Anti-Diabetic Drugs
Insulin

Administration:

• Subcutaneous injection
• Rotate site
• Check blood sugars regularly

Storage:

• Refrigerate until use
Insulin (cont)

Dosing:
- Starting daily dose: 0.5-1 unit/kg/day in divided doses
- Adjust according to fasting (premeal) blood glucose of 80-130 mg/dL and peak postprandial blood glucose < 180 mg/dL
- Provide 50% as long acting insulin and 50% as prandial insulin
- 1 unit of can account for 30 grams of carbohydrate (14-50)
- 1 unit can lower 50 mg/dL blood glucose (10-100)

Special Population Considerations:
- Renal dysfunction
  - CrCl 10-50 mL/min: 75% of normal dose
  - CrCl < 10 ml/min: 25-50% of normal dose; monitor closely
- Exercise???

---- Acute Stress???
Insulin Action

- **Rapid/immediate**
- **Fast**
- **Intermediate**
- **Slow**

Blood concentration vs. Time (hr)
## Insulin Comparison Chart

<table>
<thead>
<tr>
<th>Insulin Name</th>
<th>When does it start working? (onset)</th>
<th>When will the effect be the greatest? (peak)</th>
<th>How long will it lower blood glucose? (duration)</th>
<th>Notes for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro (Humalog™)</td>
<td>&lt;15 minutes</td>
<td>0.5-3 hours*</td>
<td>3-5 hours</td>
<td>If mixing with NPH, rapid acting insulin should be drawn into syringe first. Mixture should be given immediately to avoid effects on peak action.</td>
</tr>
<tr>
<td>Aspart (Novolog™)</td>
<td>&lt;15 minutes</td>
<td>0.5-3 hours*</td>
<td>3-5 hours</td>
<td></td>
</tr>
<tr>
<td>Glulisine (Apidra™)</td>
<td>&lt;15 minutes</td>
<td>0.5-3 hour*</td>
<td>3-5 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Short Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular (Novolin R™ or Humulin R™)</td>
<td>0.5-1 hour</td>
<td>2-4 hours</td>
<td>4-8 hours</td>
<td>May be mixed with NPH in same syringe. Mixing order should be the clear regular drawn up first, then the cloudy NPH (ie “clear to cloudy”).</td>
</tr>
<tr>
<td><strong>Intermediate Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH (Novolin N™ or Humulin N™)</td>
<td>2-4 hours</td>
<td>4-10 hours</td>
<td>10-18 hours</td>
<td>Available as pen or in vial to be used with syringe.</td>
</tr>
<tr>
<td><strong>Long Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (Lantus™)</td>
<td>4-6 hours</td>
<td>Same action throughout the day</td>
<td>24 hours</td>
<td>Do not mix with other insulins. Available as pen or in vial. Duration (clinical trial data): 6 hrs (0.1 U/kg), 12 hrs (0.2 U/kg), 20 hrs (0.4 U/kg), 23 hrs (0.8 U/kg and 1.6 U/kg)</td>
</tr>
<tr>
<td>Detemir (Levemir™)</td>
<td>2-3 hours</td>
<td>6-8 hours</td>
<td>Dose-dependent 5.7-23.2 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Combinations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin or Novolin 70/30</td>
<td>0.5-1 hour</td>
<td>2-10 hours</td>
<td>10-18 hours</td>
<td>70% NPH +30% regular insulin. Insulin action includes 2 peaks (1 from each formulation)</td>
</tr>
<tr>
<td>Novolog Mix 70/30 Humalog Mix 75/25 or 50/50</td>
<td>&lt;15 minutes</td>
<td>1-2 hours</td>
<td>10-18 hours</td>
<td>Novolog Mix: aspart protamine 70% + aspart 30% Humalog mix: 75/25=75% lispro protamine + 25% lispro 50/50=50% lispro protamine + 50% lispro. Insulin action includes 2 peaks (1 from each formulation).</td>
</tr>
</tbody>
</table>
Insulin Dosing

Normal insulin secretion

Long-acting

Long-acting & Short-acting

70/30 pre-mixed
Insulin (cont)

Cautions/Severe Adverse Reactions

• Severe hypoglycemia (seizure/coma) (BG < 40 mg/dL)

• Edema

• Lipoatrophy or lipohypertropy at injection site

CONTRAINDICATIONS

• Severe hypoglycemia

• Allergy or sensitivity to any ingredient of the product
Adjunctive Therapy in Diabetes Mellitus Type II

• **Hypoglycemia**
  – Complication of treatment!
  – Make sure patients inform the people around them of these symptoms and what to do!
  – Symptoms: Anxiety, blurred vision, palpitations, shakiness, slurred speech, sweating
  – Treatment: glucose/simple sugars: 3-4 glucose tablets, ½ can of soda (NOT diet!)
  – Treatment: **glucagon injection**
    • Dose: 1 mg IM, IV, SQ; may repeat in 20 minutes if needed
Liver
- Hepatic glucose output
  - Metformin
  - Pioglitazone

Pancreas
- Insulin secretion
  - Sulfonylureas
  - Glitinides
  - Incretins

Adipose Tissue
- Glucose uptake
  - Pioglitazone

Brain
- Appetite control
  - Incretins
  - Amylin mimetics

Kidney
- Glucose reabsorption
  - SGLT2 inhibitors

Muscle
- Glucose uptake
  - Pioglitazone
  - Metformin

Brain
- Insulin secretion
- Appetite control
- Incretins
- Amylin mimetics
- a-Glucosidase inhibitors

Liver
- Hepatic glucose output
  - Metformin
  - Pioglitazone

Kidney
- Glucose reabsorption
  - SGLT2 inhibitors
# Therapeutic Options:
## Antihyperglycemic Agents

### Enhance Insulin Secretion
- Sulfonylureas
- Meglitinides
- Incretins

### Attenuate Glucose Absorption
- Alpha-glucosidase inhibitors
- Incretins
- Amylin mimetics

### Insulin Sensitizers
- Biguanides
- Thiazolidinediones

### Reduce Hepatic Glucose Production
- Biguanides
- Insulin

### Reduce glucagon secretion
- Incretins
- Amylin mimetics

### Increase glucose disposal
- Insulin

### Increase urinary glucose excretion
- SGLT2 inhibitors

### Other
- Bile Acid Sequestrants (colesevelam)
- Dopamine-2 agonists (bromocriptine)
## Combination Therapy with Oral Antidiabetic Agents

<table>
<thead>
<tr>
<th>Combination</th>
<th>Additional Reduction in FPG (mg/dl)</th>
<th>Additional Reduction in Hemoglobin A$_{1c}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide/Acarbose</td>
<td>-34 compared to glyburide alone</td>
<td>-0.6 compared to glyburide alone</td>
</tr>
<tr>
<td>Sulfonylurea*/Pioglitazone**</td>
<td>-58 compared to sulfonylurea alone</td>
<td>-1.3 compared to sulfonylurea alone</td>
</tr>
<tr>
<td>Sulfonylurea*/Rosiglitazone^</td>
<td>-48 compared to sulfonylurea alone</td>
<td>-0.8 compared to sulfonylurea alone</td>
</tr>
<tr>
<td>Glyburide/Metformin</td>
<td>-63 compared to glyburide alone</td>
<td>-1.7 compared to glyburide alone</td>
</tr>
<tr>
<td>Metformin/Acarbose</td>
<td>-34 compared to metformin alone</td>
<td>-0.6 compared to metformin alone</td>
</tr>
<tr>
<td>Metformin/Pioglitazone**</td>
<td>-38 compared to metformin alone</td>
<td>-0.8 compared to metformin alone</td>
</tr>
<tr>
<td>Metformin/Rosiglitazone^</td>
<td>-56 compared to metformin alone</td>
<td>-0.8 compared to metformin alone</td>
</tr>
</tbody>
</table>
Metformin (Glucophage®)

- **MOA:** decreases hepatic glucose production by decreasing gluconeogenesis and also improves insulin sensitivity
- **Place in therapy:** **FIRST LINE!**
- **Advantages:**
  - Efficacy: ↓ A1C by 1-2%
  - Cost: $4 generic
  - Weight neutral
  - No hypoglycemia
  - ↓ in micro- and macrovascular complications (UKPDS)
  - Long history of use
Metformin (Glucophage®)

- **Disadvantages:**
  - GI intolerance (diarrhea, abdominal cramping)
  - Vitamin B12 deficiency
  - Multiple contraindications & precautions in package insert, including:
    - SCr > 1.5mg/dL in men or > 1.4mg/dL in women
    - Hepatic disease
    - Excessive alcohol intake
    - Elderly, age ≥ 80 years
    - Acute illness, major surgery, or severe infection
    - Hypoxic states (e.g., acute CHF, acute MI)
    - Dehydration
    - Iodinated contrast media

↑ Risk of Lactic Acidosis
Metformin (Glucophage®)

Lactic acidosis:
- Rare: 0.03 cases/1000 patient-years; 0.015 fatalities/1000 patient-years
- Most information and data from phenformin
- Symptoms: SOB, muscle aches/weakness, ataxia, altered mental status, palpitations, slurred speech, tachypnea
- Onset: Acute or Insidious (minutes, hours or days)
- True risk of lactic acidosis with metformin is controversial
  - In nearly all reported cases, the patients had an underlying condition predisposing them to lactic acidosis (most commonly acute renal failure)
  - Prospective and observational studies have not found increased risk of lactic acidosis with metformin when used as labeled
- Risks: significant renal disease, unstable/acute CHF, EtOH, elderly, IV contrast study
Proposed Recommendations for Use of Metformin based on eGFR

<table>
<thead>
<tr>
<th>eGFR (mL/min per 1.73m²)</th>
<th>Action</th>
</tr>
</thead>
</table>
| ≥60                      | No renal contraindication to metformin  
Monitor renal function annually |
| <60 and ≥45              | Continue use  
Increase monitoring of renal function (every 3-6 months) |
| <45 and ≥30              | Prescribe with caution  
Use lower dose (e.g., 50% or half-maximal)  
Closely monitor renal function (every 3 months)  
Do not start new patients on metformin |
| <30                      | Stop metformin |
Sulfonylureas

**MOA:** Increase insulin secretion

**Advantages**
- Efficacy: ↓ A1C by 1-1.5%
- Cost: $4 generics
- Generally well tolerated
- ↓ microvascular outcomes (UKPDS)
- Long history of use

**Disadvantages**
- Risk of hypoglycemia
  - More likely in elderly, debilitated, malnourished patients, or patients with renal and hepatic dysfunction
  - Greater risk with glyburide
- Weight gain (~1-3 kg)
- Low durability
Sulfonylureas

- **1st generation – rarely used**
  - Acehexamide (Dymelor®), Tolubutamide (Orinase®), Chloropropamide (Diabinese®), Tolazamide (Tolinase®)

- **2nd generation**
  - Glimepiride (Amaryl®)
  - **Glipizide (Glucotrol®, Glucotrol XL®)**
  - Glyburide (Diabeta®, Micronase®, Glynase®)
<table>
<thead>
<tr>
<th>Medicine</th>
<th>Duration (hours)</th>
<th>Clearance</th>
<th>Active Metabolites</th>
<th>Initial Dose*</th>
<th>Max/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimepiride (Amaryl®)</td>
<td>24</td>
<td>Hepatic/Renal</td>
<td>Yes, but with minimal activity</td>
<td>1-2 mg daily</td>
<td>8 mg</td>
</tr>
<tr>
<td>Glipizide (Glucotrol®)</td>
<td>10-24</td>
<td>Hepatic/Renal</td>
<td>No</td>
<td>5 mg daily to twice daily</td>
<td>40 mg</td>
</tr>
<tr>
<td>Glipizide XL</td>
<td>24</td>
<td>Hepatic/Renal</td>
<td>No</td>
<td>5-10 mg daily</td>
<td>20 mg</td>
</tr>
<tr>
<td>Glyburide ( Diabeta®)</td>
<td>12-24</td>
<td>Renal If CrCL &lt;50; avoid use</td>
<td>Yes</td>
<td>2.5-5 mg daily to twice daily</td>
<td>20 mg</td>
</tr>
</tbody>
</table>

** Start with a low dose and increase conservatively in patients at risk for hypoglycemia (e.g., elderly, renal impairment)
Sulfonylureas

Rare Adverse Drug Reactions:

- SIADH
  - Syndrome of Inappropriate Antidiuretic Hormone
  - Chlorpropamide and tolbutamide may increase release/activity of ADH
- Disulfram reactions (chlorpropamide)
- Hepatotoxicity (oxidatively mediated; may cause problems in elderly)
- Hemolytic anemia
Meglitinides

- Repaglinide (Prandin®), Nateglinide (Starlix®)

**MOA:**
- Increase insulin secretion (they bind to a different location on the sulfonylurea receptor)

**Advantages:**
- Decrease postprandial glucose excursions, dosing flexibility, rapid onset of action

**Disadvantages:**
- Hypoglycemia, weight gain, frequent dosing schedule, expensive, modest efficacy (↓ A1C by 0.5-1.0%)
### Meglitinides

<table>
<thead>
<tr>
<th></th>
<th>Duration (hours)</th>
<th>Clearance*</th>
<th>Active Metabolites</th>
<th>Initial Dose</th>
<th>Max/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide (Prandin®)</td>
<td>&lt;4</td>
<td>Hepatic; 3A4</td>
<td>Yes</td>
<td>0.5-1 mg TID</td>
<td>16 mg</td>
</tr>
<tr>
<td>Nateglinide (Starlix®)</td>
<td>0.5-2</td>
<td>Hepatic; 2C9, 3A4 (also inhibits 2C9)</td>
<td>Yes</td>
<td>60 mg TID</td>
<td>360 mg</td>
</tr>
</tbody>
</table>

**CYP 3A4 interactions – gemfibrozil, itraconazole; monitor carefully w/ potent 3A4 inhibitors/inducers**
Thiazolidinediones (TZDs)

- **Pioglitazone** (Actos®) – 15-45 mg once daily
- **MOA**: potent peroxisome proliferator-activated receptor (PPAR-γ) agonist, which increases insulin sensitivity in the muscles and the liver
- **Efficacy**: ↓ A1C by 0.5-1.4%
  - 8-12 week delay to onset of full effect
- **Cost**: $10-20/month
- **Advantages**: no hypoglycemia, durability, ↑ HDL, ↓ TG, ? ↓ CVD events (ProACTIVE)
- **Disadvantages**: weight gain, edema/HF, ? ↑ bladder cancer, ↑ risk of fractures
TZDs

Contraindications:
- Heart failure (NYHA Class III or IV)

Precautions:
- Risk factors for HF
- Edema
- Additional risk factors for fracture, e.g., female, elderly
- Active liver disease (may be beneficial in fatty liver disease, but prudent to avoid use if ALT > 2.5 x ULN)
- Combination therapy with sulfonylurea and/or insulin may exacerbate weight gain; consider TZD dose reduction if adding one of these agents
Alpha-Glucosidase Inhibitors

- Acarbose (Precose®), miglitol (Glyset®)
- **MOA:** Delays intestinal carbohydrate digestion and absorption by competitively inhibiting enzymes in the small intestine
- **Advantages:** no hypoglycemia, reduces postprandial hyperglycemia, ?↓ CVD events (STOP-NIDDM)
- **Disadvantages:** Flatulence, diarrhea, bloating/gas (70%), abdominal pain, frequent dosing schedule; modest efficacy (↓ A1C by 0.5-0.9%)
Alpha Glucosidase Inhibitors

- **Dosing:**
  - Initial dose: 25 mg TID with meals
  - Max dose: 300 mg/day

- **Monitoring:**
  - LFTs every 3 months for 1 year, then periodically

- **Contraindications:**
  - Inflammatory bowel disease, intestinal obstruction, or other GI disorders
  - Cirrhosis of the liver
  - Avoid use if Scr > 2 mg/dL
DPP-4 Inhibitors

- Sitagliptin (Januvia®), saxagliptin (Onglyza®), linagliptin (Tradjenta®), alogliptin (Nesina®)

- **MOA:** ↑ insulin secretion (glucose dependent), and ↓ glucagon secretion by inhibiting DPP-4 activity, which increases postprandial active incretin (GLP-1, GIP) concentrations
Endogenous GLP-1 is rapidly degraded by the DPP4 enzyme, so it has a very short half-life (i.e., 1-2 min).

- **↓Appetite**
- **↓Gastric Emptying**
- **↓Glucose Production**
- **↑Insulin Secretion**
- **↓Glucagon Secretion**
- **↑B-cell proliferation**
- **↓B-cell apoptosis**
DPP-4 Inhibitors

- **Advantages:**
  - no hypoglycemia
  - well-tolerated
  - weight neutral

- **Disadvantages:**
  - ?↑ pancreatitis
  - less robust long term safety data
  - relatively modest efficacy (↓ A1c by 0.5-0.8%)
  - high cost
## DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Duration (Hours)</th>
<th>Clearance</th>
<th>Active Metabolite</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sitagliptin</strong></td>
<td>24</td>
<td>Hep/Renal</td>
<td>No</td>
<td>100 mg daily</td>
</tr>
<tr>
<td>(Januvia®)</td>
<td></td>
<td>CrCl&lt;50: 50 mg/day CrCl&lt;30: 25 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Saxagliptin</strong></td>
<td>24</td>
<td>Hep/Renal</td>
<td>Yes</td>
<td>2.5-5 mg daily</td>
</tr>
<tr>
<td>(Onglyza®)</td>
<td></td>
<td>CrCl&lt;50: 2.5 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Linagliptin</strong></td>
<td>24</td>
<td>Bile; no renal or hepatic</td>
<td>No</td>
<td>5 mg daily</td>
</tr>
<tr>
<td>(Tradjenta®)</td>
<td></td>
<td>adjustment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alogliptin</strong></td>
<td>24</td>
<td>Hep/Renal</td>
<td>Yes</td>
<td>25 mg daily</td>
</tr>
<tr>
<td>(Nesina®)</td>
<td></td>
<td>CrCl&lt;60: 12.5 mg/day CrCl&lt;30: 6.25 mg/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DPP-4 Inhibitors

FDA Safety Alert (2009): Acute Pancreatitis

- Prescribing information revised to include the following:
  - Case reports of acute pancreatitis, including hemorrhagic or necrotizing pancreatitis
  - Recommendation to monitor patients carefully for the development of pancreatitis after initiation or dose increases and to discontinue if pancreatitis is suspected
  - Instructions to use with caution and with appropriate monitoring in patients with a history of pancreatitis
  - Recommendation to counsel patient on signs and symptoms of pancreatitis such as nausea, vomiting, anorexia, and persistent abdominal pain
SGLT2 Inhibitors

- canagliflozin (Invokana®), dapagliflozin (Farxiga®),
- **MOA**: Blocks glucose reabsorption in the kidney, resulting in increased glucose excretion and lower blood glucose levels
### SGLT2 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Duration (Hours)</th>
<th>Clearance</th>
<th>Active Metabolite</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (Invokana®)</td>
<td>24</td>
<td>Hepatic/Renal eGFR &lt;60: 100 mg/day eGFR &lt;45: do not use</td>
<td>No</td>
<td>100-300 mg daily</td>
</tr>
<tr>
<td>Dapagliflozin (Farxiga®)</td>
<td>24</td>
<td>Hepatic/Renal eGFR &lt;60: do not use</td>
<td>No</td>
<td>5-10 mg daily</td>
</tr>
</tbody>
</table>
SGLT2 Inhibitors

➤ **Advantages:**
  - Potential for weight loss
  - Low risk for hypoglycemia
  - Modest BP lowering

➤ **Disadvantages:**
  - 4-7 fold increase in genital mycotic infections, also increased risk of urinary tract infections
  - increased urination, fluid loss
  - hyperkalemia
  - relatively modest efficacy (↓ A1c by 0.5-1%)
  - no robust long term safety data
  - high cost
Miscellaneous Agents

Colesevelam (Welchol®)
- Bile Acid Sequestrant; Unknown MOA: ? ↓ hepatic glucose production; ? ↑ incretin levels
- Dose: 3.8 g/day
- Efficacy: ↓ A1c by 0.3-0.4%
- GI side effects, including constipation; low efficacy, high cost

Bromocriptine (Cycloset®) – Rapid release
- Ergot derived dopamine agonist; Modulates hypothalamic regulation of metabolism; ↑ insulin sensitivity
- Dose: 4.8 mg/day as monotherapy or combined with SFU
- Efficacy: ↓ A1c by 0.4-.05%
- GI side effects, dizziness/syncope, nausea, fatigue, rhinitis, modest efficacy
INJECTABLE DIABETES MEDICATIONS

GLP-1 Agonists
Amylin Analog
Insulin
GLP-1 Agonists

- exenatide (Byetta®, Bydureon®), liraglutide (Victoza®), albiglutide (Tanzeum®), dulaglutide (Trulicity®)

- **MOA:** ↑ insulin secretion (glucose dependent), ↓ glucagon secretion, slows gastric emptying, and ↑ satiety by activating GLP-1 receptors
GLP-1 Agonists

- **Efficacy**: ↓ A1C by 0.5-1.5 %
- **Advantages**: no hypoglycemia, weight reduction, potential for improved β-cell mass/function, cardiovascular protective effects
- **Disadvantages**: GI side effects (n/v), ↑ risk of pancreatitis, thyroid C-cell hyperplasia and tumors, less robust long-term safety data, high cost
Mechanism of Action

- **↓Appetite**
- **↓Gastric Emptying**
- **↓Glucose Production**
- **↑Insulin Secretion**
- **↓Glucagon Secretion**
- **↑B-cell proliferation**
- **↓B-cell apoptosis**

Endogenous GLP-1 is rapidly degraded by the DPP4 enzyme, so it has a very short half-life (i.e., 1-2 min).
GLP-1 Agonists

Byetta® and Victoza® come in pre-filled pen devices.

Bydureon® requires reconstitution.
<table>
<thead>
<tr>
<th></th>
<th>Byetta®</th>
<th>Victoza®</th>
<th>Bydureon®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>5 mcg SQ BID x 1 month, then 10 mcg twice a day</td>
<td>0.6mg SQ qday x 1 week, then 1.2 mg daily. May increase to 1.8 mg daily.</td>
<td>2 mg SQ q 7 days</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>CrCl &lt;30: do not use</td>
<td>No renal adjustment</td>
<td>CrCl &lt;30: do not use</td>
</tr>
<tr>
<td><strong>CBG effects</strong></td>
<td>Significantly reduces post-prandial blood glucose</td>
<td>Significantly reduces both post-prandial and fasting blood glucose</td>
<td>Significantly reduces both post-prandial and fasting blood glucose</td>
</tr>
<tr>
<td><strong>“Pros”</strong></td>
<td>Weight loss; minimal hypoglycemia</td>
<td>Weight loss; Once daily dosing, minimal hypoglycemia</td>
<td>Weight loss; once weekly dosing; minimal hypoglycemia</td>
</tr>
<tr>
<td><strong>“Cons”</strong></td>
<td>Pronounced GI adverse effects; pancreatitis; renal toxicity</td>
<td>Transient and mild GI adverse effects, pancreatitis,,thyroid carcinoma; renal toxicity</td>
<td>Pancreatitis, thyroid carcinoma; renal toxicity</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$391.52/#30 days</td>
<td>$366.39/#30 days</td>
<td>$443.61/#28 days</td>
</tr>
</tbody>
</table>
GLP-1 Agonists

Head-to-Head Clinical Trials

- Glycemic Control:
  - Liraglutide > ExQW > ExBID

- Nausea/GI Side Effects:
  - ExBID > Liraglutide > ExQW

- All agents associated with low rates of hypoglycemia

- Weight loss:
  - Similar between agents & trials: ~3 kg

Lancet 2009; 374: 39-47
J Clin Endocrinol Metab 2011; 96 (5): 1301-1310
Lancet 2013; 381:117-24
<table>
<thead>
<tr>
<th>GLP-1 agonists</th>
<th>DPP4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulates pharmacological levels of GLP-1</td>
<td>GLP-1 levels dependent on endogenous incretin secretion</td>
</tr>
<tr>
<td>May promote significant weight loss</td>
<td>Weight neutral</td>
</tr>
<tr>
<td>Good glucose-lowering ability, can lower both postprandial and fasting levels (A1C ↓ ~1%)</td>
<td>Moderate glucose-lowering ability; likely to work best in early disease on postprandial levels (A1C ↓ ~0.5%)</td>
</tr>
<tr>
<td>Associated with improvements in CV markers</td>
<td>Minimal impact on CV markers</td>
</tr>
</tbody>
</table>

- Low risk of hypoglycemia
- If also on SFU, may need to reduce dose
- Higher incidence of SE (nausea/vomiting)
- Typically well-tolerated
- Caution if history of gall bladder disease, alcoholism, high TG, or pancreatitis
- No dose titration relative to food intake or ambient blood glucose level
- Expensive, associated with brand name co-pay, may require PA

Adapted from: Diabetes Spectrum. 2011;24(1):26-35
Pramlintide (Symlin®)

**MOA:** slows gastric emptying, ↓ glucagon secretion, ↑ satiety

**Indication:** as an adjunct to mealtime insulin

**Efficacy:** ↓ A1c by 0.5-1%

**Advantages:** ↓ postprandial glucose, weight loss

**Disadvantages:** modest effect, GI effects (n/v), less robust long term safety, frequent dosing, increases daily injection burden, potential for hypoglycemia with insulin use, high cost
Amylin Analog

**Indications:**
- Type 1: as an adjunct to mealtime insulin
- Type 2: as an adjunct to mealtime insulin (with or without concurrent sulfonylurea or metformin)

**Dose:**
- Type 1: 2.5 units (15 mcg) prior to meals; titrate to 10 units (60 mcg) based on tolerability (nausea)
- Type 2: 10 units (60 mcg) initial, increase to 20 units (120 mcg) based on tolerability (nausea)

**Black Block Warning**

Pramlintide can contribute to episodes of severe hypoglycemia. As a result, when initiating pramlintide, the prandial insulin dose needs to be reduced by 50%; with subsequent re-titration if needed.
Adverse Effects

- Severe Hypoglycemia
  - Risk reduced by: appropriate patient selection, careful patient instruction, insulin dose adjustments
- Nausea: 30-40% (dissipates over 1-2 months)
- Decreased appetite
- Anorexia
- Vomiting
- Headache
Contraindications:

- Poor compliance with current insulin regimen
- Poor compliance with blood glucose monitoring
- A1C > 9.0%
- Recurrent severe hypoglycemia requiring assistance during past 6 months
- Hypoglycemia unawareness
- Confirmed gastroparesis diagnosis
- Use of drugs that stimulate gastrointestinal motility
- Pediatric patients
Patient Education:
- Refrigerate unopened pens
- Discard opened pens or vials after 30 days
- Can NOT be mixed with insulin
- Inject subcutaneously in abdomen or thigh
- Separate pramlintide and insulin injections by at least 2 inches
- Only take before meals of >250 cal or >30 grams of CHO
- Do not take if pre-meal BG is low or if meal contains insufficient calories or carbohydrates