Disclosure

NONE
Objectives

To identify different categories of diabetes medications

Understand the pharmacology of the diabetes medications
The Worldwide Diabetes Tsunami
Diabetes Trends Among Adults in the U.S.

2012: Over 218 billion dollars a year!

Estimate in 2050:

~33%!!!!!!
1 of 3 U.S. adults is at high risk of developing type 2 diabetes.

- **DM 29 million**
  - 9.3% of US population

- **Pre-diabetes 86 million**
  - ~33% of US population

- **Unaffected ~200 million**

FBS = 100-125
A1c = 5.7-6.4%

Get the facts about diabetes
Mealtime

Liver

Fat

Gut

Pancreas

Brain

Muscle

↑ Insulin

↓ Glucagon
Fasting

Glucose

Glycerol and Fatty Acids

Amino Acids

Insulin

Glucagon
Old Paradigm: Components of Glycemic Defects in Diabetes

- ↑ Insulin demand
- ↑ Insulin Resistance
- ↓ Insulin supply
- ↓ Beta Cell Function

Hyperglycemia
The Multifactorial Pathogenesis of Type 2 Diabetes


Hyperglycemia

- Islet β cell: Decrease Insulin Secretion
- Islet-α cell: Increased Glucagon Secretion
- Increased HGP
- Decreased Incretin Effect
- Increased Lipolysis
- Increased Renal Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction
- Increased Glucagon Secretion
Pathophysiologic Progression of T2DM and Vascular Complications

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2DM = type 2 diabetes mellitus.

<table>
<thead>
<tr>
<th>Target</th>
<th>Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>• General diabetic population</td>
</tr>
<tr>
<td>Lower than &lt;7%</td>
<td>• Short duration of diabetes</td>
</tr>
<tr>
<td></td>
<td>• Long life expectancy</td>
</tr>
<tr>
<td></td>
<td>• No significant CVD</td>
</tr>
<tr>
<td></td>
<td>• No significant hypoglycemia or other adverse effects of treatment</td>
</tr>
<tr>
<td>Less stringent&gt;7% (e.g. 7.5-8 or higher)</td>
<td>• History of severe hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>• Disabilities that prevent compliance with BG testing, etc.</td>
</tr>
<tr>
<td></td>
<td>• Limited life expectancy</td>
</tr>
<tr>
<td></td>
<td>• Advanced microvascular or macrovascular complications (e.g. s/p stroke)</td>
</tr>
<tr>
<td></td>
<td>• Extensive co morbid conditions</td>
</tr>
<tr>
<td></td>
<td>• Longstanding diabetes in which the general goal has been difficult to attain despite DSME, appropriate glucose monitoring, and effective doses of medication</td>
</tr>
</tbody>
</table>
Difficulties in Achieving A1c Targets

Challenges:

- Late diagnosis and initiation of therapy
- Therapeutic inertia
- Lack of lifestyle intervention
- Secondary drug failure (loss of insulin reserve)
- Role of postprandial glucose in failure
- Adverse events associated with diabetes drugs
- Complexity of care (inadequate time and resources)

Adapted from A. Garber
Lifestyle Modification:
Good Nutrition and Exercise
Lifestyle Modification:
Good Dietary Habits Are Essential
Behavioral Intervention: Nutrition
Increasing U.S. Portion Sizes: French Fries

20 Years Ago

210 Calories
2.4 ounces

Today

How many calories are in these fries?

610 Calories, 6.9 ounces
Calorie Difference = 400 Calories

How to burn* 400 calories:
Walk 2 hr 20 Minutes

*Based on 130 pound person
Lifestyle Modification:
Exercise Helps Control Glucose
Behavioral Intervention: Exercise

Go to the gym

Walk the dog
Treatment of Type 2 Diabetes - Too Many Drugs
Which Ones Should One Use and When?
Non-Insulin Agents

CURRENT DIABETES MEDICATIONS
9 FDA Approved Classes of Oral Medications for Type 2 Diabetes

1. **Biguanide**: metformin, metformin ER, Glucophage, glumetza (first line of therapy unless contraindicated)

2. **Sulfonylureas**: glyburide, glimepiride (amaryl), glipizide

3. **Meglitinides**: repaglinide (prandin), nateglinide (starlix)

4. **Glitazones (TZDS)**: Pioglitazone (actos)

5. **DPP-4 Inhibitors**: sitagliptin (Januvia), saxagliptin (onglyza), linagliptin (tradjenta), alogliptin (nesina)

6. **SGLT-2 inhibitors**: canagliflozin (invokana), dapagliflozin (farxiga), empagliflozin (jardiance)

7. **Alpha-glucosidase inhibitors**: acarbose (precose), miglitol (glyset)

8. **Bile acid sequestrant**: colesevemal (welchol)

9. **Dopamine receptor agonist**: bromocriptine (parlodel)
Injectables for Diabetes

1. GLP-1 Receptor Agonists: exenatide (byetta), exenatide ER (bydureon), liraglutide (victoza), dulaglutide (trulicity), albiglutide (tanzeum).

2. Amylinomimetic: pramlintide (symlin)

Insulins

1. Intermediate acting: NPH, Humulin R U-500
2. Basal or Long acting Insulin: glargine 100 units/ml (lantus), glargine 300 units/ml (toujeo), detemir (levemir), degludec (tresiba)
3. Bolus or Rapid acting Insulin: aspart (novolog), lispro (humalog), glulisine (apidra)
4. Short acting insulin: regular insulin
5. Pre-Mix Insulin: Humulin 70/30, Novolin 70/30, Novolog 70/30, Humalog 75/25, Humalog 50/50
6. Inhaled Insulin: Technosphere Inhaled insulin (afrezza)
Ten Factors to Consider When Selecting a Drug for T2DM

1) **Efficacy**: What % A1c reduction expected
2) **Safety**: Hypoglycemic Potential
3) **Effect on Weight**: Gain, neutral or loss
4) **Durability**: How long does the drug keep working
5) **Renal Function**: Dose adjustments; contraindications
6) **Cardiovascular Risk**: Increase, neutral or decrease
7) **Effect on Lipids**: Positive, negative or neutral
8) **Administration**: Oral or injectable; qd vs. bid
9) **Synergy**: With other diabetes drugs
10) **Cost**: Affordability (insurance tier; generic option)
New Paradigm: Ominous Octet

**Pancreatic Beta Cell**
Decreased Insulin Secretion

**Pancreatic Alpha Cell**
Increased Glucagon Secretion

**Muscle**
Decreased glucose uptake

**Adipose (fat)**
Increased free fatty acid production

**Brain**
Neurotransmitter dysfunction

**Liver**
Increased endogenous glucose production

**Digestive tract**
Decreased incretin effect

**Kidney**
Increased glucose reabsorption

**Hyperglycemia**

DeFronzo RA. *Diabetes*. 2009;58:773-795
Metformin

Mechanism
- Inhibit hepatic gluconeogenesis (primary effect)
- Decreases intestinal absorption of glucose
- Improves insulin sensitivity by improving peripheral glucose uptake

Renally cleared

XR tablets will occasionally be eliminated in feces intact
Metformin: Available Meds

- Metformin, Glucophage, Glumetza, Fortamet, Riomet (a liquid version)
  - May be XR or ER

With SU
- Metaglip (glipizide/metformin)
- Glucovance (glyburide/metformin)

With TZD
- ActoPlus Met (pioglitazone/metformin)
- Avandamet (rosiglitazone/metformin)

With GLN
- Prandimet (repaglinide/metformin)

With SGLT2
- Synjardy (empagliflozin/metformin)
- Xigduo (dapagliflozin/metformin)
- Invokamet (canagliflozin/metformin)

With DPP4
- Janumet (sitagliptin/metformin)
- Jentadueto (linagliptin/metformin)
- Kombiglyze (saxagliptin/metformin)
- Kazano (alogliptin/metformin)
Pharmacologically Targeting the Ominous Octet

Pancreatic Beta Cell
Decreased Insulin Secretion

Muscle
Decreased glucose uptake

Adipose (fat)
Increased free fatty acid production

Brain
Neurotransmitter dysfunction

Liver
Increased endogenous glucose production

Pancreatic Alpha Cell
Increased Glucagon Secretion

Kidney
Increased glucose reabsorption

Digestive tract
Decreased incretin effect

Metformin

DeFronzo RA. Diabetes. 2009;58:773-795
Drug of choice for T2DM, and PCOD
- Metformin in safe to use in stable CHF
- Okay to use the drug if GFR 30-45, but reduce dose
- Metformin reduces B-12 absorption
  - B-12 deficiency exacerbates diabetic polyneuropathy
  - Effect is dependent on dosage and length of time drug taken
  - Screen with B-12, methylmalonic acid and homocysteine levels
  - Patients on metformin with B-12 deficiency should be treated
- Numerous early-stage clinical trials are currently under way to investigate metformin’s potential to prevent an array of cancers, including colorectal, prostate, endometrial, and breast cancer.
Sulfonylureas (SU)

Stimulate insulin release from beta cells
Long duration of action: taken once or twice daily
Hepatic metabolism with active metabolites that are renally cleared

Glipizide (Glucotrol)
  ◦ Metaglip (glipizide/metformin)

Glyburide (Diabeta, Micronase, Glynase)
  ◦ Glucovance (glyburide/metformin)

Glimepiride (Amaryl)
  ◦ Duetact (pioglitazone/glimepiride)
  ◦ Avandaryl (rosiglitazone/glimepiride)
Meglitinides (GLN)

Stimulate insulin release from beta cells via different receptor than the SU

Have rapid onset and short duration, so taken before each meal

Hepatic metabolism with active metabolites that are renally cleared

Repaglinide (Prandin)
  ◦ Prandimet (repaglinide/metformin)

Nateglinide (Starlix)
Pharmacologically Targeting the Ominous Octet

DeFronzo RA. Diabetes. 2009;58:773-795

Muscle
- Decreased glucose uptake

Adipose (fat)
- Increased free fatty acid production

Brain
- Neurotransmitter dysfunction

Pancreatic Beta Cell
- Decreased Insulin Secretion

Liver
- Increased endogenous glucose production

Digestive tract
- Decreased incretin effect

Kidney
- Increased glucose reabsorption

Pancreatic Alpha Cell
- Increased Glucagon Secretion

Metformin

SU, GLN
TZDs

Improve insulin sensitivity by acting on adipose tissue, muscle, and the liver

Hepatic metabolism

Pioglitazone (Actos)
  ◦ ActoPlus Met (pioglitazone/metformin)
  ◦ Duetact (pioglitazone/glimepiride)
  ◦ Oseni (pioglitazone/alogliptin)

Rosiglitazone (Avandia)
  ◦ Avandamet (rosiglitazone/metformin)
  ◦ Avandaryl (rosiglitazone/glimepiride)
Pharmacologically Targeting the Ominous Octet

Muscle
- Decreased glucose uptake

Adipose (fat)
- Increased free fatty acid production

Brain
- Neurotransmitter dysfunction

Kidney
- Increased glucose reabsorption

Digestive tract
- Decreased incretin effect

Liver
- Increased endogenous glucose production

Pancreatic Beta Cell
- Decreased Insulin Secretion

Pancreatic Alpha Cell
- Increased Glucagon Secretion

T2D

SU, GLN

Metformin, T2D
Mechanism of Action of DPP-4 Inhibitors

Ingestion of food leads to the release of active incretins GLP-1 and GIP from the GI tract. These incretins then stimulate the pancreas to release insulin, which helps in glucose uptake by peripheral tissue, reducing fasting and postprandial glucose levels. In contrast, DPP-4 inhibitors (Alogliptin, Linagliptin, Saxagliptin, Sitagliptin) do not bind to DPP-4 enzyme, preventing the degradation of inactive GLP-1 and GIP, thus maintaining glucose levels.

GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide

DPP4 Inhibitors

**FDA-APPROVED AGENTS**

**Januvia (sitagliptin)**
- 25, 50, & 100 mg, adjust based on GFR

**Tradjenta (linagliptin)**
- 5 mg regardless of GFR

**Onglyza (saxagliptin)**
- 2.5 & 5 mg based on GFR

**Nesina (alogliptin)**
- 6.25, 12.5, & 25 mg based on GFR

**KEY FEATURES**

Once daily pill
Well tolerated
Increase endogenous GLP1 and GIP levels
Increase glucose-dependent insulin secretion
Suppress glucagon production

DPP4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic polypeptide; GLP1, glucagon-like peptide 1.
## Safety Considerations with DPP4 Inhibitors

<table>
<thead>
<tr>
<th>GI adverse events</th>
<th>• Minimal</th>
</tr>
</thead>
</table>
| **Pancreatitis**  | • Pancreatitis has been reported with postmarketing use of some of incretin agents, although no causal relationship has been established  
• Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents  
• Labeling for all incretins states these agents should be immediately discontinued if pancreatitis is suspected |
| **Pancreatic cancer** | • Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents  
• Further assessments required from long duration-controlled studies or epidemiological databases |
| **Renal impairment** | • Kidney function monitoring and dose reduction required for alogliptin, saxagliptin, and sitagliptin when used in patients with moderate-to-severe renal impairment  
• Linagliptin does not require dose adjustment or periodic monitoring of drug-related kidney function |
| **CHF** | • Potentially increased risk of congestive heart failure hospitalization with alogliptin and saxagliptin |

Pharmacologically Targeting the Ominous Octet

Muscle
- Decreased glucose uptake

Adipose (fat)
- Increased free fatty acid production

Brain
- Neurotransmitter dysfunction

Pancreatic Beta Cell
- Decreased Insulin Secretion
- SU, GLN, GLP1, DPP4

Pancreatic Alpha Cell
- Increased Glucagon Secretion
- GLP1, DPP4

Liver
- Increased endogenous glucose production
- Metformin, TZD, GLP1, DPP4

Digestive tract
- Decreased incretin effect

Kidney
- Increased glucose reabsorption

DeFronzo RA. Diabetes. 2009;58:773-795
Response of Insulin and Glucagon After a Meal in Persons Without Diabetes


Photomicrograph courtesy of Michael Sarras, PhD, Rosalind Franklin University of Medicine and Science.
Definition of an Incretin

In • cre • tin

Intestine  Secretion  Insulin

Gut-derived factors that increase glucose-stimulated insulin secretion

• Is a substance (hormone) originating in the GI tract and released during nutrient absorption
• Augments insulin secretion at physiologic concentrations
• Insulinotropic effects are glucose-dependent
• Some incretins also decrease glucagon secretion
• The most important incretin is GLP-1 (glucagon-like peptide)

The Incretin Effect Demonstrated as the Response to Oral vs. IV Glucose

Mean ± SE; N=6; *P≤0.05; 01-02=glucose infusion time.

Glucagon-Like Peptide1 Receptor Agonists

- Increase glucose dependent insulin secretion
- Decrease hepatic glucose production via glucagon suppression
- Increase satiety
- Slow gastric emptying

*This effect is postulated to be mediated through the central nervous system
See accompanying Prescribing Information and safety information included in this presentation
The Incretin System:
A Regulator of Post-Prandial Glucose Metabolism

GLP-1 = glucagon-like peptide-1; GIP = glucose-dependent insulinotropic polypeptide; DPP-4 = dipeptidyl peptidase-4

GLP-1 and GIP: Incretin Hormones

**GLP-1**
- Released from L cells of the ileum with meals.
- Effects
  - Stimulates insulin secretion
  - Suppresses glucagon secretion
  - Delays gastric emptying
  - Enhances satiety
- Rapidly degraded by an enzyme known as protease dipeptidyl peptidase IV (DPP-IV)
- GLP-1 levels reduced in IGT and T2DM

**GIP**
- Released from K cells of the duodenum with meals
- Similar actions as GLP-1 but no effect on satiety or weight
- GIP levels also reduced in IGT and T2DM
GLP-1 Receptor Agonists

**Tanzeum (albiglutide)** will be discontinued by July 2018

**Byetta (exenatide)**
- Twice a Day
- Two Doses (5 & 10 mcg)

**Victoza (liraglutide)**
- Once a Day
- Three Doses (0.6, 1.2, 1.8 mg)

**Bydureon (exenatide)**
- Once a Week
- One Dose (2 mg)

**Ozempic (semiglutide)**
- Once a week
- Two Doses (0.5 and 1 mg)

**Trulicity (dulaglutide)**
- Once a Week
- Two Doses (0.75 and 1.5 mg)
Potential Benefits of Combining GLP-1-based Therapies with Insulin

GLP-1-based therapies

- Insulin secretion (glucose-dependent)
- Beta-cell preservation
- Glucagon secretion (glucose-dependent)
- Risk of hypoglycaemia
- Body weight
- PPG levels
- Energy intake
- Satiety
- GI tract motility

Basal insulin therapy

- Insulin levels (insulin supplementation)
- Beta-cell rest
- Corrects glucotoxicity
- Relies on endogenous prandial insulin response
- Moderate risk of hypoglycemia
- Weight gain
- FPG levels

GLP=glucagon-like peptide-1; GI=gastrointestinal.
GLP-1 and Insulin Combos
Once Daily Injections

**SOLIQUA 100/33**

Glargine / Lixisenitide

Delivers 15 – 60 units of glargine along with 5 – 20 mg of lixisenatide

**XULTOPHY 100/3.6**

Tresiba (degludec) and Victoza (liraglutide)

Delivers 10 – 50 units of degludec and 0.36 – 1.8 mg of liraglutide
Pharmacologically Targeting the Ominous Octet

DeFronzo RA. Diabetes. 2009;58:773-795

Muscle
- Decreased glucose uptake

Liver
- Increased endogenous glucose production

Adipose (fat)
- Increased free fatty acid production

Digestive tract
- Decreased incretin effect

Brain
- Neurotransmitter dysfunction

Kidney
- Increased glucose reabsorption

Pancreatic Beta Cell
- Decreased Insulin Secretion
  - SU, GLN, GLP1

Pancreatic Alpha Cell
- Increased Glucagon Secretion
  - TZD

GLP1

Metformin, TZD, GLP1
## Safety Considerations with GLP1 Receptor Agonists

### GI adverse events
- Common
- Usually dose dependent and transient
- Usually reduced with dose titration

### Pancreatitis
- Pancreatitis has been reported with postmarketing use of some of incretin agents, although no causal relationship has been established
- Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents
- Labeling for all incretins states these agents should be immediately discontinued if pancreatitis is suspected
- Labeling for GLP1 receptor agonists suggests consideration of other therapies for patients with a history of pancreatitis

### Pancreatic cancer
- Extensive review by FDA of studies involving >80,000 patients has not uncovered reliable evidence of increased pancreatic risk with incretins vs other agents
- Further assessments required from long duration-controlled studies or epidemiological databases

### Medullary thyroid cancer
- Animal data showed an increased incidence of C-cell tumors with liraglutide and exenatide ER treatment, but confirmatory population studies are lacking
- Labeling for albiglutide, dulaglutide, exenatide ER, and liraglutide:
  - Patients should be counseled regarding medullary thyroid carcinoma and the signs/symptoms of thyroid tumors
  - Contraindicated in patients with personal/family history of MTC or multiple endocrine neoplasia syndrome type 2

### Renal impairment
- Renal impairment has been reported postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration. Use caution when initiating or escalating doses in patients with renal impairment. Exenatide should not be used in patients with severe renal insufficiency or ESRD. Liraglutide was found to be safe in patients with moderate renal impairment and may confer a beneficial effect.
The Newest Diabetes Drug Class

SGLT-2 Inhibitors
Physiologic Renal Handling of Glucose  
(Reabsorption in the Proximal Tubule)

Two sodium glucose transport proteins are responsible for glucose reabsorption:
- SGLT 1 – 10%
- SGLT 2 – 90%

In normal individuals, almost all of the filtered glucose is reabsorbed in the proximal tubule so there should never be any glucose in the urine.

*Nature Reviews Drug Discovery* | AOP, published online 28 May 2010
Renal Glucose Reabsorption In Type 2 Diabetes With SGLT-2 Inhibition

Glomerulus

Proximal Convoluted Tubule

Early

Distal

Decreased glucose reabsorption into systemic circulation

Glucose

SGLT2

SGLT2 inhibitor

SGLT1

Glucose in urine

Adapted with permission from Abdul-Ghani, DeFronzo RA.
SGLT2 Inhibitors

Increase glycosuria (and diuresis) via inhibition of SGLT2 in the proximal tubule

Increase glucagon, which is unwanted and may be why these drugs increase risk of DKA

Ineffective with CKD

Invokana (canagliflozin)
  ◦ Invokamet (canagliflozin/metformin)

Jardiance (empagliflozin)
  ◦ Synjardy (empagliflozin/metformin)
  ◦ Glyxambi (empagliflozin/linagliptin)

Farxiga (dapagliflozin)
  ◦ Xigduo (dapagliflozin/metformin)
SGLT2 Inhibitors

QTERN (Dapagliflozin/Saxagliptin)
10 mg/ 5 mg tabs

Recently approved
Steglatro
(Ertugliflozin) 5 mg, 15 mg tabs
SGLT2 Inhibitors

Available meds: all once daily pills
- Invokana (canagliflozin), 100 & 300 mg
- Jardiance (empagliflozin), 10 & 25 mg
- Farxiga (dapagliflozin), 5 & 10 mg

Lower A1C 0.5 – 1.1%
Decrease weight 2 – 3 kg in 12 weeks
Decrease BP

GFR must be > 45 for Invokana and Jardiance and > 60 for Farxiga

Typical side effects
- Mycotic infections (women, uncircumcised men)
- Polyuria
- UTIs
- Dehydration (dizziness, worsened renal func, etc)
SGLT2 Inhibitors

CV Benefit
- Jardiance and Invokana show reduced CV death and decreased CHF hospitalization
- Farxiga’s trial still pending
- I presume this is a class effect

Renal Protection: seen with both Jardiance and Invokana
- ? Class Effect

Amputations
- Seen in increased frequency with Invokana
- Avoid this drug class in anyone with active foot ulcers or high risk for foot ulcers (my opinion)

DKA: May be euglycemic (delaying diagnosis)
- Avoid in insulin deficient patients. Don’t use in a patient who needs insulin but is refusing insulin therapy
## Safety Considerations with SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary infection</td>
<td>• Increased incidence; patients should be monitored and treated if necessary</td>
</tr>
<tr>
<td>Increased LDL-C</td>
<td>• Small increases in LDL-C have been observed in clinical trials</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>• Increased incidence of bladder cancers in patients receiving dapagliflozin</td>
</tr>
<tr>
<td></td>
<td>• Dapagliflozin labeling recommends not using in patients with active bladder cancer and should be used with caution in patients with a history of bladder cancer</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>• Monitor kidney function during therapy, especially in patients with GFR &lt;60 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Bone fractures</td>
<td>• Increased incidence of bone fractures in canagliflozin and dapagliflozin clinical trials</td>
</tr>
<tr>
<td></td>
<td>• Canagliflozin labeling includes specific warning about bone fractures</td>
</tr>
<tr>
<td>DKA</td>
<td>• Potentially increased risk of diabetic ketoacidosis in patients with insulin deficiency and/or those undergoing acute metabolic stress</td>
</tr>
</tbody>
</table>

Pharmacologically Targeting the Ominous Octet

Muscle
- Decreased glucose uptake

Liver
- Increased endogenous glucose production

Adipose (fat)
- Increased free fatty acid production

Digestive tract
- Decreased incretin effect

Brain
- Neurotransmitter dysfunction

Kidney
- Increased glucose reabsorption

Pancreatic Beta Cell
- Decreased Insulin Secretion

Pancreatic Alpha Cell
- Increased Glucagon Secretion

- SU, GLN, GLP1, DPP4
- TZD
- Metformin, TZD, GLP1, DPP4
- GLP1
- GLP1, DPP4
- SGLT2

DeFronzo RA. Diabetes. 2009;58:773-795
Alpha Glucosidase Inhibitors (AGi)

Inhibit the GI tract alpha glucosidases that convert complex polysaccharide carbohydrates into monosaccharides

This slows absorption of glucose from the gut

Metabolism varies. Contraindicated with CKD

Precose (acarbose)

Glyset (miglitol)
Pharmacologically Targeting the Ominous Octet

DeFronzo RA. Diabetes. 2009;58:773-795

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- Decreased Insulin Secretion

- SU, GLN, GLP1, DPP4

Pancreatic Alpha Cell
- Increased Glucagon Secretion

- GLP1, DPP4

Metformin, TZD, GLP1, DPP4

GLP1, AGi

SGLT2
Amylin

Secreted with insulin
Amylin

- Slows gastric emptying
- Increases satiety
- Suppresses glucagon secretion
- Secreted with insulin
Symlin (pramlintide)

Amylin analogue (co-secreted with insulin)

Effects similar to GLP1 except no increase in insulin secretion
  ◦ Primarily reduces post-prandial glucose and increases satiety

For type 1 and type 2 diabetics on insulin

Injection prior to each meal
Pharmacologically Targeting the Ominous Octet

DeFronzo RA. Diabetes. 2009;58:773-795

Muscle
- Decreased glucose uptake

Liver
- Increased endogenous glucose production
  - Metformin, TZD, GLP1, DPP4, Pram

Adipose (fat)
- Increased free fatty acid production
  - TZD

Digestive tract
- Decreased incretin effect
  - GLP1, AGi

Brain
- Neurotransmitter dysfunction
  - GLP1, Pram

Kidney
- Increased glucose reabsorption
  - SGLT2

Pancreatic Beta Cell
- Decreased Insulin Secretion
  - SU, GLN, GLP1, DPP4

Pancreatic Alpha Cell
- Increased Glucagon Secretion
  - GLP1, DPP4, Pram
Bromocriptine is a dopamine agonist, usually used to treat hyperprolactinemia and Parkinsons.

A quick release version can be taken in the morning.

Reduces glucose, but exact mechanism uncertain.

Cycloset (bromocriptine QR)
Pharmacologically Targeting the Ominous Octet

**Muscle**
- Decreased glucose uptake

**Liver**
- Increased endogenous glucose production
  - Metformin, TZD, GLP1, DPP4, Pram

**Adipose (fat)**
- Increased free fatty acid production
  - TZD

**Digestive tract**
- Decreased incretin effect
  - GLP1, AGi

**Brain**
- Neurotransmitter dysfunction
  - GLP1, Pram, BQR

**Kidney**
- Increased glucose reabsorption
  - SGLT2

**Pancreatic Beta Cell**
- Decreased Insulin Secretion
  - SU, GLN, GLP1, DPP4

**Pancreatic Alpha Cell**
- Increased Glucagon Secretion
  - GLP1, DPP4, Pram

DeFronzo RA. *Diabetes*. 2009;58:773-795
Welchol (Colesevelam)

Bile acid sequestrant usually used for hypercholesterolemia

Exact mechanism unknown

Not hepatically or renally metabolized

Welchol (colesevelam)
Pharmacologically Targeting the Ominous Octet

**Muscle**
- Decreased glucose uptake

**Liver**
- Increased endogenous glucose production

**Adipose (fat)**
- Increased free fatty acid production

**Digestive tract**
- Decreased incretin effect

**Brain**
- Neurotransmitter dysfunction

**Kidney**
- Increased glucose reabsorption

**Pancreatic Beta Cell**
- Decreased insulin secretion

**Pancreatic Alpha Cell**
- Increased glucagon secretion

- **TZD**
- **SU, GLN, GLP1, DPP4**
- **Metformin, TZD, GLP1, DPP4, Pram**
- **GLP1, BQR**
- **GLP1, DPP4, Pram**
- **GLP1, AGi, COLSVM**
- **SGLT2**

DeFronzo RA. *Diabetes*. 2009;58:773-795
## Noninsulin Agents Available for T2D

<table>
<thead>
<tr>
<th>Class</th>
<th>Primary Mechanism of Action</th>
<th>Agent(s)</th>
<th>Available as</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>• Delay carbohydrate absorption from intestine</td>
<td>Acarbose</td>
<td>Precose or generic Glyset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Miglitol</td>
<td></td>
</tr>
<tr>
<td>Amylin analogue</td>
<td>• Decrease glucagon secretion</td>
<td>Pramlintide</td>
<td>Symlin</td>
</tr>
<tr>
<td></td>
<td>• Slow gastric emptying</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increase satiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanide</td>
<td>• Decrease liver glucose production</td>
<td>Metformin</td>
<td>Glucophage or generic</td>
</tr>
<tr>
<td></td>
<td>• Increase glucose uptake in muscle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>• Decrease liver glucose production?</td>
<td>Colesevelam</td>
<td>WelChol</td>
</tr>
<tr>
<td></td>
<td>• Increase incretin levels?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP4 inhibitors</td>
<td>• Increase glucose-dependent insulin secretion</td>
<td>Alogliptin</td>
<td>Nesina</td>
</tr>
<tr>
<td></td>
<td>• Decrease glucagon secretion</td>
<td>Linagliptin</td>
<td>Tradjenta</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saxagliptin</td>
<td>Onglyza</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td>Dopamine-2 agonist</td>
<td>• Activates dopaminergic receptors</td>
<td>Bromocriptine</td>
<td>Cycloset</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>• Increase insulin secretion</td>
<td>Nateglinide</td>
<td>Starlix or generic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repaglinide</td>
<td>Prandin</td>
</tr>
</tbody>
</table>

DPP4, dipeptidyl peptidase; HGP, hepatic glucose production.


<table>
<thead>
<tr>
<th>Class</th>
<th>Primary Mechanism of Action</th>
<th>Agent(s)</th>
<th>Available as</th>
</tr>
</thead>
</table>
| GLP1 receptor agonists | • Increase glucose-dependent insulin secretion  
                            • Decrease glucagon secretion  
                            • Slow gastric emptying  
                            • Increase satiety                                                               | Albiglutide  
                            Dulaglutide  
                            Exenatide  
                            Exenatide XR  
                            Liraglutide  
                            Semaglutide                                                              | Tanzeum  
                            Trulicity  
                            Byetta  
                            Bydureon  
                            Victoza  
                            Ozempic                                                                         |
| SGLT2 inhibitors       | • Increase urinary excretion of glucose                                                      | Canagliflozin  
                            Dapagliflozin  
                            Empagliflozin                                                                 | Invokana  
                            Farxiga  
                            Jardiance                                                                             |
| Sulfonylureas          | • Increase insulin secretion                                                                | Glimepiride  
                            Glipizide  
                            Glyburide                                                                 | Amaryl or generic  
                            Glucotrol or generic  
                            Diaβeta, Glynase, Micronase, or generic |
| Thiazolidinediones     | • Increase glucose uptake in muscle and fat  
                            • Decrease HGP                                                                       | Pioglitazone  
                            Rosiglitazone                                                                    | Actos  
                            Avandia                                                                         |
## Fixed-Dose Oral Combination Agents for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Class</th>
<th>Added Agent</th>
<th>Available as</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4 inhibitor + SGLT-2 inhibitor</td>
<td>Linagliptin + empagliflozin</td>
<td>Glyxambi</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin + dapagliflozin</td>
<td>Qtern</td>
</tr>
<tr>
<td>Metformin + DPP4 inhibitor</td>
<td>Alogliptin</td>
<td>Kazano</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>Jentadueto</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>Janumet</td>
</tr>
<tr>
<td>Metformin + glinide</td>
<td>Repaglinide</td>
<td>Prandinmet</td>
</tr>
<tr>
<td>Metformin + SGLT2 inhibitor</td>
<td>Canagliflozin</td>
<td>Invokamet</td>
</tr>
<tr>
<td></td>
<td>Dapagliflozin</td>
<td>Xigduo XR</td>
</tr>
<tr>
<td>Metformin + sulfonylurea</td>
<td>Glipizide</td>
<td>Metaglip and generic</td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td>Glucovance and generic</td>
</tr>
<tr>
<td>Metformin + thiazolidinedione</td>
<td>Pioglitazone</td>
<td>ACTOplus Met</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone*</td>
<td>Avandamet</td>
</tr>
<tr>
<td>Thiazolidinedione + DPP4 inhibitor</td>
<td>Pioglitazone + alogliptin</td>
<td>Oseni</td>
</tr>
<tr>
<td>Thiazolidinedione + sulfonylurea</td>
<td>Pioglutazone</td>
<td>Duetact</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td>Avandaryl</td>
</tr>
</tbody>
</table>
Insulin

DIABETES MEDICATIONS UPDATE
Benefits of Insulin Therapy for Type 2 Diabetes

- Biologic replacement of deficient hormone
- High safety profile
- Easy to titrate
- No contraindications
- No dose limits
- Therapy will ↓ A1c to < 7% in most cases
- Facilitates “β-cell rest”

- Corrects hyperglycemia and reduces glucotoxicity
- Increases glycolysis and reduces production of oxidative stressors
- Inhibits FFA production
- Improves endothelial dysfunction (antioxidant)
- Increases vasodilatation and slightly lowers BP
- Reduces CRP and cytokines (anti-inflammatory)
- May be antithrombotic

When To Start Insulin in T2DM

• When combination oral/injectable agents become inadequate
• Unacceptable side effects of other agents
• Patient with advanced hepatic or renal disease
• Special circumstances (i.e. steroids, infection, pregnancy)
• Patient with hyperglycemia in the hospital
• “Severely” uncontrolled diabetes*

*Defined as fasting glucose > 250 mg/dl, random glucose > 300 mg/dl, A1C >10%, ketonuria, or symptomatic (polyuria, polydipsia, and weight loss) After glucose controlled, oral agents can be added and insulin withdrawn if preferred.

<table>
<thead>
<tr>
<th>Type</th>
<th>Basal Insulins</th>
<th>Prandial Insulins</th>
<th>Premixed Insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humulin</td>
<td>U-100 NPH</td>
<td>U-100 regular human insulin</td>
<td>U-100 70/30</td>
</tr>
<tr>
<td>Novolin</td>
<td></td>
<td>U-500 regular human insulin</td>
<td></td>
</tr>
<tr>
<td>Relion</td>
<td></td>
<td>Afrezza: inhaled insulin</td>
<td></td>
</tr>
<tr>
<td><strong>Analog</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>U-100 Lantus (glargine)</td>
<td></td>
<td>U-100 Humalog (lispro)</td>
<td></td>
</tr>
<tr>
<td>U-100 Basaglar (glargine)</td>
<td></td>
<td>U-100 Novolog (aspart)</td>
<td></td>
</tr>
<tr>
<td>U-100 Levemir (detemir)</td>
<td></td>
<td>U-100 Apidra (glulisine)</td>
<td></td>
</tr>
<tr>
<td>U-100 Tresiba (degludec)</td>
<td></td>
<td>U-200 Humalog (lispro)</td>
<td></td>
</tr>
<tr>
<td>U-200 Tresiba (degludec)</td>
<td></td>
<td>U-100 Fiasp (aspart + Vit B3)</td>
<td></td>
</tr>
<tr>
<td>U-300 Toujeo (glargine)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analogue insulins are associated with less hypoglycemia than human insulins, although these differences are not always statistically significant.
# Pharmacokinetics of Available Insulins

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal</td>
<td>NPH</td>
<td>2-4</td>
<td>4-10</td>
<td>10-16</td>
</tr>
<tr>
<td>Glargine</td>
<td>~1-4</td>
<td>No pronounced peak*</td>
<td>Up to 24†</td>
<td>Less nocturnal hypoglycemia compared to NPH</td>
</tr>
<tr>
<td>Detemir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degludec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Basal-Prandial | Regular U-500 | ≤0.5 | ~2-3 | 12-24 | • Inject 30 min before a meal  
• Indicated for highly insulin resistant individuals  
• Use caution when measuring dosage to avoid inadvertent overdose |
| Prandial | Regular | ~0.5-1 | ~2-3 | Up to 8 | • Must be injected 30-45 min before a meal  
• Injection with or after a meal could increase risk for hypoglycemia |
| | Aspart Glulisine Lispro | | | | • Can be administered 0-15 min before a meal  
• Less risk of postprandial hypoglycemia compared to regular insulin |
| | Inhaled insulin | <0.5 | ~0.5-2.5 | ~3-5 | |

* Exhibits a peak at higher dosages.  
† Dose-dependent.  
NPH, Neutral Protamine Hagedorn.

Long Acting Insulin Action Profiles

- NPH insulin (12–16h)
- Insulin glargine U100 (~24h)
- Insulin glargine U300 (~32h)
- Insulin degludec U100 and U200 (~42h)
- Insulin detemir (~20–24h)

GIR (mg/kg per min)

Time (h)
Short Acting Insulin Action Profiles

- Regular insulin
- Rapid-acting insulin aspart
- Insulin aspart, insulin lispro and insulin glulisine
A Recommendation for Starting and Adjusting Basal Insulin

Bedtime or morning long-acting insulin OR
Bedtime intermediate-acting insulin
Daily dose: 0.1-0.2 u/kg

Check FBG daily

Increase dose by 2 units every 3 days until FPG is 70-130 mg/dL
If FPG is >180 mg/L, increase dose by 4 units every 3 days.

Continue regimen and check A1C every 3 months

In the event of hypoglycemia or FPG level <70 mg/dL:
Reduce bedtime insulin dose by 4 units, or by 10% if >40 units.

FBG=fasting blood glucose
FPG=fasting plasma glucose

When is Basal Insulin Alone is Not Enough?

When A1C values are still not at target AND…

- Basal insulin dose titrated to 0.4-0.6 units/kg/day
- Fasting BG levels at or approaching target
- Post-prandial BG values remain above target

BG=blood glucose
Algorithm for Adding/Intensifying Insulin

Start basal (long-acting insulin)

- **HbA₁c <8%**
  - Total daily dose 0.1-0.2 U/kg
  - Insulin titration every 2-3 days to reach glycemic goal

- **HbA₁c >8%**
  - Total daily dose 0.2-0.3 U/kg

Intensify (prandial control)

- Add GLP-1 RA or DPP-4-I
- Add prandial insulin
  - Total daily dose: 0.3-0.5 U/kg
  - 50% basal analog
  - 50% prandial analog
  - Less desirable: NPH and regular insulin or premixed insulin

Glycemic control not at goal

- Insulin titration every 2-3 days to reach glycemic goal

What’s New With Insulin

Ultra-rapid insulin
Biosimilars
More concentrations
Inhaled insulins
Patch delivery device
Fiasp (aspart)

Ultra rapid acting insulin
Aspart (Novolog) with niacinamide (vitamin B3) added
Approved by FDA
Fiasp (aspart + B3) vs Novolog (aspart)

Novorapid is the European and Canadian tradename for Novolog (aspart)
What’s New With Insulin

- Ultra-rapid insulin
- Biosimilars
- More concentrations
- Inhaled insulins
- Patch delivery device
Generic vs Biosimilar

**GENERIC**

Copies of brand name drugs with the same chemical structure and active ingredient. Are the same in regards to dosage form, safety, strength, route of administration, performance characteristics, and intended use.

Generic and brand are bioequivalent and can be substituted for one another without intervention of HCP.

**BIOSIMILAR**

Biologic products made from living organisms, highly similar to reference product. Undergoes thorough structural and functional characterization of the product.

Intended to produce the same effects.

Not identical copies of biologic products and cannot be substituted without authorization of HCP.
Biosimilar Glargine

Original product: Lantus
  ◦ Available in vials and pens

Biosimilar product: Basaglar
  ◦ Available in pens only

Other biosimilars will be coming
What’s New With Insulin

Ultra-rapid insulin
Biosimilars
More concentrations
Inhaled insulins
Patch delivery device
### Insulin Concentrations

Most insulins have been U-100. The U-100 indicates there are 100 units of insulin per every 1 mL. Nearly all insulin syringes are made for U-100 insulin.

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Types</th>
<th>Units per mL</th>
<th>Units per Vial</th>
<th>Units per Pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100</td>
<td>Many</td>
<td>100</td>
<td>1000 (10 mL vial)</td>
<td>300 (3 mL pen)</td>
</tr>
<tr>
<td>U-200</td>
<td>Humalog (lispro)</td>
<td>200</td>
<td>No Vials</td>
<td>600 (3 mL pen)</td>
</tr>
<tr>
<td></td>
<td>Tresiba (degludec)</td>
<td>200</td>
<td>No Vials</td>
<td>600 (3 mL pen)</td>
</tr>
<tr>
<td>U-300</td>
<td>Toujeo (glargine)</td>
<td>300</td>
<td>No Vials</td>
<td>450 (1.5 mL pen)</td>
</tr>
<tr>
<td>U-500</td>
<td>Humulin Regular</td>
<td>500</td>
<td>10,000 (20 mL vial)</td>
<td>1500 (1.5 mL pen)</td>
</tr>
</tbody>
</table>
U300 Provides Slower Insulin Glargine Release After Subcutaneous Injection

- More concentrated formulation (X3)
- Reduced volume (1/3) and reduced surface area (1/2) of insulin glargine subcutaneous depot
- Slower release rate of insulin glargine
Humulin U-500

• Regular insulin at 5 X the typical concentration
• Action profile is a mix of Regular and NPH
• For patients with significant insulin resistance
• High risk of dosing error which is minimized with the U-500 pen and the dedicated U-500 syringe
  • Only use a U-100 syringe or tuberculin syringe with the vial when everyone is aware of the dose and concentration
What’s New With Insulin

- Ultra-rapid insulin
- Biosimilars
- More concentrations
- Inhaled insulins
- Patch delivery device
Afrezza: Technosphere Formulation of Human Insulin

Inhaled human insulin which is very rapidly absorbed

For mealtimes only

4, 8, and 12 unit cartridges
What’s New With Insulin

- Ultra-rapid insulin
- Biosimilars
- More concentrations
- Inhaled insulins
- Patch delivery device
V-Go

Mechanical pump that patients fill with rapid acting insulin
Changed daily
Delivers 20, 30, or 40 units of background insulin over 24 hours
36 units are available for boluses, 2 units per click
## Agents of Concern in Patients with CKD

<table>
<thead>
<tr>
<th>Avoid/Restrict if GFR &lt; 30</th>
<th>Safe or Dose Adjust if CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Metformin</td>
<td>• Insulin</td>
</tr>
<tr>
<td>• Glyburide</td>
<td>• DPP4 Inhibitors**</td>
</tr>
<tr>
<td>• Glimepiride</td>
<td>• Glipizide (short acting)</td>
</tr>
<tr>
<td>• SGLT2 Inhibitors</td>
<td>• Meglitinides</td>
</tr>
<tr>
<td>• GLP-1 Receptor Agonists*</td>
<td>• Glitazones (TZDs)</td>
</tr>
</tbody>
</table>

* GLP-1 agonists: avoid if GFR < 30 (< 15 for Albiglutide)
** DPP4-I: If GFR < 60: adjust dose except for Linagliptin
Agents of Concern in Patients with CHF

- Glitazones (TZDs)
- Metformin (may use if CHF stable)
- Combination Drugs (that have MF or TZD)
- Sulfonylureas (↑in hypoglycemia in CHF)
# Agents for the Elderly: Safety is the Main Concern

<table>
<thead>
<tr>
<th>Safest Drugs</th>
<th>Most Dangerous Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Metformin (if GFR OK)</td>
<td>– Sulfonylureas</td>
</tr>
<tr>
<td>– All DPP4 Inhibitors (dose for GFR except Linagliptin)</td>
<td></td>
</tr>
<tr>
<td>– Basal Insulins (Analogue are safer than NPH)</td>
<td></td>
</tr>
<tr>
<td>– ? GLP-1 receptor agonists</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– 70/30 Insulin</td>
</tr>
<tr>
<td></td>
<td>– SGLT2 Inhibitors (based on GFR)</td>
</tr>
<tr>
<td></td>
<td>– Pioglitazone (if history of CHF or osteoporosis)</td>
</tr>
</tbody>
</table>
Some Drugs Are Unaffordable for Our Patients

EXPENSIVE

- GLP-1 Agonisits
- DPP4- Inhibitors
- SGLT2 Inhibitors
- Pramlintide
- All Analogue insulins
  - Pens more expensive than vials
- U-500 Insulin
- Most Combo drugs

GENERIC (“CHEAP”)

- Metformin
- Sulfonylureas
- Relion™ Insulins (Wal-Mart)
  - R
  - N
  - 70/30
- Standard insulins (same but cost more than Relion)
- Pioglitazone
Summary and Conclusions

- Start insulin for patients who are symptomatic (polyuria, weight loss) and/or poor control (any BG > 300, FPG >250 or A1c >10%) OR if patients cannot get A1c < 7% on 2-3 drugs

- If patients fail basal insulin + orals or a GLP-1 agonist add a short acting insulin to largest meal first, then progress to MDI

- Refer patients with recurrent or severe hypoglycemia or those requiring more than 300 units of insulin/day to a diabetes specialist for consideration of real-time glucose sensors w/alarms or treatment with U-500 insulin respectively

- Never forget non-glycemic therapies (e.g. statins, ACE-I or ARB, ASA, and smoking cessation) to reduce CVD risk
Questions?