Incretin Mimetics: Friend or Foe?

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Disclosures

- Neither speaker has relevant financial relationships to report.

Pharmacist Objectives

- Describe the mechanism of action and place in therapy of incretin mimetics.
- Compare and contrast the efficacy and safety concerns of DPP-4 inhibitors and GLP-1 agonists based on available biomedical data.
- Discuss the benefits and risks of incretin mimetics using a patient-centered approach.

Pharmacy Technician Objectives

- List 2 GLP-1 receptor agonists and 2 DPP-IV inhibitors.
- Recognize potential adverse drug effects of incretin mimetics.
- List special storage requirements of GLP-1 receptor agonists.

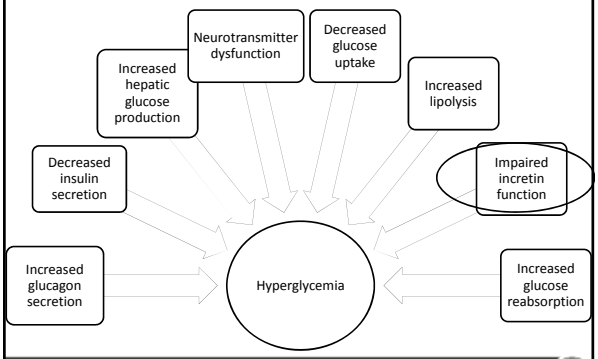
A Common Diabetes Story

A 48 y/o WM with a 10-year history of diabetes has an A1C of 8.4% and BMI of 32 kg/m^2 on metformin 1000 mg BID, glipizide ER 20 mg daily, and citalopram 20 mg daily. She has declined to start insulin per last PCM note. PMH: depression. estCrCl > 90 ml/min. Family history: CVA, DM

What is an ideal add-on therapy to better control her diabetes?

a. exenatide
b. liraglutide
c. linagliptin
d. sitaglitpin

Pathophysiology of T2DM



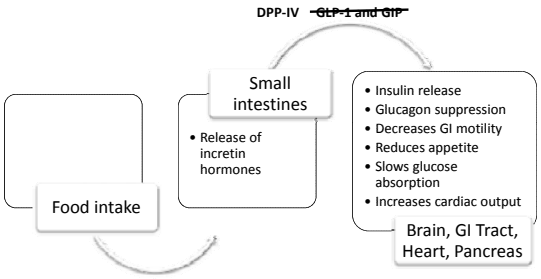
What is the mechanism of incretin-based medications?

a. increase muscular glucose uptake
b. decrease glucose reabsorption
c. decrease lipolysis
d. increase glucose-dependent insulin release and decrease glucagon secretion

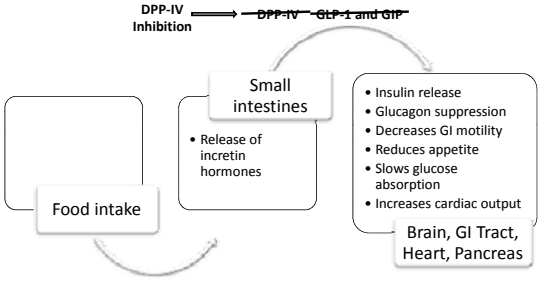
Incretin System

- Incretins are naturally occurring glucoregulatory hormones.
- Glucose-dependent release by the gut
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP)
- Incretin hormones are rapidly degraded by dipeptidyl peptidase IV (DPP-IV)

Incretin System



Incretin Enhancement



Current DPP-IV Inhibitors

- Alogliptin (Nesina®)
- Linagliptin (Tradjenta®)
- Saxagliptin (Onglyza®)
- Sitagliptin (Januvia®)
- Vildagliptin (Galvus®)*

*Approved for use in Europe

Overview of DPP-IV Inhibitors

- Supplied as oral formulations
- Once daily administration, without regards to meals
- A1C reduction 0.2-1.15%
- Minimal weight loss to weight neutral
- Low incidence of hypoglycemia
- Studied as combination and monotherapy

Comparison of DPP-IV Inhibitors

Drug	Usual Dose	Dose Adjustment	Unique Warnings	A1C (%) Change	FPG (mg/dl) Change	2h PPG (mg/dl) Change
Alogliptin 6.25 mg, 12.5 mg, 25 mg	25 mg/d	Renal impairment CrCl: 30-60 ml/min=12.5 mg < 30 ml/min=6.25 mg	Hepatic failure	-0.5 to -1.0	-8 to -26	-43
Linagliptin 5 mg	5 mg/d	None (Decreased effectiveness with P-glycoproteins/CYP 3A4 inducers)		-0.2 to -0.7	-5 to -13	-34 to -49
Saxagliptin 2.5 mg, 5 mg	2.5 or 5 mg/d	Renal impairment CrCl: < 50 ml/min=2.5 mg Strong CYP 3A4 inhibitors=2.5 mg	Increased edema with TZDs	-0.4 to -0.9	-7 to -22	-12 to -65
Sitagliptin 25 mg, 50 mg, 100 mg	100 mg/d	Renal impairment CrCl: 30-49 ml/min=50 mg < 30 ml/min=25 mg	Acute renal failure	-0.3 to -1.15	-1 to -30	-31 to -62

Safety Concerns

- Most common ADRs: upper respiratory infection, nasopharyngitis, headache
- Hypersensitivity reactions: angioedema, anaphylaxis, Steven's-Johnson syndrome
- Acute pancreatitis

Grab a Partner

Mr. Starch is a 49 y/o admitted to the hospital for his 1st episode of acute pancreatitis. You two are part of the medical team that is planning for Mr. Starch's discharge. His pre-admission medications (metformin, saxagliptin, and glimepiride) have been held during this admission. The blood sugars have been controlled with insulin during this stay.

What do you recommend as a discharge diabetes plan?

DPP-IV Inhibitors and CV Outcomes

- Preliminary findings from SAVOR-TIMI-53 trial: saxagliptin failed to show superiority vs. placebo in reducing CV death, heart attack, and stroke
- Small decreases in blood pressure noted with sitagliptin (2-3/1.6-1.8 mmHg)
- Ongoing study: sitagliptin cardiovascular outcome study, expected completion 12/2014

Summary of DPP-IV Inhibitors

- Can be used in combination with orals or basal insulin
- Similar A1c reduction (up to ~1%) between individual drugs
  - Linagliptin lowest A1c reduction (max 0.7%)
  - No head-to-head trials
- No renal dosing with linagliptin
- Pancreatitis warnings
- No long term outcomes
- Choice likely dependent on formulary/cost

A Classic Diabetes Story

A 48 y/o WM with a 10-year history of diabetes has an A1C of 8.4% and BMI of 34 kg/m^2 on metformin 1000 mg BID, glipizide ER 20 mg daily, and citalopram 20 mg daily. She has declined to start insulin per last PCM note. PMH: depression, IBS. estCrCl > 90 ml/min. Family history: CVA, DM

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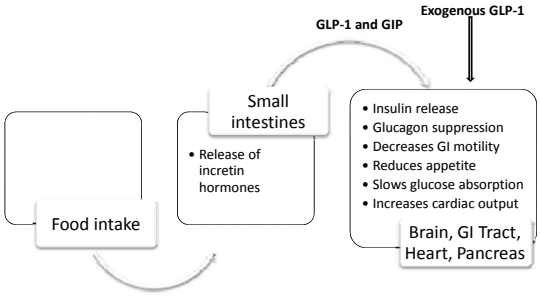
GLP-Agonists

Incretin Mimetic



Current GLP-1 Agonists

- Exenatide (Byetta®) 2005
- Exenatide (Victoza®) 2010
- Liraglutide (Victoza®) 2012

- In studies
  - Taspoglutide
  - Lixisenatide
  - Albiglutide

Overview of GLP-1 Agonists

- Supplied as subcutaneous injections
- Twice daily to once weekly administration
- A1C reduction 0.5-1.6%
- Weight loss about 2.5 kg
- Low incidence of hypoglycemia
- Can be used with basal insulin (exenatide ER not well studied)

Grab a Partner

- Write down the warnings/precautions for GLP-1 agonists

Safety Concerns

- Most common ADRs: GI, headache, injection site reaction
- Hypersensitivity reactions: angioedema, anaphylaxis, acute renal failure
- Acute pancreatitis: avoid in chronic
- Gastroparesis: increased risk of GI SE's
- DI: caution with narrow therapeutic window drugs
- Cancer: Thyroid C-cell tumors

Comparison of GLP-1 Agonists

Drug	Injection schedule	Usual Dose	Administration	A1C (%) Change	Weight Loss
Exenatide IR 5 mcg BID x 4 weeks 10mcg BID (Pen)	BID	Up to 20 mcg/d	Administer w/i 60 min of 2 biggest meals (6 hrs apart)	-0.5 to -1.0	-2.9 kg
Exenatide ER 2 mg once weekly (Reconstitution kit)	Once weekly	2 mg/week	Administer immediately after reconstituting. Rotate injection sites	-1.5 to – 1.9 (mfr says 1.6)	-2.3 kg
Liraglutide 0.6 mg daily x 1 week 1.2 mg daily Up to 1.8 mg (Pen)	Daily	1.2-1.8 mg/d	Administer regardless of meal timing	-0.8 to -1.5	-2.5 kg

Comparison of GLP-1 Agonists

Drug	Unique Warnings	Side Effect Comparison	Dose Adjustment	Storage
Exenatide IR BID	No cancer warning	Nausea (up to 44%)	Renal impairment CrCl: 30-50 ml/min= caution < 30 ml/min= not recommended	Refrigerate until opened. Discard 30 days once opened (room temp-fridge)
Exenatide ER weekly	Thyroid C-cell tumors (CI)	Injection site reactions (nodules, hematoma, pruritus)	Renal impairment CrCl: 30-50 ml/min= caution < 30 ml/min= not recommended	Refrigerate. Good for 4 weeks at room temperature.
Liraglutide Daily	Thyroid C-cell tumors (CI)	More GI than exenatide ER with less injection site reactions	Renal impairment Use with caution with mild-moderate disease	Refrigerate until opened. Discard 30 days once opened (room temp-fridge)

A Classic Diabetes Story

A 48 y/o WM with a 10-year history of diabetes has an A1C of 8.4% and BMI of 34 kg/m^2 on metformin 1000 mg BID, glipizide ER 20 mg daily, and citalopram 20 mg daily. She has declined to start insulin per last PCM note. PMH: depression, IBS. estCrCl > 90 ml/min. Family history: CVA, DM

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Help Mrs. Sugar

Mrs. Sugar calls for your advice. She is scheduled to take her weekly exenatide today and she just found her medication in the kitchen cabinet with 2 remaining weekly trays. She picked up the kit with 4 weekly trays August 23rd and assumes they have been out of the fridge since then. Which of the following are correct?

a. She should discard all remaining trays and obtain a new supply today prior to administration.
b. She may use the remaining 2 trays for today and next Friday's injections.
c. She may use 1 tray today but will need a new supply prior to next week.
d. She may use 1 tray today and will need to freeze and thaw the remaining tray prior to next week.

GLP-1 Agonists and Thyroid Cancer

- Exenatide ER and liraglutide have Boxed Warning for thyroid tumors
  - Thyroid C-cell tumors observed in animal studies
  - Contraindicated with or a family history of medullary thyroid cancer (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2)
  - Human reports with liraglutide (<1%)
    - 8 cases of C-cell hyperplasia in clinical trials
      - 6 were liraglutide and 5 of the 6 had elevated calcitonin at baseline and throughout
    - 2 post-market reports of MTC
- Ongoing surveillance
- Educate on signs/symptoms

GLP-1 Agonists and CV Outcomes

- Meta-analysis of CV outcomes
  - Significant reduction of events compared to placebo
  - No difference between liraglutide and exenatide
- Direct CV benefits
  - Reduced BP 1.2-6.7 mmHg
  - Reduced TG and hs-CRP
  - LDL mixed results (no change to -6%)
  - Weight loss

Long-Term CV Outcomes

- Ongoing Trials
  - Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): A Trial To Evaluate Cardiovascular Outcomes After Treatment With Exenatide Once Weekly In Patients With Type 2 Diabetes Mellitus.
    - Completion date 2017
  - Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results - A Long Term Evaluation (LEADER®)
    - Completion date 2016

Summary of GLP-1 Agonists

- Can be used in combination with orals or basal insulin Exenatide ER not studied with insulin)
- Exenatide ER has least SE
- Liraglutide has better A1c lowering in head-to-head studies (not clinically significant)
- Similar cancer and pancreatitis profiles (no cancer warning for Byetta)
- No long term outcomes
- Potential for cardiovascular benefit beyond diabetes
- Choice likely dependent on formulary, cost, and patient preference for dosing

Pancreatic Pathology and Incretin Therapies

- Population-based, rodent, and human autopsy studies caused concern that incretin-based therapy may be associated with pancreatic changes.
- Since March 2013, FDA has been evaluating this information.

Pancreatic Pathology and Incretin Therapies

- June 2013 joint statement from ADA/EASD/IDF: no concern for pancreatic disease with incretins after review of data
- July 2013 European Medicines Agency: present data do not confirm increased pancreatic risk with incretin-based therapy

Diabetes and Cancer

- Long-standing diabetes is a risk factor for malignancy.
- Optimal treatment of diabetes and reversal of obesity can lower cancer risk.
- Pancreatic cancer can cause diabetes and appears 1-3 years before cancer is found.

Patients at Pancreatitis Risk

- Diagnosis of diabetes
- Hypertriglyceridemia
- Alcohol use
- Gallstones
- Obesity
- Tobacco abuse

Help Mr. Candy

Mr. Candy is a 56 y/o with Type 2 Diabetes and is struggling to gain control. Last A1C was 8.2%.Current medications: Metformin 1000mg BID, Glipizide 10mg BID, Lantus 20 units HS.
PMH: Hyperlipidemia (LDL 116, TG 390, HDL 30), HTN (BP 130/80). CrCl 48 ml/min. Family history includes unknown thyroid cancer in brother. EtOH (-)

Which of the following is the most appropriate addition to his regimen?

a. Sitagliptin 50 mg daily
b. Exenatide ER once weekly
c. Exenatide IR BID
d. Saxagliptin 5 mg daily

Management of Type 2 Diabetes

- Bottom line: take a patient-centered approach
- Always encourage weight control, healthy eating, and physical activity.
- ADA: metformin initial monotherapy, add-on with incretin-based therapy, sulfonylurea, thiazolidinedione, or insulin
- AACE: depending on A1C, monotherapy, dual, or triple therapy is recommended with incretin-based therapy as an option at any tier

Key Points

- Incretin-based therapies primarily increase glucose-dependent insulin secretion and suppress glucagon release.
- DPP-IV inhibitors are well tolerated, weight neutral, and have modest effects on A1C.
- GLP-1 agonists may cause GI upset initially, promote weight loss, and may cause significant A1C reduction.
- Acute pancreatitis has been reported with incretin-based medications.

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Post Test Questions – Pharmacist:

1. Which of the following is a mechanism of action of incretin-based therapies?
    a. decrease insulin resistance in skeletal muscle cells
    b. increase glucose-dependent insulin release
    c. increase glucagon secretion
    d. inhibit glucose reabsorption

2. A patient asks you as her pharmacist if her sitagliptin will give her cancer. She saw something about it on the news recently. Which of the following is an appropriate response?
    a. Tell her that is correct and stop taking the medication immediately.
    b. Tell her that is correct and suggest she switch to saxagliptin instead.
    c. Tell her that is incorrect. There have been no reports of any type of pancreatic disease with this drug. She should discontinue the medication until able to discuss with her primary provider.
    d. Tell her that is incorrect. There is not conclusive evidence at this time. She should continue taking her medication unless her primary provider advises her to discontinue it.

3. Which of the following patients with diabetes would be the best candidate to initiate exenatide ER?
    a. HTN, gout, history of acute pancreatitis
    b. Hypothyroidism and family history of gastroporesis
    c. Asthma, seasonal allergies, and family history of medullary thyroid carcinoma
    d. Severe renal disease, heart failure, hyperlipidemia

4. The clinic physician asks you which of the following can be initiated as add on therapy for a patient already on metformin 1000mg BID, glipizide 5mg daily, Lantus 40 units HS, and Novolog 10 units before meals?
    a. Exenatide IR
    b. Liraglutide
    c. Exenatide ER
    d. Linagliptin

5. Which of the following education points should be discussed with a patient picking up liraglutide?
    a. Pen should be discarded in 30 days once opened
    b. Inject twice daily before meals
    c. Inject intramuscularly using provided pen needles
    d. Inject 30 minutes prior to meals

Post Test Questions - Technician

1. Which of the following are DPP-IV inhibitors?
    a. metformin and pioglitazone
    b. glipizide and exenatide
    c. alogliptin and sitagliptin
    d. acarbose and bromocriptine

2. Which of the following are potential adverse drug effects of sitagliptin?
    a. thyroid cancer
    b. severe hypoglycemia
    c. vomiting

d. upper respiratory infection

3. Which of the following are potential adverse drug effects of both DPP-IV inhibitors and GLP-1 agonists?

a. pancreatitis
b. thyroid cancer
c. severe hypoglycemia
d. fungal infections

4. Which of the following is appropriate storage for exenatide IR?

a. Unopened pens may be kept at room temperature until expiration date
b. Unopened pens should be refrigerated until dispensed
c. Opened pens may be kept at room temperature for 3 months
d. Opened penss should be refrigerated to extend time to disposal to 3 months

5. Which of the following are potential adverse drug effects of GLP-1 agonists?

a. Nausea
b. Weight gain
c. Rapid heartbeat
d. Nightmares