Maximizing the Role of GLP-1 Agonists in Our Patients with Type 2 Diabetes

128th Annual TPA Convention & Exposition – Murfreesboro – July 15
2015 ICHP Annual Meeting – Oakbrook Terrace – September 10
KSHP 2015 Fall Meeting – Louisville – October 1
NMSHP 2015 Balloon Fiesta Symposium – Albuquerque – October 4
GSHP Fall Meeting – Young Harris – October 17

Planned by ASHP Advantage and supported by educational grants from AstraZeneca and Lilly.

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Maximizing the Role of GLP-1 Agonists in Our Patients with Type 2 Diabetes

Activity Overview

This educational activity will provide pharmacists with an overview of new and emerging GLP-1 based therapies. Important differences among the GLP-1 agonists will be reviewed, including preparation and administration technique required for the various agents.

Learning Objectives

After the conclusion of this application-based educational activity, participants should be able to

- Review the effect of GLP-1 on glucose metabolism.
- Compare pathophysiologic mechanisms of GLP-1 agonists to other diabetes medications.
- Discuss the differentiating characteristics of available GLP-1 agonists including long-term safety.
- Explain the importance of proper injection device technique in the preparation and administration of GLP-1 agonists in the management of type 2 diabetes.
- Strategize how to overcome barriers in GLP-1 agonist use.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity # 0204-0000-15-428-L01-P).

Participants will process CPE credit online at http://elearning.ashp.org/my-activities. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home study activity.

Additional Educational Activities on this Topic

- **On-Demand Activity:** "Case Studies in the Use of GLP-1 Agonists in Type 2 Diabetes Management: An Individualized Approach to Patient Care"—Coming in mid-August to www.leadingdiabetescare.org.

Activity Faculty

Susan Cornell, Pharm.D., CDE, FAPhA, FAADE
Assistant Director of Experiential Education
Associate Professor
Department of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois

Susan Cornell, Pharm.D., CDE, FAPhA, FAADE, is Assistant Director of Experiential Education and Associate Professor, Department of Pharmacy Practice at Midwestern University Chicago College of Pharmacy in Downers Grove, Illinois. Dr. Cornell is also a certified diabetes educator and clinical pharmacy consultant, specializing in community and ambulatory care practice.

Dr. Cornell has over 24 years of practice in community pharmacy where she has practiced as a clinical pharmacist, diabetes educator, and preceptor, as well as the inaugural coordinator of the American Diabetes Association (ADA)-recognized Dominick's Pharmacy Diabetes Self-Management Education program. Dr. Cornell's current clinical practice is with the Access Community Health Network, where she trains, educates, and supervises students from the colleges of medicine, pharmacy, and health sciences as they provide diabetes education classes for patients in underserved community clinics.

Dr. Cornell received her Bachelor of Science degree in pharmacy from the University of Illinois, College of Pharmacy in 1986 and her Doctor of Pharmacy degree from Midwestern University in 2002.

Dr. Cornell recently completed her term as President of the Illinois Pharmacists Association in October 2011. She has received numerous awards and recognitions, including the 2010 Teacher of the Year Award, the 2010 American Association of Colleges of Pharmacy Student Engaged Community Service Award, and the 2005 Midwestern University Golden Apple Teaching Award. In 2008, she received fellow recognition from the American Association of Diabetes Educators (AADE) and the American Pharmacists Association. She is an active member of the ADA, as well as the AADE, where she served on the board of directors from 2004 to 2007.

Dr. Cornell has served as an invited speaker nationally and internationally on diabetes and its related conditions and is recognized as a key opinion leader in the field of diabetes education. She has contributed to many peer-reviewed print and online publications in this field.

Maximizing the Role of GLP-1 Agonists in Our Patients with Type 2 Diabetes

Curtis L. Triplitt, Pharm.D., CDE
Associate Director, Diabetes Research Center, Texas Diabetes Institute
Associate Professor, Department of Medicine, Division of Diabetes
University of Texas Health Science Center at San Antonio
San Antonio, Texas

Curtis L. Triplitt, Pharm.D., CDE, is Associate Professor and Certified Diabetes Educator at the University of Texas Health Science Center at San Antonio (UTHSCSA) where he oversees many diabetes research projects. In addition, he clinically manages people with diabetes with an endocrinologist at the Texas Diabetes Institute.

Dr. Triplitt earned his Bachelor of Science degree in pharmacy from the University of Iowa and his Doctor of Pharmacy degree from the University of Texas at Austin and the Health Science Center at San Antonio. He completed a primary-care residency accredited by the American Society of Health-System Pharmacists at the William S. Middleton Veteran Administration's Hospital in Madison, Wisconsin.

Dr. Triplitt is well respected as a clinician, researcher, and author. He is an investigator in several ongoing research studies related to diabetes, and he has published several book chapters on diabetes, as well as articles in peer-reviewed journals, including *Diabetes Care, Diabetes Spectrum, Expert Review of Endocrinology & Metabolism, Pharmacotherapy, and Drugs*. Dr. Triplitt is currently Secretary of the Texas Diabetes Council (TDC), which is legislatively mandated to develop and implement a state plan for diabetes treatment, education, and training. The TDC's mission is also to develop standards of care for the prevention, identification, and treatment of patients with diabetes mellitus in Texas.

Disclosure Statement

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- Curtis Triplitt, Pharm.D., CDE, declares he has served on the speakers bureau for AstraZeneca and Boehringer Ingelheim.
- All other faculty and planners report no financial relationships relevant to this activity.

Improving Patient Outcomes

Maximizing the Role of the GLP-1 Based Therapies in Our Patients with Type 2 Diabetes

Maximizing the Role of GLP-1 Agonists in Our Patients with Type 2 Diabetes

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ashp Advantage Planned by ASHP Advantage and supported by educational grants from AstraZeneca and Lilly

1.0 hr. CPE

Disclosures

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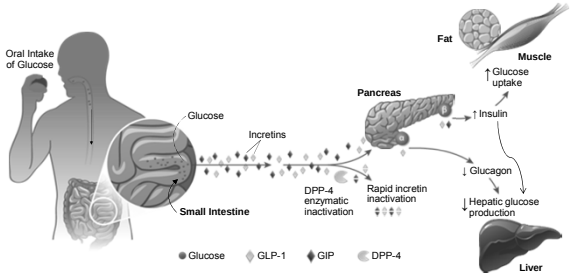
Objectives

- Review the effect of GLP-1 on glucose metabolism.
- Compare pathophysiologic mechanisms of GLP-1 agonists to other diabetes medications.
- Discuss the differentiating characteristics of available GLP-1 agonists including long-term safety.
- Explain the importance of proper injection device technique in the preparation and administration of GLP-1 agonists in the management of type 2 diabetes.
- Strategize how to overcome barriers in GLP-1 agonist use.

Objectives

- Review the effect of GLP-1 on glucose metabolism.

Incretin Glucose Regulation

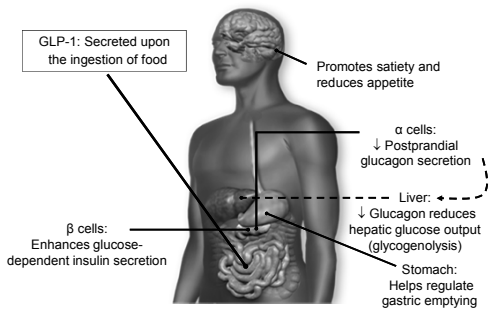


DPP=dipeptidyl peptidase, GLP=glucagon-like peptide, GIP=glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide

Drucker DJ et al. *Lancet*. 2006; 368:1696-1705. Nauck MA. *Eur J Intern Med*. 2009; 20:S303-8. Kendal DM et al. *Am J Med*. 2009; 122:S37-50.

See enlargement, p. 17

GLP-1 Modulates Numerous Functions in Humans



Flint A et al. *J Clin Invest*. 1998; 101:515-20, Drucker DJ. *Diabetes*. 1998; 47:159-69.

See enlargement, p. 17

GLP-1 Agonists

- Actions:
  - Restore glucose-stimulated insulin secretion and first phase insulin
  - Suppress inappropriate glucagon secretion
  - Slow gastric emptying
  - Increase satiety
  - Resistant to DPP-4 enzyme
- Treatment options
  - Exenatide
    - Exenatide BID
    - Exenatide long-acting release (LAR) weekly
  - Liraglutide
  - Albiglutide
  - Dulaglutide

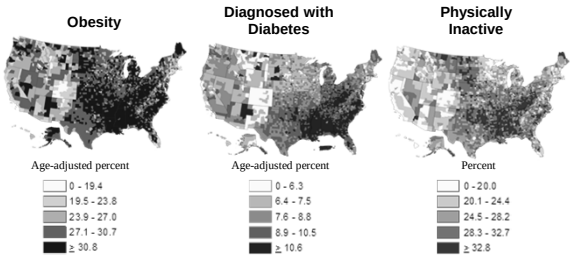
If we wanted to give a weekly GLP-1 agonist, what would be our choices?

a. Exenatide LAR
b. Albiglutide
c. Dulaglutide
d. All of the above

Objectives

- Compare pathophysiologic mechanisms of GLP-1 agonists to other diabetes medications.

The Diabesity Epidemic



Centers for Disease Control and Prevention: National Diabetes Surveillance System. www.cdc.gov/diabetes/data (accessed 2011 Jul 7)

See enlargement, p. 18

Insulin Resistance

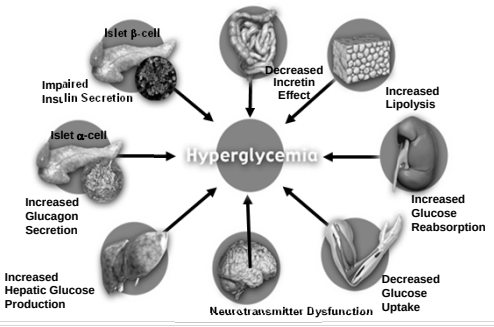
- Major defect in individuals with type 2 diabetes (T2DM)
- Reduced biological response to insulin
- Closely associated with obesity
- Associated with cardiovascular risk
- Type 1 diabetes patients can be insulin resistant as well

American Diabetes Association. *Diabetes Care* 1998; 21:310–14. Beck-Nielsen H et al. *J Clin Invest* 1994; 94:1714–21. Bloomgarden ZT. *Clin Ther* 1998; 20:216–31. Boden G. *Diabetes* 1997; 46:3–10.

Insulin Resistance

- Diet & Exercise
  - Additive effects: 3X higher improvement than diet or exercise alone
  - Even if a person cannot exercise, can improve insulin sensitivity with 5-10% weight loss
  - Calorie reduced diet of any composition is effective
  - Exercise typically 30-45 minutes moderate 3-5 times per week

Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet



DeFronzo RA. *Diabetes*. 2009; 58:773-95.

See enlargement, p. 18

12 Pharmacotherapy Options

Insulin

- Bolus insulin
  - Insulin lispro (Humalog)
  - Insulin aspart (Novolog)
  - Insulin glulisine (Apidra)
  - Insulin human inhaled (Afrezza)
  - Regular human insulin
    - (Humulin R)
    - (Novolin R)
- Basal insulin
  - Insulin NPH
    - (Humulin N)
    - (Novolin N)
  - Insulin detemir (Levemir)
  - Insulin glargine U100 (Lantus)
  - Insulin glargine U300 (Toujeo)

- Oral Medications
  - α-glucosidase inhibitors (AGI)
  - Biguanides
  - Bile acid sequestrants (BAS)
  - Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)
  - Dopamine agonists
  - Glinides
  - Sulfonylureas (SU)
  - Sodium Glucose Co-Transporter-2 inhibitors
  - Thiazolidinediones (TZDs or glitazones)
- Non-insulin injectable agents
  - Glucagon-like peptide-1 (GLP-1) agonists
  - Amylinomimetic

Cornell S et al. *Postgrad Med*. 2012;124:84-94. www.pdr.net (accessed 2015 Jan 30). www.pdr.net (accessed 2015 Mar 26).

Which dysfunctional organs do GLP-1 agonists target?

a. Brain and adipose fat
b. Muscle and adipose fat
c. Muscle, pancreas, and liver
d. Pancreas and liver
e. Pancreas, liver, brain, and GI tract

Glucose Lowering Comparison

Monotherapy	Route	Targets insulin resistance	Target Organs	Target Glucose: FPG or PPG	A1c Reduction %
Sulfonylurea	Oral	No	Pancreas	Both	1.5-2.0
Metformin	Oral	Yes	Liver	FPG	1.5
Glitazones	Oral	Yes	Muscle & adipose fat	Both	1.0-1.5
Meglitinides	Oral	No	Pancreas	PPG	0.5-2.0
AGIs	Oral	No	GI tract	PPG	0.5-1.0
DDP-4 inhibitors	Oral	No	Pancreas & liver	PPG	0.5-0.7
Bile acid sequestrant	Oral	No	GI tract	PPG	0.4
Dopamine agonists	Oral	No	Brain, possibly adipose fat	PPG	0.4
SGLT-2 inhibitors	Oral	Maybe	Kidney, possibly adipose fat	FPG	0.7 – 1.1
GLP-1 agonists	Injectable	No	Pancreas, liver, brain & GI tract	Short-acting—PPG Long-acting—Both	0.8-1.5
Amylin analogs	Injectable	No	Pancreas, liver, brain & GI tract	PPG	0.6
Insulin	Injectable	Yes (to a degree)		Basal - FPG Bolus – PPG	↓ as much as needed

FPG=fasting plasma glucose, PPG=postprandial glucose, GI=gastrointestinal.

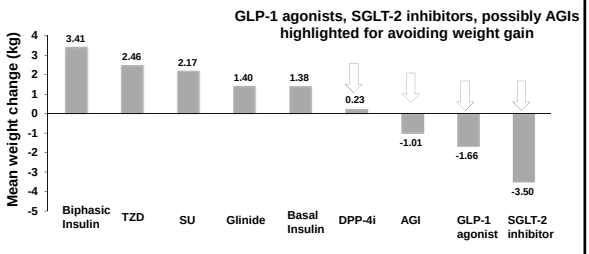
Unger J et al. *Postgrad Med*. 2010; 122:145-57. Cornell S et al. *Postgrad Med*. 2012; 124:84-94.

See enlargement, p. 19

Selection of Pharmacotherapy

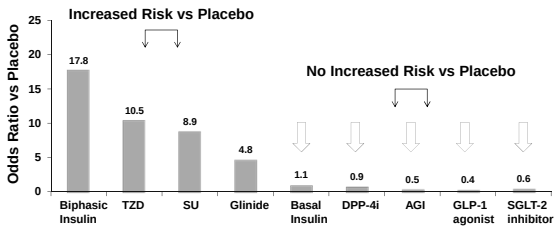
- Desired drug effects
  - Efficacious
  - Protect remaining β-cell function
  - Minimize hypoglycemic risks
  - Minimize weight gain
  - Minimize adverse effects and drug interactions
  - Cardiovascular benefit

Meta-Analysis: Weight Changes with Antihyperglycemic Agents Added to Metformin



Liu S et al. *Diabetes Obes Metab*. 2012; 14:810-20.

Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin



Liu S et al. Diabetes Obes Metab. 2012; 14:810-20.

GLP-1 Agonists

Short-acting GLP-1 agonists

- Exenatide BID (Byetta®)
  - 5 mcg & 10 mcg
  - Twice-daily dosing

Long-acting GLP-1 agonists

- Liraglutide (Victoza®)
  - 0.6 mg, 1.2 mg, & 1.8 mg
  - Once-daily dosing
- Exenatide LAR (Bydureon®)
  - 2 mg
  - Once-weekly dosing
- Albiglutide (Tanzeum®)
  - 30mg & 50mg
  - Once-weekly dosing
- Dulaglutide (Trulicity®)
  - 0.75 mg & 1.5 mg
  - Once-weekly dosing

GLP-1 Agonists

- Short-acting agonists lower postprandial glucose
  - Decreases A1c by 0.8% to 1.5% (~20-45 mg/dL; most postprandial)
- Long-acting agonists lower fasting and postprandial glucose
  - Decreases A1c by 0.8% to 1.8% (~20-50 mg/dL)
- Most common side effects
  - Weight loss
  - Stomach upset
  - Caution in patients at risk for pancreatitis

Cornell S et al. *Postgrad Med*. 2012; 124:84-94.

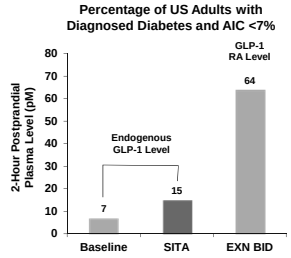
Comparison of Short-acting vs Long-acting GLP-1 Agonists

Parameter	Short-Acting	Long-Acting
HbA1c reduction	~0.5%-1.2%	~0.8%-1.9%
Body Weight Reduction	~1-4 kg	~1-4 kg
SBP Reduction	~3-4 mm Hg	Up to 6 mm Hg
Heart Rate Increase	No effect or small increase (0-2 beats/min)	2-4 beats/min
Lipids	Small improvement in some studies	Small improvement in some studies

Not head-to-head comparison
HbA1c=glycated hemoglobin, SBP=systolic blood pressure

Lund A et al. *Eur J Intern Med*. 2014; 25:407-14.

Comparing DPP-4 inhibitors and GLP-1 Agonists



- DPP-4 inhibitors (e.g., sitagliptin)
  - Oral administration
  - Block DPP-4 degradation of GLP-1
  - Increase endogenous GLP-1 levels ≈ 2-fold
- GLP-1 agonists
  - Subcutaneous administration
  - Add exogenous GLP-1 activity
  - Increase GLP-1 activity ≈ 9-fold
  - Greater A1c and weight effects than DPP-4 inhibitors

EXN BID=exenatide twice daily, SITA=sitagliptin

DeFronzo RA et al. *Curr Med Res Opin*. 2008; 24:2943-52. Inzucchi S et al. *Diabetes Care*. 2012; 35:1364-79.

Objectives

- Discuss the differentiating characteristics of available GLP-1 agonists including long-term safety.

Overview of Approved Incretin Therapies

Properties/Effects	Long Acting GLP-1 agonists	Short-acting GLP-1 agonists	DPP-4 inhibitors
Administration	SQ Daily or Weekly	SQ Twice Daily	Oral Daily
Glucose-dependent insulin increase	Yes	Yes	Yes
Glucose-dependent glucagon decrease	Yes	Yes	Yes
Slows Gastric Emptying	Yes	Yes	No
Lower hypoglycemia risk (in absence of SUs)	Yes	Yes	Yes
Effect on Body Weight	Loss	Loss	Neutral
Effect on A1c	High Efficacy	Moderate Efficacy	Moderate Efficacy
Effect on Fasting Plasma Glucose	Good	Modest	Modest
Major Adverse Effects	GI, nausea	GI, nausea	Well-tolerated
Adjustment/restriction in renal impairment	No, but GI SE in renally impaired patients - Caution	Yes, avoid in Severe/ ESRD	Yes, varies per medication

SQ=subcutaneous

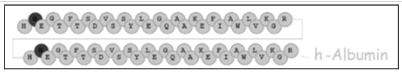
See enlargement, p. 19

Differences Between Incretin Mimetics

	Liraglutide	Exenatide*	Albiglutide	Dulaglutide
Dosing (SQ)	1.2-1.8 mg QD (after initial 0.6 mg QD x 7 days)	5-10 mcg within 60 min of AM/PM meals	30-50 mg weekly	0.75-1.5 mg weekly
Half-life	13 hr	2-4 hr	5 days	5 days
Max dose	1.8 mg QD	10 mcg BID	50 mg weekly	1.5 mg weekly
Renal elimination	No	Yes	No	No
Homology to GLP-1	97%	53%	97%	90%
Antibodies	8.6%	44%	2.5%	2%
Other effects	Less persistent nausea vs exenatide BID. Greater effects on FPG vs exenatide BID.	Exenatide BID - greater effects on PPG (*exenatide LAR has more effect on FPG, less nausea)	Nausea seems to be similar to other agents	No reconstitution Available as one-time use pens or pre-filled syringes

See enlargement, p. 20

Albiglutide



- Background
  - 97% homology to native GLP-1(7-36)
  - 2 copies of a modified GLP-1 fused to human albumin (C-terminus end of the modified GLP-1 sequence to the N-terminus of the human albumin)
  - Manufactured by rDNA technology - *Saccharomyces cerevisiae*
  - Resistant to DPP-4 metabolism - glycine replaces native GLP-1 alanine
  - Gives a half-life of 3.6 - 6.8 days

Tanzeum (albiglutide) prescribing information 2015 March.

Albiglutide

- Pharmacokinetics
  - Due to t1/2 - reaches steady state in 3-4 weeks
  - Distribution is not large due to albumin binding
  - Metabolism - ubiquitous proteolytic enzymes
- Dosing
  - 30 mg weekly
  - May increase to 50 mg weekly

Tanzeum (albiglutide) prescribing information 2015 March.

Albiglutide - Efficacy

- 3-year data, double-blind, placebo-controlled trial
  - Mean A1c 8.1%, Duration of diabetes 4 years
  - A1c reduction
    - Albiglutide 30 mg (n=30) -0.96%, SD 0.968
    - Albiglutide 50 mg (n=32) -1.07%, SD 0.887
    - Placebo (n=14) 0.61%, SD 0.644
- Albiglutide 50 mg weekly vs Liraglutide1.8 mg daily
  - At week 32 (n=422)
  - A1c - Albiglutide -0.78%, Liraglutide -0.99% (difference 0.21%; 0.08—0.34; non-inferiority p value=0.0846)
  - GI SE - Albiglutide 36%, Liraglutide 49%
  - Injection site reactions - Albiglutide 12.9%, Liraglutide 5.4%

ADA 74th Scientific Sessions, San Francisco, June 2014, P-959, P-1339. Pratley RE et al. Lancet Diabetes Endocrinol. 2014; 2:289-97.

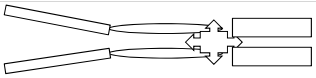
Albiglutide

- Side effect profile and warnings
- Similar to other long-acting GLP-1 agonists
  - MTC - 1 case of MTC with Albiglutide and 1 case in placebo
  - Warnings - similar to other long-acting GLP-1 agonists
    - Pancreatitis
    - Renal failure - do not use if eGFR <30 mL/min/1.73m^2
    - Hypoglycemia - if used with SU, glinide, or insulin
    - Hypersensitivity - mild injection site pruritus mostly, but 1 case of anaphylaxis in trials

MTC=medullary thyroid carcinoma

Tanzeum (albiglutide) prescribing information 2015 March.

Dulaglutide



- Recombinant GLP-1 Fc fusion protein linking GLP-1 analog to a human IgG4 Fc fragment
- Results in:
  - Prolonged t1/2: ~5 days
  - Once-weekly dosing
  - A solution - no reconstitution needed
  - Minimal renal clearance
  - Low immunogenicity risk

ADA 74th Scientific Sessions, San Francisco, June 2014, LB-110, P-979, P-962. Trulicity (dulaglutide) prescribing information. 20015 March.

Dulaglutide

Baseline (means)	D vs Lira AWARD-6	D vs Glar AWARD-2	D vs Glar AWARD-4
HbA1c (%)	8.1 vs 8.1	8.1 to 8.2	8.4 to 8.5
FPG (mg/dL)	167 vs 165	NR	150-157
Age (years)	56 vs 57	56-57	59-60
Weight (kg)	94 vs 94	85-88	91-92
Duration of diabetes (yr)	7 vs 7	~9	12-13
Background treatment	Metformin ~2 g/day	Maximum tolerated metformin and glimepiride	Poorly controlled on conventional insulin - added lispro TID to D or G

D=dulaglutide, Lira=liraglutide, Glar=glargine

ADA 74th Scientific Sessions, San Francisco, LB-110, P-979, P-962. Dungan K et al. *Lancet.* 2014; 384:1349-57.

Dulaglutide - Results

Outcomes (Means Reported)	D vs Lira AWARD-6 (26 week)		D vs Glar AWARD-2 (78 week)			D vs Glar AWARD-4 (52 week)		
Medication	D 1.5 mg	Lira 1.8 mg	D 0.75 mg	D 1.5 mg	G	D 0.75 mg	D 1.5 mg	G
HbA1c (%)	-1.42	-1.36	-0.62	-0.9	-0.59	-1.42	-1.48	-1.23
Weight change (kg)	-2.9	-3.6	-1.54	-1.96	1.28	1.6	0.6	3.7
TDD insulin	n/a		NR			97	93	132
% at goal <7%	68.3	67.9	NR			56	59	49
Other Info	All reported side effects comparable between treatments		PRO-less behavior & worry-hypoglycemia			Glargine ~64 units/day		

ADA 74th Scientific Sessions, San Francisco, LB-110, P-979, P-962. Dungan K et al. *Lancet.* 2014; 384:1349-57.

See enlargement, p. 20

Dulaglutide - Side Effects

Outcomes (%)	D vs Lira AWARD-6 (26 week)		D vs Glar AWARD-4 (@ 52 week)		
GI (%)	D 1.5 mg	Lira 1.8 mg	D 0.75 mg	D 1.5 mg	G
Nausea	20.4	8.0	17.7	25.8	3.4
Vomiting	7.3	8.3	10.6	12.2	1.7
Diarrhea	12.0	12.0	15.7	16.6	6.1
Injection site reaction	0.3	0.7	1.4	0.3	0.0
Hypoglycemia	≤70 mg/dL +/- Sx, Events/ pt/yr 0.34	0.52	Severe 1.7	2.1	3.7
			≤70 mg/dL 88.4	85.9	89.5
Other Info	D/C due to SE 6% in each group No pancreatitis or pancreatic cancer		No pancreatitis or pancreatic cancer reported		

ADA 74th Scientific Sessions, San Francisco, LB-110, P-979, P-962. Dungan K et al. *Lancet.* 2014; 384:1349-57.

See enlargement, p. 21

Head-to-Head Studies: HbA1c

Study Acronym	Drugs Comparison	HbA1c reduction (%)
DURATION-1	Exenatide BID	-1.5
	Exenatide LAR weekly	-1.9*
DURATION-5	Exenatide BID	-0.9
	Exenatide LAR weekly	-1.6*
DURATION-6	Exenatide LAR weekly	-1.28
	Liraglutide	-1.48*
LEAD-6	Exenatide BID	-0.79
	Liraglutide	-1.2*
GetGoal-X	Lixisenatide daily	-0.79
	Exenatide BID	-0.96

*Significant difference

Head-to-Head Studies: HbA1c

Study Acronym	Drugs Comparison	HbA1c reduction (%)
HARMONY-7	Albiglutide	-0.78
	Liraglutide	-0.99
AWARD-1	Dulaglutide 1.5 mg weekly	-1.51*
	Dulaglutide 0.75 mg weekly	-1.30*
	Exenatide BID	-0.99
AWARD-6	Dulaglutide	-1.42 (non-inferior)
	Liraglutide	-1.36

*Significant difference

Though all in the same class of medications, efficacy varies per product

Head-to-Head Studies: Weight

Study Acronym	Drugs Comparison	Weight Change (kg)
DURATION-1	Exenatide BID	-3.7
	Exenatide LAR weekly	-3.6
DURATION-5	Exenatide BID	Not Reported
	Exenatide LAR weekly	Not Reported
DURATION-6	Exenatide LAR weekly	-2.68
	Liraglutide	-3.57*
LEAD-6	Exenatide BID	-2.87
	Liraglutide	-3.24
GetGoal-X	Lixisenatide daily	-2.96
	Exenatide BID	-3.98

*Significant difference

Head-to-Head Studies: Weight

Study Acronym	Drugs Comparison	Weight Change (kg)
HARMONY-7	Albiglutide	-0.64
	Liraglutide	-2.16*
AWARD-1	Dulaglutide 1.5 mg weekly	-1.3
	Dulaglutide 0.75 mg weekly	-0.3
	Exenatide BID	-1.07
AWARD-6	Dulaglutide	-2.90
	Liraglutide	-3.61*

*Significant difference

Weight loss is slightly less with albiglutide and dulaglutide
Similar among other products

Side Effect Comparison

- DURATION-1 and DURATION-5
  - Exenatide BID more N/V vs exenatide LAR weekly
- DURATION-6
  - Liraglutide more nausea, vomiting, diarrhea vs exenatide LAR weekly
- LEAD-6
  - Adverse events less likely, but less severe with exenatide BID vs liraglutide
- GetGoal-X
  - Lixisenatide less side effects than exenatide BID
- HARMONY-7
  - More injection site reactions with albiglutide than liraglutide

Long-term Safety Concerns

- MTC/C-cell hyperplasia
  - Rodents - increase incidence
  - Humans - no increased incidence to date
  - Possible - GLP-1 receptors on C-cell tumors
- Pancreatitis
  - No causality, but continued association
  - Large observational studies do not show a risk
- Pancreatic cancer
  - No risk to date

Egan AG. *N Engl J Med*. 2014; 370:794-7. Geir B. *J Clin Endocrinol Metab*. 2012; 97:121-31.

Effect of GLP-1 Agonists on CVD Risk Factors

Lixisenatide press release-neutral for CV events

Risk Factor	Exenatide 10 mcg BID (3.5 years)[1]	Liraglutide 1.2 mg qd (26 weeks)[2]	Exenatide LAR 2.0 mg weekly (1 year)[3]	Albiglutide 30–50 mg weekly (32 weeks)[4]	Dulaglutide 1.5 mg weekly (26 weeks)[5]
SBP (mm Hg)	–3.5*	–6.7†	–6.2*	N/A	–1.7†
DBP (mm Hg)	–3.3*	–2.3	–2.8*	N/A	–0.4
TC (mg/dL)	–10.8*	–8.1	-7.9*	ND	–0.8 to –8.1‡
LDL-C (mg/dL)	–11.8*	–10.8†	–2.2	ND	–1.9 to –7.0‡
HDL-C (mg/dL)	8.5*	–1.2	N/A	ND	N/A
Triglycerides (mg/dL)	–44.4*	–14.7†	–40.0*	ND	–12.4 to –16.8

N/A=not available, ND=no difference vs placebo
*P <0.05 vs baseline, †P <0.005 vs placebo, ‡P <0.001 vs placebo

Klonoff DC et al. *Curr Med Res Opin*. 2008; 24:275–86. Zinman B et al. *Diabetes Care*. 2009; 32:1224–30. Bergenstal R et al. *Diabetes*. 2009; 58:165-OR. Pratley RE et al. *Lancet Diabetes Endocrinol.* 2014; 2:289–97. Nauck MA et al. *Diabetes Care*. 2014; 37:2149–58.

See enlargement, p. 21

Objectives

- Explain the importance of proper injection device technique in the preparation and administration of GLP-1 agonists in the management of type 2 diabetes.

Which statement regarding GLP-1 agonist pen administration is NOT true?

a. Prime before each use
b. Some devices will require "mixing"
c. Inject straight into the skin
d. Hold for 5 -10 seconds before removing the needle from skin

GLP-1 Agonist Comparison

GLP-1 Agent	Device	Mixing required	Pre injection waiting time	Refrigerated	Once Used (opened)
Exenatide BID Twice-daily dosing	Pen	No	No	Expiration Date	Do not refrigerate 30 days
Liraglutide Once-daily dosing	Pen	No	No	Expiration Date	Do not refrigerate 30 days
Exenatide LAR weekly Once-weekly dosing	Kit	Yes	No	Expiration Date	Can be stored at room temperature for 4 weeks
Exenatide LAR weekly Once-weekly dosing	Pen	Yes	No	Expiration Date	Can be stored at room temperature for 4 weeks
Albiglutide Once-weekly dosing	Pen	Yes	Yes (15-30 min)	Expiration Date	Can be stored at room temperature for 4 weeks
Dulaglutide Once-weekly dosing	Pen	No	No	Expiration Date	Can be stored at room temperature for 4 weeks

www.pdr.net (accessed 2015 April 20).

See enlargement, p. 22

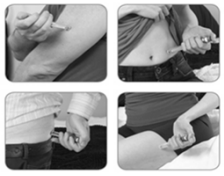
GLP-1 Agonist Delivery Systems

- Disposable pens (similar to insulin pens)
- Disposable single-use pen needles
  - 30 or 31 gauge pen for most
- Pen must be prepared before initial use;
  - priming not needed before each dose

Injection Technique

- Inject straight into the skin
  - Depress the button to release insulin into SQ tissue
- Hold for 5 to 10 seconds before removing the needle from skin
- Remove needle and dispose into sharps container
- Always have the patient demonstrate their technique
  - At first education of the device
  - At first follow-up visit
  - At frequent intervals thereafter

Inject "straight in" flush with skin



Exenatide BID (Byetta)

- Requires a one time priming of the device
- Subsequent doses can be given in the thigh, abdomen or back of the upper arms

- Starting position is →
- Pull knob until ↑ appears
- Rotate knob clockwise until 5 or 10 appears
- Pierce skin and press button down on knob for 5 seconds, ↑ will appear
- Rotate knob clockwise until → appears

Liraglutide (Victoza)

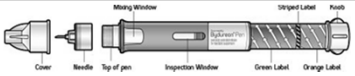
- Requires a one-time priming of the device
  - Dose is dialed to this marker and the button is pressed until a drop of solution is produced

- Subsequent doses can be given in the thigh, abdomen, or back of the upper arms
  - Button is held down for 6 seconds during administration

Exenatide LAR Weekly Kit (Bydureon)

- 4 parts (Single dose tray)
  - Needle
  - Vial Connector
  - Syringe (Diluent)
  - Vial (Powder)
- Complex preparation
- Dose can be given in the thigh, abdomen, or back of the upper arms
- Dose must be given immediately
- Push down on plunger until it stops

Exenatide LAR Weekly Pen Device (Bydureon)



- Same dosing, just new device-out "later this year"
- At least 15 minutes at room temperature prior to mixing steps

Major steps in preparation

- Twist until mix diluent with microspheres (audible click noted upon mixing)
- Gently move pen back and forth (oscillate) at least 80 times (about 1- 1 ½ minutes)
- Check Mixing Window for proper mixing-should see uniform grey color; If not - continue until uniform color seen in mixing window
- Twist until dosing plunger comes out of knob and will hear a second "click"
- Attach needle → ready for injection

Albiglutide (Tanzeum)

- Single reconstitutable pen
- Must be used within 8 hours of reconstitution

- Hold pen vertically with #1 visible
- Pen is turned clockwise until a click is heard and #2 appears
- Gently rock the pen side to side like a window wiper five times (0° to 180°)
- If 30 mg, let rest for 15 minutes and if 50 mg, let rest for 30 minutes upright
- After time has elapsed, rock the pen with similar technique five more times
- Solution should be yellow in appearance
- Attach the supplied needle and tap the pen gently to dislodge bubbles
- Turn the pen clockwise until #3 appears
- Inject into thigh, abdomen, or back of the upper arms
- Button is held down for 5 seconds during administration

Dulaglutide (Trulicity)

- Single prefilled syringe
- Can be injected into thigh, abdomen, or back of the upper arms

- Uncap the pen
- Place the pen on the desired injection area
- Turn the lock ring of the pen from the locked to unlocked position
- Press and hold the button down for 5 - 10 seconds
- The patient will hear a click when the button is pressed
- A second click will indicate the dose was administered

Patient Education

- What to expect
  - The most common side effects include
    - Headache
    - Nausea (usually mild to moderate)
    - Diarrhea
  - Tips to minimize/eliminate nausea
    - Eat smaller meals
    - Avoid overeating
    - Cut down on fatty foods
    - Wear comfortable clothes.
      - Tight waistbands can make you feel worse
  - If nausea is severe, call your health care professional

Objectives

- Strategize how to overcome barriers in GLP-1 agonist use.

Barriers to GLP-1 Agonist Use

Patient

- Unfamiliar with the drug
- Injectable
- Fear of side effects
- Cost

Prescriber

- Unfamiliar with the drug
- Unfamiliar with current treatment guidelines for hyperglycemia
- Injectable
- Fear of side effects
- Cost

Overcoming Barriers

- Education about benefits of GLP-1 agonist as monotherapy and in combination
  - Recognized as first and/or second choice in current guidelines (ADA/EASD and AACE/ACE)
- What is the reason for not wanting to try an injectable drug?
- Education and strategies for overcoming side effects
- Options for cost saving measures
  - Insurance plans
  - Patient assistance programs
  - 340B clinics

ADA/EASD=American Diabetes Assoc/European Assoc for the Study of Diabetes, AACE/ACE=American Assoc of Clinical Endocrinologists, and American College of Endocrinology

Inzucchi SE et al. *Diabetes Care*. 2015; 38:140-9. Handelsman Y et al. *Endocr Pract*. 2015; 21 (suppl 1):1-87.

Tips for Medication Adherence

- Education
  - What is the importance of this medication?
    - How does it work to help lower BG, BP, or decrease complications?
- Timing
  - When is the best time to take the medication to get the maximum benefit?
- Monitoring
  - When should the patient self-monitor blood glucose in order to know the medication is effective?
  - What are common adverse effects?

BG=blood glucose, BP=blood pressure

Patient JZ needs help with scheduling doses. Which GLP-1 agonist must be dosed prior to a meal?

a. Albiglutide
b. Dulaglutide
c. Exenatide BID
d. Liraglutide

Exenatide BID and Liraglutide

- Exenatide BID - good for postprandial control
  - Compliance - make sure taking evening dose
  - Space doses more away from meal for more satiety (up to 1-2 hours prior)
- Liraglutide - easy device to use
  - Compliance - Ask: Out of 7 injections in a week (once daily), how many are you usually able to take?

BG-Lowering Agents and the "Best" Time to Take Them

- Agents to be taken before meals
  - AGIs
  - Dopamine agonists
  - Glinides
  - Short-acting GLP-1 agonists
  - Bolus insulin
- Agents to be taken with or after meals
  - SU
  - Metformin
  - Bolus insulin
- Agents that can be taken with or without food
  - TZDs
  - DPP-4 inhibitors
  - Long-acting GLP-1 agonists
  - SGLT-2 inhibitors
  - Basal insulin

Cornell S et al. *Postgrad Med*. 2012; 124:84-94.

Six Key Questions to Ask Patients for EVERY Medication They Take

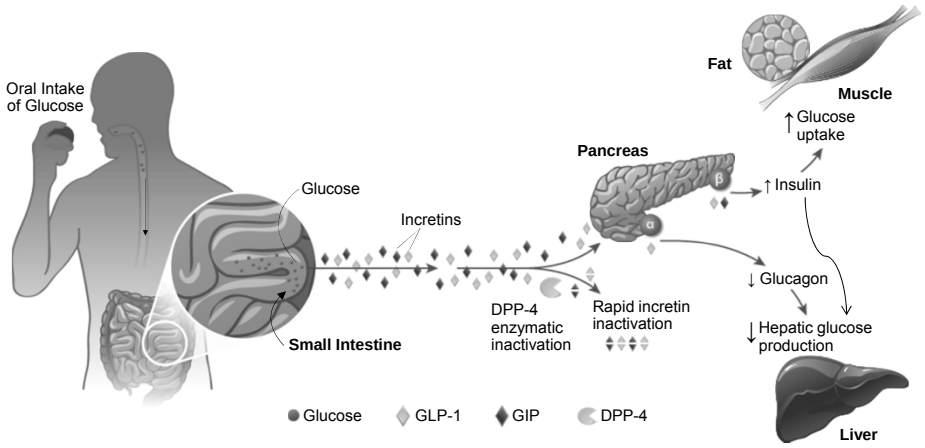
1. What are you taking this medication for?
2. How are you currently taking it?
3. What problems have you noticed since starting this medication?
4. What side effect concerns do you have about your medication?
5. What cost concerns do you have about your medications?
6. What days of the week do you NOT take your medication?
   - How often does this happen?

Cornell S et al. *Diabetes Trends*. 2009; 21(suppl A):3-11.

Summary

- T2DM is a result of 8 dysfunctional organs
  - Insulin resistance is a major contributor to T2DM
  - There is no single drug (when used as monotherapy) that fixes all 8 of the broken organs
- GLP-1 agonists fix 5 of the organs
  - Patient education can overcome barriers to use, enhance adherence and improve therapeutic outcomes
- Pharmacists should perform regular medication check-ups and routine assessment of device technique

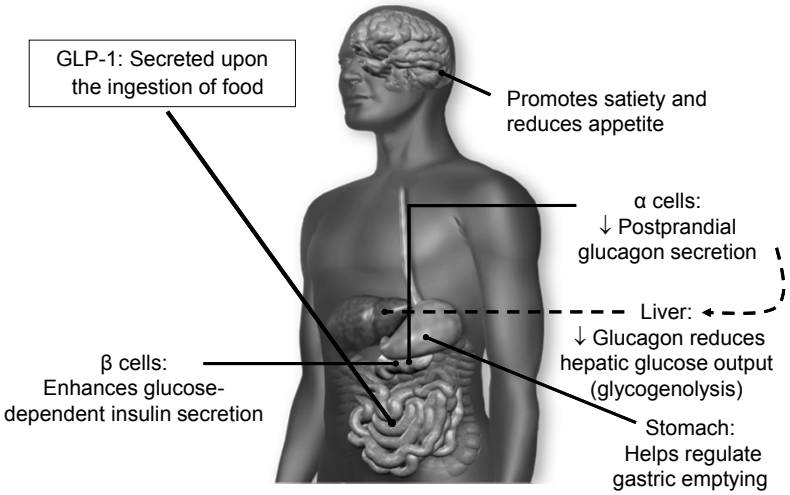
Incretin Glucose Regulation



DPP=dipeptidyl peptidase, GLP=glucagon-like peptide, GIP=glucose-dependent insulinotropic polypeptide or gastric inhibitory polypeptide

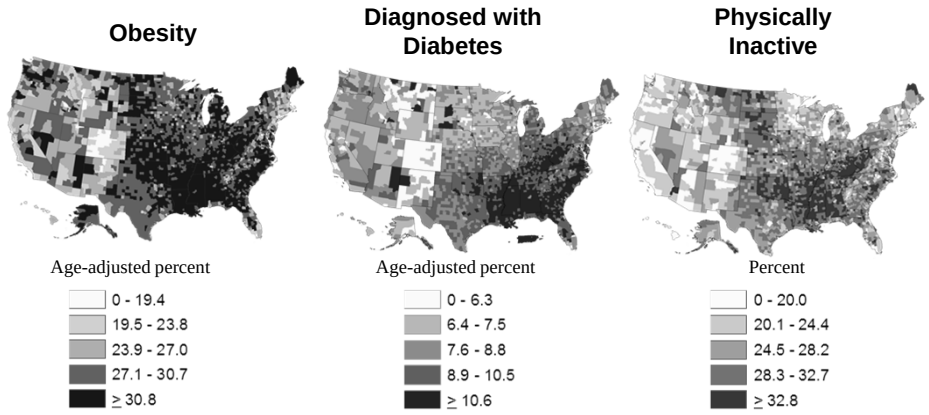
Drucker DJ et al. *Lancet*. 2006; 368:1696-1705. Nauck MA. *Eur J Intern Med*. 2009; 20:S303-8. Kendal DM et al. *Am J Med*. 2009; 122:S37-50.

GLP-1 Modulates Numerous Functions in Humans



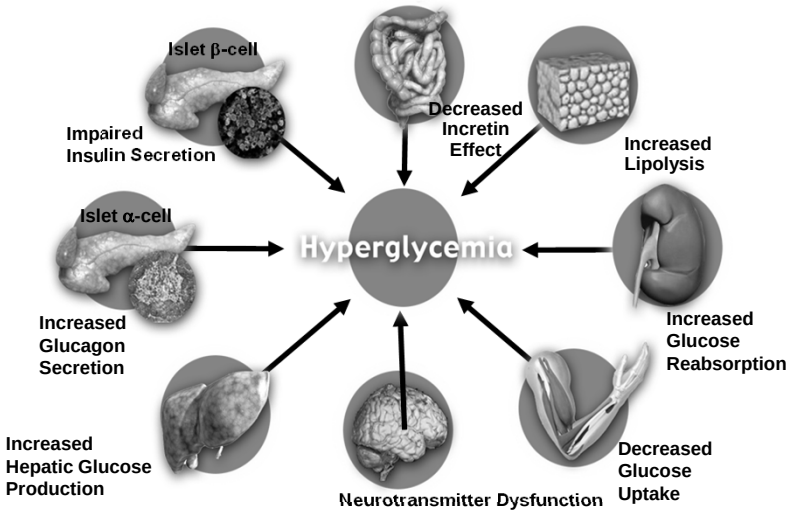
Flint A et al. *J Clin Invest*. 1998; 101:515-20, Drucker DJ. *Diabetes*. 1998; 47:159-69.

The Diabesity Epidemic



Centers for Disease Control and Prevention: National Diabetes Surveillance System. www.cdc.gov/diabetes/data (accessed 2011 Jul 7)

Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet



DeFronzo RA. *Diabetes*. 2009; 58:773-95.

Glucose Lowering Comparison

Monotherapy	Route	Targets insulin resistance	Target Organs	Target Glucose: FPG or PPG	A1c Reduction %
Sulfonylurea	Oral	No	Pancreas	Both	1.5-2.0
Metformin	Oral	Yes	Liver	FPG	1.5
Glitazones	Oral	Yes	Muscle & adipose fat	Both	1.0-1.5
Meglitinides	Oral	No	Pancreas	PPG	0.5-2.0
AGIs	Oral	No	GI tract	PPG	0.5-1.0
DDP-4 inhibitors	Oral	No	Pancreas & liver	PPG	0.5-0.7
Bile acid sequestrant	Oral	No	GI tract	PPG	0.4
Dopamine agonists	Oral	No	Brain, possibly adipose fat	PPG	0.4
SGLT-2 inhibitors	Oral	Maybe	Kidney, possibly adipose fat	FPG	0.7 – 1.1
GLP-1 agonists	Injectable	No	Pancreas, liver, brain & GI tract	Short-acting—PPG Long-acting—Both	0.8-1.5
Amylin analogs	Injectable	No	Pancreas, liver, brain & GI tract	PPG	0.6
Insulin	Injectable	Yes (to a degree)		Basal - FPG Bolus – PPG	↓ as much as needed

FPG=fasting plasma glucose, PPG=postprandial glucose, GI=gastrointestinal.

Unger J et al. *Postgrad Med*. 2010; 122:145-57. Cornell S et al. *Postgrad Med*. 2012; 124:84-94.

Overview of Approved Incretin Therapies

Properties/Effects	Long Acting GLP-1 agonists	Short-acting GLP-1 agonists	DPP-4 inhibitors
Administration	SQ Daily or Weekly	SQ Twice Daily	Oral Daily
Glucose-dependent insulin increase	Yes	Yes	Yes
Glucose-dependent glucagon decrease	Yes	Yes	Yes
Slows Gastric Emptying	Yes	Yes	No
Lower hypoglycemia risk (in absence of SUs)	Yes	Yes	Yes
Effect on Body Weight	Loss	Loss	Neutral
Effect on A1c	High Efficacy	Moderate Efficacy	Moderate Efficacy
Effect on Fasting Plasma Glucose	Good	Modest	Modest
Major Adverse Effects	GI, nausea	GI, nausea	Well-tolerated
Adjustment/restriction in renal impairment	No, but GI SE in renally impaired patients - Caution	Yes, avoid in Severe/ ESRD	Yes, varies per medication

SQ=subcutaneous

Differences Between Incretin Mimetics

	Liraglutide	Exenatide*	Albiglutide	Dulaglutide
Dosing (SQ)	1.2-1.8 mg QD (after initial 0.6mg QD x7 days)	5-10 mcg within 60 min of AM/PM meals	30-50 mg weekly	0.75-1.5 mg weekly
Half-life	13 hr	2-4 hr	5 days	5 days
Max dose	1.8 mg QD	10 mcg BID	50 mg weekly	1.5 mg weekly
Renal elimination	No	Yes	No	No
Homology to GLP-1	97%	53%	97%	90%
Antibodies	8.6%	44%	2.5%	2%
Other effects	Less persistent nausea vs exenatide BID. Greater effects on FPG vs exenatide BID.	Exenatide BID - greater effects on PPG (*exenatide LAR has more effect on FPG, less nausea)	Nausea seems to be similar to other agents	No reconstitution Available as one-time use pens or pre-filled syringes

Dulaglutide - Results

Outcomes (Means Reported)	D vs Lira AWARD-6 (26 week)		D vs Glar AWARD-2 (78 week)			D vs Glar AWARD-4 (52 week)		
Medication	D 1.5 mg	Lira 1.8 mg	D 0.75 mg	D 1.5 mg	G	D 0.75 mg	D 1.5 mg	G
HbA1c (%)	-1.42	-1.36	-0.62	-0.9	-0.59	-1.42	-1.48	-1.23
Weight change (kg)	-2.9	-3.6	-1.54	-1.96	1.28	1.6	0.6	3.7
TDD insulin	n/a		NR			97	93	132
% at goal <7%	68.3	67.9	NR			56	59	49
Other Info	All reported side effects comparable between treatments		PRO-less behavior & worry-hypoglycemia			Glargine ~64 units/day		

ADA 74th Scientific Sessions, San Francisco, LB-110, P-979, P-962. Dungan K et al. *Lancet*. 2014; 384:1349-57.

Dulaglutide - Side Effects

Outcomes (%)	D vs Lira AWARD-6 (26 week)		D vs Glar AWARD-4 (@ 52 week)		
GI (%)	D 1.5 mg	Lira 1.8 mg	D 0.75 mg	D 1.5 mg	G
Nausea	20.4	8.0	17.7	25.8	3.4
Vomiting	7.3	8.3	10.6	12.2	1.7
Diarrhea	12.0	12.0	15.7	16.6	6.1
Injection site reaction	0.3	0.7	1.4	0.3	0.0
Hypoglycemia	≤70 mg/dL +/- Sx, Events/ pt/yr		Severe		
	0.34	0.52	1.7	2.1	3.7
			≤70 mg/dL		
			88.4	85.9	89.5
Other Info	D/C due to SE 6% in each group No pancreatitis or pancreatic cancer		No pancreatitis or pancreatic cancer reported		

ADA 74th Scientific Sessions, San Francisco, LB-110, P-979, P-962. Dungan K et al. *Lancet*. 2014; 384:1349-57.

Effect of GLP-1 Agonists on CVD Risk Factors

Lixisenatide press release-neutral for CV events

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HDL-C (mg/dL)	8.5*	–1.2	N/A	ND	N/A
Triglycerides (mg/dL)	–44.4*	–14.7†	–40.0*	ND	–12.4 to –16.8

N/A=not available, ND=no difference vs placebo
*P <0.05 vs baseline, †P <0.005 vs placebo, ‡P <0.001 vs placebo

Klonoff DC et al. *Curr Med Res Opin*. 2008; 24:275–86. Zinman B et al. *Diabetes Care*. 2009; 32:1224–30. Bergenstal R et al. *Diabetes*. 2009; 58:165-OR. Pratley RE et al. *Lancet Diabetes Endocrinol.* 2014; 2:289–97. Nauck MA et al. *Diabetes Care*. 2014; 37:2149–58.

GLP-1 Agonist Comparison

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Albiglutide Once-weekly dosing	Pen	Yes	Yes (15-30 min)	Expiration Date	Can be stored at room temperature for 4 weeks
Dulaglutide Once-weekly dosing	Pen	No	No	Expiration Date	Can be stored at room temperature for 4 weeks

www.pdr.net (accessed 2015 April 20).

Self-Assessment Questions

The self-assessment questions included in this presentation are listed below for your review. You may wish to note the correct answers as you follow along with the speaker.

1. If we wanted to give a weekly GLP-1 agonist, what would be our choices?
    a. Exenatide LAR
    b. Albiglutide
    c. Dulaglutide
    d. All of the above

2. Which dysfunctional organs do GLP-1 agonists target?
    a. Brain and adipose fat
    b. Muscle and adipose fat
    c. Muscle, pancreas and liver
    d. Pancreas and liver
    e. Pancreas, liver, brain and GI tract

3. Which statement regarding GLP-1 agonist pen administration is NOT true?
    a. Prime before each use
    b. Some devices will require “mixing”
    c. Inject straight into the skin
    d. Hold for 5 -10 seconds before removing the needle from skin

4. Patient JZ needs help with scheduling doses. Which GLP-1 agonist must be dosed prior to a meal?
    a. Albiglutide
    b. Dulaglutide
    c. Exenatide BID
    d. Liraglutide

Instructions for Processing CE Credit with Enrollment Code

Claim CPE within 60 days

Pharmacists and Technicians:
Per ACPE, CPE credit must be claimed **no later than 60 days** from the date of the live activity or completion of a home study activity. All ACPE accredited activities which are processed on the eLearning site will be reported directly to CPE Monitor. To claim pharmacy credit, you must have your NABP e-Profile ID, birth month, and birth day. If you do not have an NABP e-Profile ID, go to www.MyCPEMonitor.net for information and application. Please follow the instructions below to process your CPE credit for this activity.

1. The **ASHP eLearning** site allows participants to obtain statements of continuing education credit conveniently and immediately using any computer with an internet connection. Type the following link into your web browser to access the e-Learning site: **http://elearning.ashp.org/my-activities**
2. If you already have an account registered with ASHP, log in using your username and password.

   If you have not logged in to any of the ASHP sites before and/or are not a member of ASHP, you will need to set up an account. Click on the **Register** link and follow the registration instructions.
3. Once logged in to the site, enter the enrollment code for this activity in the field provided and click **Redeem**.

   Note: The Enrollment Code was announced at the end of the live activity.
   Please record the Enrollment Code in the grid below for your records.
4. The title of this activity should now appear in a pop-up box on your screen. Click on the **Go** button or the **activity title.**
5. Complete all required elements. A green ✔ should appear as each required element is completed. You can now claim your credit.
6. Available credit(s) will appear beneath the completed required activities. Look for your profession in the list of available credits and click the appropriate **Claim** button. You might have to click to see more credit options if you don't see your profession listed.

   CPE Credit for Pharmacists and Technicians: To claim continuing pharmacy education (CPE) credit, you will need to enter your NABP e-Profile ID, birth month, and birth day. Once you have entered this information the first time, it will auto fill in the future. Please note: All CPE credit processed on the eLearning site will be reported directly to CPE Monitor.
7. Review the information for the credit you are claiming. If all information appears to be correct, check the box at the bottom and click **Claim**. You will see a message if there are any problems claiming your credit.
8. Your credit will be reported directly to CPE Monitor.

Date of Activity	Activity Title	Enrollment Code	Credit Hours
9/10/15	Maximizing the Role of GLP-1 Agonists in Our Patients with Type 2 Diabetes		1.0

NEED HELP? Contact **eLearning@ashp.org**.