in sulfonylurea dose
- Exenatide LAR:
Emerging Treatment
- Exenatide LAR Maintains Improvements
in Glycemic Control Over 2 Years
- DPP-4 Inhibitors
- Incretin Secretion and
DPP-4-Mediated Inactivation
- Structure of DPP-4 Inhibitors
- Comparison of DPP-4 Inhibitors
- DPP-4 Inhibitors Alter the Plasma Profile
of Endogenous GLP-1
- Saxagliptin Versus Metformin Versus Combination Therapy
- DPP-4 Inhibitors: Safety

General Considerations

- Dosage adjustment recommended for patients with moderate or severe renal insufficiency or ESRD^{1,2}
- Increased risk of hypoglycemia when added to sulfonylurea or insulin. Consider lowering the dose of sulfonylurea or insulin^{1,2}
 - Saxagliptin has not been studied in combination with insulin
- All DPP-4 inhibitors have the potential to interfere with immune system function³
- DPP-4 Inhibitors: Safety (*cont*)
 - Postmarketing reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue sitagliptin
 - Postmarketing reports of serious allergic and hypersensitivity reactions. Drug should be promptly stopped
 - Most common adverse reactions were upper respiratory tract infection, nasopharyngitis, and headache
 - Recommended dose 2.5 mg once daily in patients receiving a strong CYP3A4/5 inhibitor
 - Peripheral edema reported at higher rates than placebo in patients co-administered a thiazolidinedione
 - Hypersensitivity reactions reported
 - Most common adverse reactions were upper respiratory tract infection, urinary tract infection, headache

- Unmet Needs Potentially Addressed by Incretin-related Treatment

- Improved glycemia with weight maintenance or loss
- Low risk for hypoglycemia
- Reduction of postprandial hyperglycemia
- Potential to reduce glycemic fluctuations
- Potential to maintain long-term glycemic control if incretin effects in animals are found with incretin-related therapy in man
- 56-Year-Old Caucasian Man With Type 2 Diabetes

History

- 5-year history of type 2 diabetes

- 8-year history of hypertension

Physical examination

- Height 5'8", weight 230 lb, BMI 35 kg/m²
- BP 140/84 mm Hg
- 1+ ankle edema

Laboratory results

- A1C 7.7%; FPG 122 mg/dL
- LDL-C 96 mg/dL, HDL-C 34 mg/dL, TG 240 mg/dL
- Creatinine 1.2 mg/dL
- SMBG: 2 hour pc 181-245 mg/dL

Current medications

- Metformin 1500 mg daily
- HCTZ 25 mg daily
- Olmesartan 20 mg daily
- Atorvastatin 20 mg daily

- Are there other studies that you would perform before deciding how to manage this patient?
- Besides reinforcing lifestyle recommendations what would you do to improve glycemia?
 - Add a sulfonylurea
 - Add a TZD
 - Add a glinide
 - Add colesevalam
 - Add sitagliptin
 - Add exenatide
 - Add liraglutide
 - Add insulin

You decide to add exenatide

- Plan: Start with 5 µg bid 0-60 min before breakfast and dinner

- The patient is instructed in SQ injection in the office and given a sample pen. (Instruct the patient on: priming and dosing, storage, side effects, and adverse reactions)
 - Note: patients on sulfonylureas may need dose adjustment to prevent hypoglycemia
- The patient calls after 1 week: he is taking exenatide 1 hour before meals and having moderate to severe nausea for several hours after each dose
- Plan: Instruct the patient to take exenatide immediately before meals to minimize nausea; later can move farther back to maximize satiety effect
- Helping Patients Initiate GLP-1 Mimetics
 - Supplied in pre-filled injection “pens” with premeasured doses
 - Demonstrate use of pen, including a “dry-run” injection (without injecting drug)
 - Explain that injection is relatively painless
 - Placed into fatty tissue, not muscle
 - Use the smallest needle possible
- Minimizing and Managing Nausea Associated With GLP-1 Mimetics
 - Gradually titrate dose
 - For exenatide, inject closer to mealtime
 - Eat smaller portions
 - Keep track of, and avoid, foods that cause nausea until nausea subsides
 - Reduce meal fat content
 - Some simple nausea remedies
 - Foods: ginger, sugar-free mints, soda crackers, rice crackers, hot water sipped slowly
 - Other: deep breaths, long walks

- The patient returns to your office after 1 month and is still experiencing some mild nausea after taking exenatide. His glucose levels and weight at this point are
 - FBG 110-118 mg/dL
 - 2-h pc BG 142-183 mg/dL
 - Weight decreased by 2 lbs
- Plan: Usually would titrate to full dose of 10 μ g bid but because of mild nausea will keep on 5 μ g dose for 1 more month, and if nausea resolves will increase to 10 μ g dose thereafter (a small number of patients will not be able to tolerate the 10 μ g dose and can remain on 5 μ g)

You decide to add liraglutide (review rationale)

- Plan: Start with 0.6 mg SQ once every 24 hours, without relation to meals
- The patient is instructed in SQ injection in the office and given a sample pen. (Instruct the patient on: priming and dosing, storage, side effects, and adverse reactions)
- Titration steps: (all doses available in same pen)
 - 0.6 mg qd for wk 1
 - 1.2 mg qd for wk 2
 - 1.8 mg qd thereafter
 Titration can be modified if significant nausea

- Conclusions
- In type 2 diabetes, β -cell function progressively decreases over time, which results in progressive worsening of glycemic control
- Conventional treatments (ie, oral hypoglycemic agents and insulin) fail to slow and may accentuate the decline in β -cell function
- GLP-1 has a pivotal role in the pathophysiology of diabetes
- GLP-1 also exerts positive metabolic effects in type 2 diabetes, including decreased gastric emptying, reduced weight, and enhanced glycemic control
- Drugs that sustain the effect of GLP-1, including GLP-1 agonists and DPP-4 inhibitors, have the potential to change the long-term control and outcome in patients with type 2 diabetes

Question-and-Answer Session
Thank you for participating!