The AADE 2017 Pharmacotherapy Bootcamp

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Disclosure to Participants

• Notice of Requirements For Successful Completion
  – Please refer to learning goals and objectives
  – Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours

• Conflict of Interest (COI) and Financial Relationship Disclosures:
  – Presenter: Susan Cornell, BS, PharmD, CDE, FAPhA, FAADE –
    • Advanced Practitioner Advisory Board and Speakers Bureau for Novo Nordisk, Sanofi
  – Planner: Ken Zielske - No COI/financial relationship to disclose

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Requirements for completing this CE activity are attendance of the entire course and completion and submission of the course evaluation submitted electronically.

**Registered Nurses**

The American Association of Diabetes Educators is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

This educational program will provide 4 contact hours.

The American Association of Diabetes Educators is accredited as a provider of continuing nursing education by the California Board of Registered Nursing (CEP #10977).

**Registered Dietitians**

The American Association of Diabetes Educators (provider #AM001) is a Continuing Professional Education (CPE) Accredited Provider with the Commission on Dietetic Registration (CDR). Registered dietitians (RDs) and dietetic technicians, registered (DTRs), will receive 4 continuing professional education units (CPEUs) for completion of this program. Continuing Professional Education Provider Accreditation does not constitute endorsement by CDR of a provider, program or materials.

**Registered Pharmacists**

The American Association of Diabetes Educators is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing education. This program provides a total of 4 contact hours (or .4 CEUs).

ACPE Universal Program Number: 0069-0000-15-178-L01-P Effective date: 08/04/2015
Agenda

• Normal Physiology & Pathophysiology

• Pharmacology

• Insulin Management
Adherence Declines Over First Year of Therapy

## Adherence to Prescribed Drugs

<table>
<thead>
<tr>
<th>Drug class</th>
<th>n</th>
<th>% Adherent</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral antidiabetic drugs</td>
<td>66</td>
<td>50.0</td>
<td>37.9-62.1</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>62</td>
<td>50.0</td>
<td>37.6-62.4</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>33</td>
<td>69.7</td>
<td>54.0-85.4</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>40</td>
<td>77.5</td>
<td>64.6-90.4</td>
</tr>
<tr>
<td>All drugs</td>
<td>82</td>
<td>35.4</td>
<td>25.0-45.7</td>
</tr>
</tbody>
</table>

Need for Improved Glycemic Control in the United States

• Glycemic targets must be individualized

• The ADA recommends an A1C of <7% as a reasonable goal for many non-pregnant adults

• Many US adults with diagnosed diabetes do not have an A1C of <7%

ADA = American Diabetes Association.
Normal Physiology & Pathophysiology
Normal Physiology & Pathophysiology: Objectives

At the conclusion of the session the participant will be able to:

- List and describe at least two major classifications of diabetes mellitus (Type 1 and 2)
- Discuss the basic pathophysiologic changes that occur with these types of diabetes discussed.
- Identify pathways of energy handling with normal physiology and in various diabetes related conditions.
Types of Diabetes

• Type 1
  – Pre-Diabetes – type 1 (???)
• Type 1.5
  – Latent autoimmune diabetes in adults (LADA)
• Monogenic
  – Maturity onset diabetes in youth (MODY)
• Type 2
  – Pre-Diabetes – type 2
• Gestational Diabetes Mellitus (GDM)
Today we will focus on.....

- Type 1
- Type 2
Why is Glucose Control Important?

- 60% of people with type 2 diabetes have at least one complication because of diabetes
  - Complications are often present at time of diagnosis

Natural History of Type 2 Diabetes

Years from diagnosis: -10, -5, 0, 5, 10, 15

- Insulin resistance
- Insulin secretion
- Postprandial glucose
- Fasting glucose

Pre-diabetes
Type 2 diabetes

Macrovascular complications
Microvascular complications

Onset
Diagnosis

B-cell decline in Pre-diabetes and T2DM

DeFronzo RA. Diabetes. 2009:58(4)
Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Decreased Glucose Uptake
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neuronal Transmitter Dysfunction

Screening for Type 2 Diabetes

- **Adult**
  - Begin screening at age 45 years, then every 3 year intervals in the absence of risks. (ADA)
  - Screen at risk persons at age 30 years and yearly thereafter (AACE)
  - Use the ADA Diabetes Risk Test for Community Screenings

- **Children**
  - Overweight, BMI >85th percentile plus 2 risk factors
    - Family history
    - Race/ethnicity – at risk
    - Signs of insulin resistance
    - Maternal history or GDM
  - Screen at risk children at age 10 years or at onset of puberty, if puberty starts earlier, then every 3 years pending results

ADA Standards, 2015
Type 2 Diabetes: Assess Risk

• Family history
  – First degree relative
• CV disease
• Overweight*
  – Asian American BMI >23 Kg/m2 for screening purposes
• Sedentary lifestyle
• Ethnic-at-risk
• Previous IGT or IFG or HbA1c >5.7%

• Hypertension
• Abnormal lipids
• History of GDM
• Baby > 9 pounds
• Polycystic Ovarian Disease
Type 1: Pathophysiology

- Type 1 results from an autoimmune disorder that destroys the pancreatic beta cells
  - Acute onset (???)
  - Possible pre-diabetes in type 1 based on seroconversion

- 3 stages:
  - Genetic susceptibility
    - Predisposition to the disease from a human leukocyte antigen- (HLA) related immunogenotype
  - Autoimmunity
    - Enterovirus (???)
  - Clinical diabetes

Standards of Medical Care in Diabetes-2014.
Diabetes Care. Vol 37, Supplement 1, Jan 2014
Organ Defects in Diabetes

• Type 1
  – More acute onset
    • Months – few years
  – **Pancreas**
    • B-cell
      – No insulin
      – No amylin
    » **Brain**
      - satiety
Type 1: Etiology

- Genetic
- Environmental
  - < 50% concordance in identical twins
  - Pancreatic toxins
  - Viruses
  - Internal (Interleukin I; Tumor necrosis factors; Free radicals)
- Autoimmune
  - Begins years prior to symptoms
  - Islet cell auto-antibodies (ICA’s)
  - Insulin auto-antibodies (IAA’s)
  - Auto-antibodies - Islet cell proteins
  - Glutamic acid decarboxylase (GAD)
Natural history of Beta cell Defect in T1DM

Immunologic Abnormalities

Genetic Predisposition

Beta Cell Mass %

Time (yr)

Normal Insulin

Impaired Insulin

Overt Diabetes

“Honeymoon”

20 %

ADA. Medical Management of Type 1 Diabetes, 6th ed., 2012.
## Differences in Types of Diabetes

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual clinical course</td>
<td>Insulin –dependent</td>
<td>May not require insulin</td>
</tr>
<tr>
<td>Age onset</td>
<td>&lt; 20 yrs (but ~50% &gt; 20 yrs)</td>
<td>&gt;40 yrs (becoming younger)</td>
</tr>
<tr>
<td>Weight</td>
<td>Lean</td>
<td>Obese</td>
</tr>
<tr>
<td>Onset</td>
<td>Often acute</td>
<td>Slow</td>
</tr>
<tr>
<td>Ketosis-prone</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Family history</td>
<td>≤15%</td>
<td>Common</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Non-Caucasian</td>
</tr>
<tr>
<td>HLA antigens</td>
<td>Increased</td>
<td>Not increased</td>
</tr>
<tr>
<td>Islet autoantibodies</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>
Classification and Treatment

• Leaders in Diabetes are calling for a change in how diabetes is classified
  – Focus should be β-cell centric
    • Opposed to Type 1, Type 1.5, Type 2, monogenic, etc.

• Abnormal or genetically pre-disposed B-cells lead to:
  – Insulin resistance
  – Susceptibility to environmental influences
  – Immune dysregulation
    • Inflammation

B-cell Centric Model

Type 1
- Not obese
- Metabolic syndrome
- TCF7L2
- FTO
- Auto-antibodies
- T-cells
- Systemic inflammation
- C-peptide
- Insulin treatment

Type 1.5
- HLA DQB1

Type 2
- Age

1) Pancreatic β-cell↓ β-cell function↓ β-cell mass↓ amylin
2) ↓ incretin effect
3) α-cell defect↑ glucagon

Hyperglycemia

10) ↓ immune dysregulation / inflammation

GI tract
8) Colon/biome - abnormal microbiota↓ GLP-1 production

9) Stomach and small intestine↑ glucose absorption

7) Brain↑ appetite↓ morning dopamine

Insulin resistance
4) Adipose↑ lipolysis

5) Muscle↓ uptake

6) Liver↑ glucose production

11) Kidney↑ glucose reabsorption

## Glucose Targets in Diabetes

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal</th>
<th>ADA Goal</th>
<th>AACE Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial</td>
<td>&lt;100</td>
<td>70–130</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Postprandial (2 h)</td>
<td>&lt;140</td>
<td>&lt;180*</td>
<td>&lt;140</td>
</tr>
<tr>
<td>A1C</td>
<td>&lt;6.0%</td>
<td>&lt;7.0%+</td>
<td>&lt;6.5%</td>
</tr>
</tbody>
</table>

*Peak value

+ In general, though patients recently diagnosed may benefit from near normal A1C goals and patients with severe comorbidities may need less stringent A1C goals.
Setting Glucose Targets

Less Stringent (< 8%)

- Longer duration of diabetes
  - Limited life expectancy
  - Presence of complications
  - Greater concern about hypoglycemia

(ADA < 7%; AACE ≤ 6.5%)

More Stringent (as close to normal [6%] as possible)

- Shorter duration of diabetes
  - Longer life expectancy
  - No significant CVD

## Approach to Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Factor</th>
<th>More Stringent</th>
<th>Less Stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>highly motivated, adherent, excellent self-care capacities</td>
<td>less motivated, non-adherent, poor self-care capacities</td>
</tr>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>few / mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>readily available</td>
<td>limited</td>
</tr>
</tbody>
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### ADA Standards of Medical Care (2017)

#### Start with Monotherapy unless:

- AIC is greater than or equal to 9%, consider Dual Therapy.
- AIC is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is manifestly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
<td></td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral/loss</td>
<td></td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>GL/lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>COSTS*</td>
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If AIC target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

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<th>Dual Therapy</th>
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<td>EFFICACY*</td>
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<tr>
<td>HYPO RISK</td>
<td>moderate risk</td>
<td></td>
</tr>
<tr>
<td>WEIGHT</td>
<td>gain</td>
<td></td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>COSTS*</td>
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If AIC target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

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If AIC target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

#### Combination Injectable Therapy

(See Figure 8.2)
Fasting vs. Postprandial Glucose Relationship to Complications

- **Fasting Glucose**
  - Microvascular complications
    - Retinopathy
    - Neuropathy
    - Nephropathy

- **Postprandial Glucose**
  - Macrovascular complications
    - Dyslipidemia
    - Hypertension
Pharmacology:
Pharmacology: Objectives

• At the conclusion of the session the participant will be able to:
  – Discuss the pharmacological treatment of diabetes mellitus including medication classes:
  – Describe the potential advantages and disadvantages of medications for the treatment of diabetes
  – Apply knowledge of diabetes medications to identify and correct drug-related issues with a diabetes patient
## 12 Pharmacotherapy Options

### Insulin
- **Bolus insulin**
  - Insulin lispro
    - U100
    - U200
  - Insulin aspart
  - Insulin glulisine
  - Insulin human inhaled
  - Regular human insulin

- **Basal insulin**
  - Insulin NPH
  - Insulin detemir
  - Insulin degludec
    - U100
    - U200
  - Insulin glargine
    - U100
    - U300

### Oral Medications
- $\alpha$-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

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Key Points to Consider When Selecting Pharmacotherapy for T2DM

- How long the patient has had diabetes (duration of disease – preservation of β-cell function)
- Which blood glucose level is not at target (eg, fasting, postprandial, or both)
- The degree of A1C-lowering effect required to achieve goal
- The side effect profile and the patient’s tolerability
  - Minimize hypoglycemia
  - Monitor weight gain
- Co-existing conditions (eg, CVD, depression, osteoporosis)
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
Break into your “Number” group

1. **α**-glucosidase inhibitors (AGI)
2. Amylinomimetic
3. Biguanides
4. Bile acid sequestrants (BAS)
5. Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)
6. Dopamine agonists
7. Glucagon-like peptide-1 (GLP-1) agonists
8. Glinides
9. Insulin - Basal
10. Insulin - Bolus
11. Sulfonylureas (SU)
12. Sodium Glucose Co-Transporter-2 inhibitors
13. Thiazolidinediones (TZDs or glitazones)
In your group....... 

- Review and discuss the following regarding your “drug class”
  - Names of drug(s) in this class
  - Target organ(s)
    - How does the drug work?
  - Does the drug target FPG, PPG, or both?
  - What is the A1c lowering potential?
  - What are common side effects?
  - What is the hypoglycemic risk?
  - What is the weight gain risk?
  - What is the CV profile?
## ADA Standards of Medical Care (2017)

### Monotherapy

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<td>GI/lactic acidosis</td>
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<tr>
<td><strong>COSTS</strong></td>
<td>low</td>
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If AIC target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):  

### Dual Therapy

<table>
<thead>
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<td>hypoglycemia</td>
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If AIC target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):  

### Triple Therapy

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</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea</strong></td>
<td>Thiazolidinedione</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitor</strong></td>
<td>SGLT2 inhibitor</td>
</tr>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>low risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>loss</td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>dehydration, fx</td>
</tr>
<tr>
<td><strong>COSTS</strong></td>
<td>high</td>
</tr>
</tbody>
</table>

If AIC target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or metformin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).
**Biguanides (Metformin)**

- **Impaired Insulin Secretion**
- **Increased Glucagon Secretion**
- **Increased Hepatic Glucose Production**
- **Neurotransmitter Dysfunction**
- **Increased Glucose Reabsorption**
- **Decreased Glucose Uptake**
- **Increased Lipolysis**

Biguanides (Metformin)

• Decreases **liver** glucose production
  – Can be used throughout duration of disease; if no contraindication
  – Good durability

• Lowers **fasting** glucose
• Decreases A1c by 1.5-2% (~45-60 mg/dl)

• Most common side effects
  • Stomach and intestine distress
  • Favorable lipid profile improvements
    – ↑ good cholesterol (HDL)
    – ↓ bad cholesterol (LDL) & ugly cholesterol (triglycerides).

• Caution in patients with renal & hepatic dysfunction
  – CrCl < 1.4 in women and < 1.5 in men

Metformin

- **Dosing**
  - Start with 500mg QD-BID or 850mg QD
  - Individualize titration based on GI side effects
  - May Adjust dose every week (or q 7-10 days)
  - Max dose: 2550mg/day adults; 2000 mg children.
  - Max effective dose is 2000mg/day
  - A liquid dose is available approved for children 10 yrs+
  - Take with food to reduce GI side effects
  - **Metformin XR**
    - May be helpful if immediate release GI SE bothersome
    - DOSING: Start XR 500mg – XR 750mg QD
    - Individualize titration of dose to maximum dose
  - Dose titration based on response/tolerability
  - Monitor: A1C, Serum Creatinine, eGFR, B12 levels?
Metformin

• Advantages
  – Good first response rate and A1C reduction
  – Weight loss (2-5kg)
  – Positive lipid effects
  – Low risk of hypoglycemia as monotherapy
  – Combination therapies common

• Disadvantages
  – GI: N/V/diarrhea
    • take with food, split dose, or try XR
  – Metallic taste, HA, sweating
  – May reduce B-12 levels after long-term use
  – Rare: Lactic acidosis (vague symptoms similar to the flu)

• Contraindications/Cautions to Avoid Lactic Acidosis
  – Renal Impairment
    • SCr ≥1.4 female; ≥1.5 male
  – Hold for iodinated contrast dye (~48 hr)
Metformin: Labeling changes

- Historically, serum creatinine was the measure used to determine if a patient could be prescribed metformin.

- More recent studies support the use of the glomerular filtration rate estimating equation (eGFR).
  - The rationale is that eGFR accounts for more than just a single laboratory parameter
    - it takes into account the patient’s age, gender, race and weight.
Metformin: Labeling changes

• eGFR between 30 to 45 mL/minute/1.73 m².
  – Not recommended
• eGFR below 30 mL/minute/1.73 m²
  – Contraindicated

• If a patient is already on metformin
  – eGFR falls below 45 mL/minute/1.73 m²
    • Weigh benefits of continuation versus discontinuation.
  – eGFR falls below 30 mL/minute/1.73 m²
    • Discontinue metformin
TZD’s (Glitazones)

- Pioglitazone
  - Actos ®
  - 15mg, 30mg, 45mg
  - Once daily

- Rosiglitazone
  - Avandia ®
  - 2mg, 4mg, 8mg
  - Once to twice daily
TZD’s (Glitazones)

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Increased Glucose Reabsorption
- Increased Lipolysis
- Decreased Glucose Uptake
- Increased GI tract/Incretin Effect
- Neurtanmitter Dysfunction

**TZD’ s (Glitazones)**

- Stimulates PPRA γ to increase GLUT-4 transporter production; thereby moving glucose from the blood into the **peripheral tissue**.
  - Can be used thru duration provided insulin is present
  - Good durability

- Lowers **fasting and postprandial glucose**
- Decreases A1c by 1.0-1.5% (~30-45 mg/dl)

- Most common side effects
  - Edema (swelling) usually in the legs
  - Weight gain
  - Possible ↑ risk of fractures.

- **Takes 4-6 weeks (or more) to take affect** and requires insulin (endogenous or exogenous)

TZD-Overview

• Advantages
  – Hypoglycemia- low risk
  – Excellent insulin sensitizer
  – No renal adjustments

• Disadvantages
  – Fluid retention side effects- can be severe
  – Weight gain common
  – Fear of bladder cancer, fractures limit use
Sulfonylureas

- **Glimepiride**
  - *Amaryl ®*
    - 1mg, 2mg, 4mg
    - Once daily

- **Glipizide**
  - *Glucotrol ®*
    - 5mg, 10mg
    - Once to twice daily
  - *Glucotrol XL ®*
    - 2.5mg, 5mg, 10mg
    - Once daily

- **Glyburide**
  - *Micronase ®*
    - 1.25mg, 2.5mg, 5mg
    - Once to twice daily
  - *Diabeta ®*
    - 1.25mg, 2.5mg, 5mg
    - Once to twice daily
  - *Glynase ®*
    - 1.5mg, 3mg, 6mg
    - Once to twice daily
Sulfonylureas

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Increased Glucose Reabsorption
- Increased Glucose Uptake
- Decreased Incretin Effect
- GI tract/Decreased Lipolysis
- Increased Glucose Production

Hyperglycemia

## Sulfonylureas: 1st Generation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Daily Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetohexamide (DYMELOR®)</td>
<td>1-2 daily</td>
<td>250–1500mg</td>
</tr>
<tr>
<td>Chlorpropamide (DIABINESE®)</td>
<td>Daily</td>
<td>100-500mg</td>
</tr>
<tr>
<td>Tolbutamide (ORINASE®)</td>
<td>3 times daily</td>
<td>500-3000mg</td>
</tr>
<tr>
<td>Tolazamide (TOLINASE®)</td>
<td>1-2 daily</td>
<td>100-1000mg</td>
</tr>
</tbody>
</table>

Titrate every 2-4 weeks based on FPG
### Second & “Third” Generation Sulfonylureas

<table>
<thead>
<tr>
<th>Drug</th>
<th>Equivalent Daily dose</th>
<th>Frequency</th>
<th>Daily Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glimepiride (Amaryl®)</td>
<td>2 mg</td>
<td>QD</td>
<td>1-8 mg</td>
</tr>
<tr>
<td>Glipizide (Glucotrol®)</td>
<td>5-10 mg</td>
<td>QD-BID</td>
<td>2.5-40 mg</td>
</tr>
<tr>
<td>Glipizide extended release (Glucotrol XL®)</td>
<td>5 mg</td>
<td>QD</td>
<td>5-20 mg</td>
</tr>
<tr>
<td>Glyburide (Diabeta®, Micronase®)</td>
<td>2.5-5 mg</td>
<td>QD-BID</td>
<td>1.25-20 mg</td>
</tr>
<tr>
<td>Micronized glyburide (Glynase PresTab®)</td>
<td>3 mg</td>
<td>QD</td>
<td>1-12 mg</td>
</tr>
</tbody>
</table>

Remembering sulfonylurea names: end in “-mide” “-ride” or “-zide”
Sulfonylureas

- Stimulates insulin release from the pancreas
  - Long acting stimulation (>6 hours)
  - Requires endogenous insulin to be affective; therefore better used early in the disease; if necessary
  - Short durability

- Lowers fasting and postprandial glucose
  Decreases A1c by 1.5-2% (~45-60 mg/dl)

- Most common side effects
  - Hypoglycemia
  - Weight gain
  - may inhibit ischemic pre-conditioning

DPP4 Inhibitors (gliptins)

• Sitagliptin (*Januvia®*)
  – 25 mg, 50 mg, & 100 mg
  – Once-daily dosing
  – Dose adjustment in renal impairment

• Saxagliptin (*Onglyza®*)
  – 2.5 mg & 5 mg
  – Once-daily dosing
  – Dose adjustment in renal impairment

• Linagliptin (*Tradjenta®*)
  – 5 mg
  – Once-daily dosing

• Alogliptin (*Nesina®*)
  – 6.25 mg, 12.5 mg, & 25 mg
  – Once-daily dosing
  – Dose adjustment in renal impairment
DPP4 Inhibitors (gliptins)

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Decreased Incretin Effect

Neurotransmitter Dysfunction

DPP4 Inhibitors (gliptins)

- Inhibits DPP-4 enzyme in the GI tract that breaks down GLP-1 resulting in ↑ endogenous GLP-1.
  - glucagon suppression results in ↓ liver glucose production
  - Enhances appropriate insulin and amylin secretion from the pancreas
  - Can be used thru duration provided insulin is present
    • Promising durability

- Lowers postprandial glucose
  - Decrease A1c by 0.5 to 0.7% (~15-20 mg/dl; most postprandial)

- Most common side effects
  - Stuffy, runny nose
  - Headache
  - Upper respiratory tract infection

DPP-IV inhibitors-Renal Adjustment

• Drug exposure issue, not safety issue to date
  – These are enzyme inhibitors-can only block 100% of the enzyme-drug above this level is not needed

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CrCl</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>CrCL &lt; 50 mL/min</td>
<td>12.5 mg daily</td>
</tr>
<tr>
<td></td>
<td>&lt; 30 mL/min</td>
<td>6.25 mg daily</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>CrCL &lt; 50 mL/min</td>
<td>2.5 mg</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>CrCL &lt; 50 mL/min</td>
<td>50 mg daily</td>
</tr>
<tr>
<td></td>
<td>&lt; 30 mL/min</td>
<td>25 mg daily</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>No adjustment</td>
<td></td>
</tr>
</tbody>
</table>
Sodium Glucose Co-Transporter-2 Inhibitors (SGLT-2i)

• Canagliflozin
  – *Invokana®*
    • 100mg & 300mg
    • taken once daily before first meal of the day.

• Dapagliflozin
  – *Farxiga®*
    • 5mg & 10mg
    • taken once daily (ideally, before first meal of the day).

• Empagliflozin
  – *Jardiance®*
    • 10mg & 25mg
    • taken once daily (ideally, before first meal of the day).
Neurotransmitter Dysfunction

SGLT-2i


- Islet b-cell Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- GI Tract/Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

SGLT-2i

- ↓ renal glucose reabsorption in the early proximal tubule of the kidney
  - body fat - Possibly due to ↑ water and fat urination (elimination)

- Lowers fasting glucose
  - Decreases A1c by 0.7-1% (~20-30 mg/dl)

- Most common side effects
  - Weight loss
  - Vaginal and male genital infections
  - Rash
  - UTI
  - Frequent urination
  - Increased thirst
  - GI problems (when combined with metformin)

Clinical Findings: Safety of SGLT2 Inhibition

- **Renal Adjustment or Stoppage:**
  - **Dapagliflozin**-
    - Do not initiate or discontinue if currently taking if eGFR is persistently below 60 mL/min/1.73 m²
  - **Canagliflozin and Empagliflozin**-
    - Do not initiate if eGFR is below 45 mL/min/1.73 m²
  - **Canagliflozin**-
    - 100mg if eGFR is below 60 mL/min/1.73 m²,
    - stop if eGFR is below 45 mL/min/1.73 m²
GLP-1 Agonists

short-acting GLP-1 agonists

• Exenatide (*Byetta ®*)
  – 5 mcg & 10 mcg
  – Twice-daily dosing

• Lixisenatide (*Lyxumia ®, Adlyxin ®*)
  – 10 mcg & 20 mcg
  – once-daily dosing

long-acting GLP-1 agonists

• Liraglutide (*Victoza ®*)
  – 0.6 mg, 1.2 mg, & 1.8 mg
  – Once-daily dosing

• Exenatide (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

- Islet b-cell: Impaired Insulin Secretion
- Islet a-cell: Increased Glucagon Secretion
- GI Tract/ Decreased Increased Lipolysis
- GI Tract/ Decreased Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Increased Hepatic Glucose Production
- Neurotransmitter Dysfunction

GLP-1 Agonists

• GLP-1 agonists “fix” 4 dysfunctional organs in T2DM
  – glucagon suppression
    • Results in ↓ liver glucose production
  – Enhances appropriate insulin and amylin secretion from the pancreas
    • Results in brain satiety
  – Regulates the GI tract to slow gastric emptying time
  – Can be used thru duration provided insulin is present
    • Promising durability

• Short acting agonists lowers postprandial glucose
  – Decreases A1c by 0.8-1.5% (~20-45 mg/dl; most postprandial)
• Long acting agonists lowers fasting and postprandial glucose
  – Decreases A1c by 0.8-1.8% (~20-50 mg/dl)

• Most common side effects
  – Weight loss
  – Stomach upset
  – Caution in patients at risk for pancreatitis
## Differences in GLP-1 agonists

<table>
<thead>
<tr>
<th></th>
<th>Exenatide (BID)</th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Exenatide (QW)</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>5 &amp; 10 mcg BID (within 30-60 min of am/pm meal)</td>
<td>10 &amp; 20 mcg (within 60 min of same meal once daily)</td>
<td>0.6 mg initial, then ↑ to 1.2 &amp; 1.8 mg</td>
<td>2 mg weekly</td>
<td>30mg &amp; 50mg weekly</td>
<td>0.75 mg &amp; 1.5 mg weekly</td>
</tr>
<tr>
<td><strong>Max dose</strong></td>
<td>10 mcg BID</td>
<td>20 mcg daily</td>
<td>1.8 mg daily</td>
<td>2mg weekly</td>
<td>50 mg weekly</td>
<td>1.5 mg weekly</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>2-4 hours</td>
<td>2-4 hours</td>
<td>13 hours</td>
<td>5 days</td>
<td>5 days</td>
<td>5 days</td>
</tr>
<tr>
<td><strong>Homology to GLP-1</strong></td>
<td>53%</td>
<td>50%</td>
<td>97%</td>
<td>53%</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td>44%</td>
<td>69.8%</td>
<td>8.6%</td>
<td>44%</td>
<td>2.5%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>FPG or PPG effects</strong></td>
<td>PPG</td>
<td>PPG</td>
<td>Both, FPG &amp; PPG</td>
<td>Both, FPG &amp; PPG</td>
<td>Both, FPG &amp; PPG</td>
<td>Both, FPG &amp; PPG</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial plasma glucose
## Results of CV Outcomes Trials in T2DM

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Study</th>
<th>Drug vs. placebo</th>
<th>N</th>
<th>Results (year published)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4i</td>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>5400</td>
<td>Neutral (2013)</td>
</tr>
<tr>
<td></td>
<td>SAVOR-TIMI</td>
<td>Saxagliptin</td>
<td>16500</td>
<td>Neutral (2013)</td>
</tr>
<tr>
<td></td>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>14000</td>
<td>Neutral (2015)</td>
</tr>
<tr>
<td></td>
<td>CARMELINA</td>
<td>Linagliptin</td>
<td>8300</td>
<td>Expected (2017)</td>
</tr>
<tr>
<td>GLP-1 agonist</td>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>14000</td>
<td>Neutral (2015)</td>
</tr>
<tr>
<td></td>
<td>LEADER</td>
<td>Liraglutide</td>
<td>16500</td>
<td>Positive (2016)</td>
</tr>
<tr>
<td></td>
<td>EXSCEL</td>
<td>Exenatide QW</td>
<td>5400</td>
<td>Expected (2018)</td>
</tr>
<tr>
<td></td>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>8300</td>
<td>Expected (2019)</td>
</tr>
<tr>
<td>SGLT-2i</td>
<td>EMPA-REG</td>
<td>Empagliflozin</td>
<td>7300</td>
<td>Positive (2015)</td>
</tr>
<tr>
<td></td>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>4300</td>
<td>Expected (2017)</td>
</tr>
<tr>
<td></td>
<td>DECLARE</td>
<td>Dapagliflozin</td>
<td>22200</td>
<td>Expected (2019)</td>
</tr>
</tbody>
</table>

DPP4i = dipeptidyl peptidase 4 inhibitor  
GLP-1 = glucagon like peptide -1  
SGLT-2i = sodium glucose cotransporter 2 inhibitor  

Adapted from: Handelsman Y. Endocrine Today. 2016
Meglitinides

- **Repaglinide**
  - *Prandin®*
    - 0.5mg, 1mg, 2mg
    - Up to three times daily before meals

- **Nateglinide**
  - *Starlix®*
    - 60mg, 120mg
    - Up to three times daily before meals
Neurotransmitter Dysfunction

Meglitinides

Glinides

- Stimulates insulin release from the **pancreas**
  - Short acting stimulation (30 minutes to 4 hours)
  - Requires endogenous insulin to be affective; therefore better used early in the disease; if necessary
  - Short durability

- Lowers **postprandial** glucose
- Decreases A1c by 0.5-1% (~15-30 mg/dl; more postprandial)

- Most common side effects
  - Hypoglycemia
  - Weight gain

Alpha Glucosidase Inhibitors

• Acarbose
  – *Precose* ®
    • 25mg, 50mg, 100mg
    • Up to three times daily before meals

• Miglitol
  – *Glyset* ®
    • 25mg, 50mg, 100mg
    • Up to three times daily before meals

**Dosing:**
Start with 25mg TID / adjust every 2-8 weeks
Max: 50mg TID for pts. <60 kg
Max: 100mg TID for pts. >60 kg
Take with first bite of meal or large snack
Individualize titration of dose base on GI side effects
Alpha Glucosidase Inhibitors

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Increased Glucose Reabsorption
- Increased Glucose Uptake
- Increased Lipolysis

Hyperglycemia

Alpha Glucosidase Inhibitors

• Slows the breakdown (or metabolism) of carbohydrates to help regulate the movement of food through **GI tract**
  – Best used in pre-diabetes or early disease due to ↑ GI motility

• Lowers **postprandial** glucose
  – Decreases A1c by 0.5-1.0% (~15-30 mg/dl; more postprandial)

• Most common side effects
  • Stomach and intestinal discomfort
  • Flatulence (gas)

• Caution in patients with GI disorders or taking meds that inhibit macronutrient enzymes

Dopamine Agonist

• Bromocriptine Mesylate
  – *Cycloset®*
  • 1.6 mg to 4.8 mg
  • taken once daily within two hours of waking in the morning with food.
  • Increase by 0.8mg weekly to tolerability or max dose
Dopamine Agonist

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Increased Glucose Reabsorption
- Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Uptake
- Neurotransmitter Dysfunction

Dopamine Agonist

- ↑ Dopamine in the brain to change circadian neuro-endocrine rhythms (similar to that in hibernation)
  - body fat - Possibly due to ↓ TG from diet
  - ↓ liver glucose output - Possibility from over production of cortisol in T2DM
  - Best used in pre-diabetes or early disease due to ↑ insulin resistance; though, potential beneficial throughout duration of disease.

- Lowers postprandial glucose
  - Decreases A1c by 0.5-1% (~15-30 mg/dl)

- Most common side effects
  - Nausea, vomiting
  - headache
  - fatigue
  - hypotension
  - ↓ TG

Scranton RE et al. BMC Endocrine Disorders 2007, 7:3
Bile Acid Sequestrant

• Colesevelam HCl
  – Welchol®
  – 1.875 grams BID or 3.75 grams daily
    • 625mg tablets or single dose suspensions available
Bile Acid Sequestrant

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased Hepatic Glucose Production
- Increased Glucose Reabsorption
- Increased Lipolysis
- Decreased Incretin Effect
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

Hyperglycemia

Bile Acid Sequestrant

- **Target:** Gut  Block glucose absorption/GLP-1?

- **Lowers postprandial glucose**
  - Decreases A1c by 0.5 (~15 mg/dl)
  - May reduce LDL cholesterol

- **Adverse Effects:**
  - Constipation
  - indigestion, nausea
  - muscle aches
  - may increase TG

- **Cautions:** Patients w/ GI disorders, TG>500, history of pancreatitis or hypertriglyceridemia

- May affect concurrent meds.
  - esp. Verapamil & fat-soluble vitamins
  - take 4 hrs. away from Welchol
Amylin Analog

- **Pramlintide**
  - *Symlin®*
  - 60mcg, 120mcg prefilled pens
    - 15-120mcg per dose
    - Up to three times daily before meals

- **Adjunct to Insulin therapy in Type 1 and 2 DM**
  - **Dosing**
    - ↓ dose of preprandial insulin by 50% at initiation
      - Type 1 DM: 15mcg → 60mcg 4 step titration
      - Type 2 DM: 60mcg → 120 2 step titration
      - Dose escalated every 3-7 days based on GI tolerance
Neurotransmitter Dysfunction

Amylin Analog

Amylin Analog

- Mimics endogenous amylin action
  - Enhances appropriate insulin and amylin secretion from the pancreas
    - Results in brain satiety
  - Regulates the GI tract to slow gastric emptying time
  - Can be used thru duration of disease.

- Lowers postprandial glucose
  - Decreases A1c by 0.4-0.6% (~20 mg/dl; most postprandial)

- Most common side effects
  - Weight loss
  - Stomach upset
  - Headache

- Caution in patients on insulin and/or drugs that alter GI motility
  - May need to ↓ insulin dose
  - May need to reschedule dose of other drugs

Rational Choices for Oral Agent Combinations

• Drugs that target different metabolic defects
  • Combine medications that work at different tissue sites for synergy

• Drugs that target fasting and postprandial glucose control

• Select therapies that support patient goals
  • Low hypo risk
  • Weight neutral, loss
<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Route</th>
<th>Targets insulin resistance</th>
<th>Target Organs</th>
<th>Target Glucose: FPG or PPG</th>
<th>A1c Reduction %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Oral</td>
<td>No</td>
<td>Pancreas</td>
<td>Both</td>
<td>1.5-2.0</td>
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<tr>
<td>Metformin</td>
<td>Oral</td>
<td>Yes</td>
<td>Liver</td>
<td>FPG</td>
<td>1.5</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Oral</td>
<td>Yes</td>
<td>Muscle &amp; adipose fat</td>
<td>Both</td>
<td>1.0-1.5</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Oral</td>
<td>No</td>
<td>Pancreas</td>
<td>PPG</td>
<td>0.5-2.0</td>
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<tr>
<td>AGIs</td>
<td>Oral</td>
<td>No</td>
<td>GI tract</td>
<td>PPG</td>
<td>0.5-1.0</td>
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<tr>
<td>DDP-4 inhibitors</td>
<td>Oral</td>
<td>No</td>
<td>Pancreas &amp; liver</td>
<td>PPG</td>
<td>0.5-0.7</td>
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<tr>
<td>Bile acid sequestrant</td>
<td>Oral</td>
<td>No</td>
<td>GI tract</td>
<td>PPG</td>
<td>0.4</td>
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<tr>
<td>Dopamine agonists</td>
<td>Oral</td>
<td>No</td>
<td>Brain, possibly adipose fat</td>
<td>PPG</td>
<td>0.4</td>
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<tr>
<td>SGLT-2 inhibitors</td>
<td>Oral</td>
<td>Maybe</td>
<td>Kidney, possibly adipose fat</td>
<td>FPG</td>
<td>0.7 – 1.1</td>
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<tr>
<td>GLP-1 agonists</td>
<td>Injectable</td>
<td>No</td>
<td>Pancreas, liver, brain &amp; GI tract</td>
<td>Short-acting—PPG Long-acting—Both</td>
<td>0.8-1.5</td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Injectable</td>
<td>No</td>
<td>Pancreas, liver, brain &amp; GI tract</td>
<td>PPG</td>
<td>0.6</td>
</tr>
<tr>
<td>Insulin</td>
<td>Injectable</td>
<td>Yes (to a degree)</td>
<td>Basal - FPG Bolus – PPG</td>
<td>↓ as much as needed</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Weight Effect</th>
<th>Hypoglycemia</th>
<th>β-Cell Protection</th>
<th>CVD Benefits</th>
<th>Cost</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGIs</td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
<td>Possible</td>
<td>$ to $$$</td>
<td>GI adverse effects (gas), dose frequency</td>
</tr>
<tr>
<td>Amylinomimetic</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$</td>
<td>GI adverse effects (nausea), injectable, dose frequency</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Neutral or loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$</td>
<td>GI adverse effects (constipation), dose frequency</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$</td>
<td>GI adverse effects (diabetes), renal and hepatic impairment</td>
</tr>
<tr>
<td>DPP-4 inhibitors (gliptins)</td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$$</td>
<td>Minimal adverse effects</td>
</tr>
<tr>
<td>Dopamine agonist</td>
<td>Neutral or loss</td>
<td>Low risk</td>
<td>Unknown</td>
<td>Yes/no</td>
<td>$$$</td>
<td>GI adverse effects (nausea), hypotension, dizziness</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$$</td>
<td>GI adverse effects (nausea), injectable</td>
</tr>
<tr>
<td>Insulin</td>
<td>Gain or loss</td>
<td>Risk—bolus</td>
<td>Possible</td>
<td>Possible</td>
<td>$ to $$$</td>
<td>Injectable, dose frequency (bolus), increased SMBG</td>
</tr>
<tr>
<td>Secretagogues sulfonfonylureas and glinides</td>
<td>Gain</td>
<td>Risk</td>
<td>No</td>
<td>No</td>
<td>$ to $$$</td>
<td>Immediate short-term response, increased SMBG, dose frequency (glinides)</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>Loss</td>
<td>Low risk</td>
<td>??</td>
<td>Yes</td>
<td>$$$</td>
<td>Urinary tract and urogenital infections</td>
</tr>
<tr>
<td>TZDs (glitazones)</td>
<td>Gain</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes/no</td>
<td>$$</td>
<td>4-8 weeks for response, redistribution of SC/visceral fat, edema, bone loss, fracture, bladder cancer</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial glucose; GI = gastrointestinal; SMBG = self-monitoring of blood glucose. 
Insulin Management: Objectives

• At the conclusion of the session the participant will be able to:
  – Describe insulin preparation and specialty products (U500).
  – Discuss insulin use for Type 2 diabetes.
  – Discuss insulin use for Type 1 diabetes.
  – Apply knowledge of insulin to dosage, mixing and treatment options
  – Describe pattern management.
12 Pharmacotherapy Options

**Insulin**
- **Bolus insulin**
  - Insulin lispro
    - U100
    - U200
  - Insulin aspart
  - Insulin glulisine
  - Insulin human inhaled
  - Regular human insulin
- **Basal insulin**
  - Insulin NPH
  - Insulin detemir
  - Insulin degludec
    - U100
    - U200
  - Insulin glargine
    - U100
    - U300

**Oral Medications**
- \(\alpha\)-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

Insulin

Neurotransmitter Dysfunction

Insulin

Islet b-cell
Impaired Insulin Secretion

Islet a-cell
Increased Glucagon Secretion

Increased Glucagon Production

Increased Hepatic Glucose Production

Increased Glucose Uptake

Increased Glucose Reabsorption

GI Tract/ Decreased Incretin Effect

Increased Lipolysis

Decreased Glucose Uptake

Thinking like a Pancreas

- Basal
- Bolus

More for “Dawn phenomenon”
Less overnight
Insulin Release

• **Basal:** ~50% TDD secreted during basal periods to suppress lipolysis, proteolysis and glycongenolysis
  – (~ 1 unit/hr)

• **Prandial:** ~50% secretion in response to nutrient ingestion
  (a meal contains 6 to 20 times the glucose content of the blood)
  – First-phase release:
    • Within 2 min. of nutrient ingestion
    • Continues 10-15 min.
    • Diminished or missing in T2DM
  – Second phase sustained until normoglycemia restored
Ideal Insulin Replacement Strategy

Pharmacokinetic Profile of Currently Available Insulins

Plasma Insulin Levels

Aspart, Lispro, Glulisine, Insulin human inhaled

Regular

Intermediate (NPH insulin)

Long (Insulin detemir)

Long (Insulin glargine)

Ultralong degludec U100, U200

Ultralong (glargine U300)

Time (h)
# Insulin Comparison

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset (hr)</th>
<th>Peak (hr)</th>
<th>Duration (hr)</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Lispro U100 &amp; U200</td>
<td>within 15 min</td>
<td>0.5-1.5</td>
<td>3-5</td>
<td>Clear</td>
</tr>
<tr>
<td>Insulin Aspart</td>
<td>within 15 min</td>
<td>1-3</td>
<td>3-5</td>
<td>Clear</td>
</tr>
<tr>
<td>Insulin Glulisine</td>
<td>0.25-0.5</td>
<td>0.5-1</td>
<td>4</td>
<td>Clear</td>
</tr>
<tr>
<td>Regular U100</td>
<td>0.5 – 1</td>
<td>2-4</td>
<td>5-8</td>
<td>Clear</td>
</tr>
<tr>
<td>Regular inhaled</td>
<td>Within 5 min</td>
<td>20-40 min</td>
<td>3</td>
<td>Powder</td>
</tr>
<tr>
<td>Regular U-500</td>
<td>30 min</td>
<td>2-4</td>
<td>Up to 24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>NPH</td>
<td>1-2</td>
<td>4-10</td>
<td>14+</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Insulin Detemir</td>
<td>3-4</td>
<td>6-8 (though relatively flat)</td>
<td>up to 20-24</td>
<td>Clear</td>
</tr>
<tr>
<td>Insulin Glargine U100</td>
<td>1.5</td>
<td>flat</td>
<td>24</td>
<td>Clear</td>
</tr>
<tr>
<td>Insulin Glargine U300</td>
<td>1.5</td>
<td>flat</td>
<td>26</td>
<td>Clear</td>
</tr>
<tr>
<td>Insulin Degludec U100 &amp; U200</td>
<td>0.5 – 1</td>
<td>flat</td>
<td>&gt;30</td>
<td>Clear</td>
</tr>
<tr>
<td>Lispro Mix 50/50</td>
<td>0.25-0.5</td>
<td>0.5-3</td>
<td>14-24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Lispro Mix 75/25</td>
<td>0.25-0.5</td>
<td>0.5-2.5</td>
<td>14-24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Aspart Mix 70/30</td>
<td>0.1-0.2</td>
<td>1-4</td>
<td>18-24</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Degludec/aspart Mix 70/30</td>
<td>0.23 – 1.2</td>
<td>2.3</td>
<td>&gt;24</td>
<td>Cloudy</td>
</tr>
</tbody>
</table>

Note: Patient specific onset, peak, duration may vary from times listed in table, Peak and duration are often very dose dependent with shorter duration of actions with smaller doses and vice versa
When is it Time for Insulin Therapy?

- **Type 1 Diabetes**
  - Type 1.5
- **Gestational**
- **Type 2 Diabetes**
  - Unmet glycemic goals on non-insulin meds
  - Unable to tolerate non-insulin meds
  - Glucose toxicity
  - Stress of illness / surgery
  - Hyperosmolar Hyperglycemic State (HHS)
Insulin Regimen Consideration

- Readiness
- Cost
- Glucose goals
- Eating patterns
- Work schedules
- Patient willingness / confidence
- Availability of assistance
Insulin Regimens- Type 1DM

• TDD 0.3 – 1.0 units / kg / day
  – 40-60 % Basal
  – 40-60 % Prandial

• Insulin choices based on regimen
  – BID split-mixed dosing (rare)
    • May start with 2/3 TDD in AM and 1/3 TDD in PM
  – Multiple Daily Injections (MDI) for increased lifestyle flexibility
    • Typical regimen for type 1 DM

• Monitor for hypoglycemia
  – Somogyi, Dawn, Waning Insulin

• Less insulin during “honeymoon” phase

• May start with Correction Factor of 1:50 (ISF)
The Basal-Bolus Concept

- Basal insulin: 50% of daily needs
  Controls nighttime and between-meal glucose at a nearly constant level

- Bolus insulin: 50% of daily needs
  Controls mealtime glucose
  10% to 20% of total daily insulin requirement at each meal

- Correction dose (sensitivity factor)
  Correct hyperglycemia reactively
Key Barriers to Insulin Therapy for Type 2

Patient Barriers
• Patient reluctance
• Sense of failure
• Loss of independence
• Belief that insulin is ineffective
• Fear of injections
• Fear of hypoglycemia
• Weight gain

Provider Barriers
• Clinical inertia
• Lack of insulin training, time, and/or support
• Fear of hypoglycemia
• Weight gain
Overcoming Barriers to Insulin Therapy

• Avoid using insulin as a “threat,” but as a solution; discuss it as an option early
• Use insulin pens and regimens that offer maximum flexibility
• Give a “limited” trial of insulin
• Tell patient that injection is less painful than finger stick; give an injection in the office
• Teach patient to recognize and treat hypoglycemia; use basal analog insulin to minimize hypoglycemia
• Meet with dietitian before initiation of insulin
Considerations for Insulin Titration and Education

• First, do no harm
  – Halt the hypoglycemia
• Fix the fastings
• Pare the postprandials
Insulin Strategies in T2DM

• Metformin + basal insulin
  – Fasting coverage
  – Hypoglycemic risk
    • Glargine, detemir, degludec – lower risk
    • Human insulin isophane (NPH) – higher risk
  – Weight gain/neutral

• Basal insulin + bolus insulin (with or without metformin)
  – Fasting and postprandial coverage
  – High hypoglycemic risk (mostly from bolus)
    • Regular, aspart, lispro, glulisine
  – Weight gain

• Basal insulin + GLP-1 agonist (with or without metformin)
  – Fasting and postprandial coverage
  – Low hypoglycemic risk (glargine, detemir, degludec)
  – Weight neutral/loss

### Approach To Starting and Adjusting Insulin in T2D

<table>
<thead>
<tr>
<th>Initiate Basal Insulin</th>
<th>Usually with metformin +/- other noninsulin agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start:</strong> 10 U/day or 0.1-0.2 U/kg/day</td>
<td></td>
</tr>
<tr>
<td><strong>Adjust:</strong> 10-15% or 2-4 units once/twice weekly to reach FBG target</td>
<td></td>
</tr>
<tr>
<td><strong>For hypo:</strong> identify/fix cause; can decrease doses by 10-20% or 4 units.</td>
<td></td>
</tr>
</tbody>
</table>

#### Add 1 rapid-acting insulin injection before largest meal

**Start:** 4 units, .01U/kg, or 10% basal dose.
If A1c <8%, Can ↓ basal by same amount
**Adjust:** ↑ dose by 1-2 units or 10-15% once/week until reach SMBG target
**For hypo:** identify/fix cause; can ↓ does by 2-4 units or 10-20%

#### If A1c not controlled - Consider

- Add GLP-1RA
  - **Start:** Divide current basal dose into 2/3 AM & 1/3 PM or ½ AM & ½ PM
  - **Adjust:** ↑ dose by 1-2 units or 10-15% once/week until reach SMBG target
  - **For hypo:** identify/fix cause; can ↓ does by 2-4 units or 10-20%

#### Change to premixed insulin twice daily

**Start:** 4 units, .01U/kg, or 10% basal dose.
If A1c <8%, Can ↓ basal by same amount
**Adjust:** ↑ dose by 1-2 units or 10-15% once/week until reach SMBG target
**For hypo:** identify/fix cause; can ↓ does by 2-4 units or 10-20%

#### If A1c not controlled - Consider

- Add ≥ 2 rapid-acting insulin injection before meals (basal-bolus)
  - **Start:** 4 units, .01U/kg, or 10% basal dose.
  - If A1c <8%, Can ↓ basal by same amount
  - **Adjust:** ↑ dose by 1-2 units or 10-15% once/week until reach SMBG target
  - **For hypo:** identify/fix cause; can ↓ does by 2-4 units or 10-20%

#### Change to premixed analog insulin 3 times daily

**Start:** add additional injection before lunch
**Adjust:** ↑ dose by 1-2 units or 10-15% once/week until reach SMBG target
**For hypo:** identify/fix cause; can ↓ does by 2-4 units or 10-20%

---

Adapted from Approaches to Glycemic Treatment. Diabetes Care 2017;40(suppl 1):S67.
Adjusting Basal Insulin

• Must Check FBG daily
  • If basal insulin dose reaches >0.5 units/kg (more than ½ TBW kg) consider adding mealtime insulin!
  • If average FBG AT GOAL, but A1C NOT at goal then check 2hr PPG and assess need for mealtime insulin

• Long-acting basal insulin
  • DO NOT use to cover meals or use as supplemental insulin
Premixed Insulin

- Pre-mixed combinations of short and intermediate acting insulins (biphasic)
- Usually given twice a day
- Convenient but not flexible
- Cloudy (needs re-suspending)
- Short + NPH = Humulin or Novolin 70/30
  - 70/30 Mixture = 70% NPH + 30% R
  - Humulin 50/50
- Rapid + NPH analog
  - Humalog 75/25
  - Novolog 70/30
- Caution: potential for error!!
Dosing Option: Split-mixed Insulin Regimen BID

- **Basal needs**: NPH
- **Bolus needs**: Regular or Rapid

*Insulin effect images are theoretical representations and are not derived from clinical trial data

Dosing Options: Three Injection Regimen

- HYPO IN MIDDLE OF THE NIGHT?
- Move Evening NPH to Bedtime to avoid

*Insulin effect images are theoretical representations and are not derived from clinical trial data

Dosing Options: Multiple Daily Injections (MDI)

- Basal needs: Glargine, Detemir
- Bolus needs: Lispro, Aspart, Glulisine

*Insulin effect images are theoretical representations and are not derived from clinical trial data.
CONCENTRATED INSULIN
Insulin Resistance

• Major defect in individuals with type 2 diabetes
• Reduced biological response to insulin
• Closely associated with obesity
• Associated with cardiovascular risk
• Type 1 diabetes patients can be insulin resistant as well
## Candidates for Concentrated / Low Volume Insulin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rationale</th>
<th>Product to Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal hypoglycemia</td>
<td>Needs peak-less (flat) basal insulin profile</td>
<td>Degludec U-100, U-200, Glargine U-300</td>
</tr>
<tr>
<td>Insulin resistance (severe with high insulin requirements; e.g. &gt;200 units TDD)</td>
<td>Temporary “fix” for insulin resistance</td>
<td>Regular U-500</td>
</tr>
<tr>
<td>High basal insulin needs (&gt; 80 units per injection)</td>
<td>High dose requires 2+ basal injections/day</td>
<td>Degludec U-200, Glargine U-300</td>
</tr>
<tr>
<td>High bolus insulin needs (&gt; 20 units per day)</td>
<td>Reduces the number of pen changes per month</td>
<td>Lispro U-200</td>
</tr>
</tbody>
</table>

**TDD = total daily dose**

Adapted from Smith J, Rx Consultant 2016
Safety Concerns with “Newer” Insulins

- Familiarity with new products
- Understanding of pharmacokinetic and pharmacodynamic nuances
- Knowledge on dose adjustments and conversions
- “Lack” of interchangeability
Rationale for Concentrated Insulin Use

• When daily insulin requirements are in excess of 200 units/day, the volume of U-100 injected insulin may become an issue

• Physically too large for a single subcutaneous administration

• Multiple injections are required to deliver a single dose

• Increased injections may lead to compliance issues and poor glycemic control

• Discomfort
Insulin Human Regular U-500

• Insulin characteristics
  – Five times as concentrated as U-100 insulin
  – Decreased injection volume (vs. U-100)
  – Solely for severely insulin-resistant patients
    • Total daily dose exceeding 200 units/day

• Pharmacokinetics/pharmacodynamics
  – Mean onset of action 15 minutes
  – Mean duration of action 21 hours (range 13-24 hours)
    • Each individual patient varies in their response depending on:
      – Site of injection
      – Exercise patterns
      – Other variables

• Clinical pearls
  – Time to onset: similar to U-100 regular insulin
  – Duration of effect: similar to NPH insulin
  – Consider it a “mixed short/intermediate” type insulin
Human Regular U-500

- Now available in an insulin pen:
  - 1500 units/pen
  - Maximum 300 units/injection
  - No “dose conversions” needed
  - Dials in increments of 5 units

- Still available in vial form (20 mL)
  - New syringe dedicated for U-500 approved July 2016
    - Use with U-500 insulin only
Regular U-100 to U-500 Dosing

• Converting from any U-100 insulin to U-500 human regular insulin:
  – A1C ≤ 8%: empiric reductions in total daily dose (TDD) of 10-20% have been recommended
  – A1C ≥ 10%: empiric increases in TDD of 10-20% can be considered

• Distributing the Total Daily Dose (TDD):
  – Recommendations vary from 2-3 doses per day
    • Algorithm available
  – Administer 30 minutes before meals due to the relatively short onset of action

Regular U-500 to U-100 Dosing

• No recommendations are currently available on how to convert from Regular U-500 to basal-bolus U100 dosing
  – Can differ based on delivery device used
    • Pen vs. U-100 insulin syringe or TB syringe

• Clinical expertise warranted
Concentrated Glargine (U-300)

- Smaller depot surface area
- Reduced rate of absorption
- Relatively flat and prolonged PK/PD profiles
  - Half-life ~23 hours
  - Steady state in 4 days
  - Duration of action ≤ 36 hours
- Available only in a pen
  - 450 units/pen (1.5 mL)
  - Maximum 80 units/injection
  - 3 pens per box

Garber AJ. Diabetes Obes Metab. 2014;16(6):483-491.

US Food and Drug Administration. www.accessdata.fda.gov/scripts/cder/drugsatfda/
Glargine U-100 to U-300 Dosing

- Changing from once daily long-acting:
  - Initial dose can be same U-100 insulin glargine
  - Expect that a higher daily dose of U-300 insulin glargine will be needed to maintain the same level of glycemic control

- Changing from BID NPH insulin:
  - Initial dose is 80% of the total daily NPH dosage
Glargine U-300 to U-100 Dosing

- When converting from U-300 to U-100
  - A 20% reduction is recommended to minimize hypoglycemic risk with the U-100 insulin product
Insulin Degludec (U-100 & U-200)

• “Ultra long acting” insulin
• Relatively flat and prolonged PK/PD profiles
  – Duration of action ~42 hours (at least)
  – Half-life ~25 hours
  – Steady state in 3 to 4 days
  – Less patient insulin variability
• Flexible dosing schedule
• Available only in a pen
  – U-200: 600 units/pen (3 mL), max 160 units/injection
    • Dial in increments of 2 units!
  – U-100: 300 units/pen (3 mL), max 80 units/injection

Garber AJ. Diabetes Obes Metab. 2014;16(6):483-491.
US Food and Drug Administration. www.accessdata.fda.gov/scripts/cder/drugsatfda/
Degludec U-200 Dosing

• Changing from once daily long-acting:
  – The dose is 1 to 1
    • Initial degludec dose can be same as the current U-100 insulin the patient is using
      – Glargine/detemir/degludec

• Changing from BID NPH insulin:
  – The dose is 1 to 1:
    • Initial degludec (once daily) dose is same as the total daily NPH dosage

Tresiba (insulin degludec injection) PI. Novo Nordisk Inc; 2016 Sept.
Degludec U-200 to U-100 Dosing

• When converting from U-200 to U-100
  – The dose is a 1 to 1 conversion
    • No change in the initial dose is necessary
## Concentrated Basal Insulin Dosing Conversion Comparison

<table>
<thead>
<tr>
<th>Glargine U-300</th>
<th>Degludec U-200</th>
<th>Human R U-500</th>
</tr>
</thead>
<tbody>
<tr>
<td>True basal insulin</td>
<td>True basal insulin</td>
<td>Mixed basal/bolus insulin</td>
</tr>
<tr>
<td>1 daily injection</td>
<td>1 daily injection</td>
<td>1 to 1</td>
</tr>
<tr>
<td>2 daily injections</td>
<td>2 daily injections</td>
<td>1 to 1</td>
</tr>
<tr>
<td>80% of total daily basal dose</td>
<td>80% of total daily basal dose</td>
<td>Multiple daily injections of basal-bolus</td>
</tr>
<tr>
<td>Maximum single-dose injection</td>
<td>Maximum single-dose injection</td>
<td>Total daily dose divided into 2 or 3</td>
</tr>
<tr>
<td>80 units</td>
<td>160 units</td>
<td>300 units</td>
</tr>
<tr>
<td>Dialed in 1-unit increments</td>
<td>Dialed in 2-unit increments</td>
<td>Dialed in 5-unit increments</td>
</tr>
<tr>
<td>450 units of insulin per pen</td>
<td>600 units of insulin per pen</td>
<td>1500 units of insulin per pen</td>
</tr>
<tr>
<td>Expect higher daily dose of glargine U-300 to maintain glycemic control</td>
<td></td>
<td>Monitor for hypoglycemia; administer with meals</td>
</tr>
</tbody>
</table>

- Tresiba package insert, Toujeo package insert, Insulin regular U-500 package insert
<table>
<thead>
<tr>
<th>Products/Device</th>
<th>Refrigerated</th>
<th>Unrefrigerated</th>
<th>Once used (opened)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro U-100</td>
<td>Expiration Date</td>
<td>28 days</td>
<td>28 days</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin human N</td>
<td>Expiration Date</td>
<td>31 days</td>
<td>31 days</td>
</tr>
<tr>
<td>Insulin human R</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro U-100, U-200</td>
<td>Expiration Date</td>
<td>28 days</td>
<td>Glargine U-300: 42 days</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vials &amp; pens:</strong> Insulin detemir</td>
<td>Expiration Date</td>
<td>42 days</td>
<td>42 days (pens should not be refrigerated)</td>
</tr>
<tr>
<td><strong>Pens:</strong> Insulin degludec U-100, U-200</td>
<td>Expiration Date</td>
<td>56 days</td>
<td>56 days (pens should not be refrigerated)</td>
</tr>
<tr>
<td><strong>Inhaled:</strong> Insulin human</td>
<td></td>
<td>Expiration Date</td>
<td>15 days for device</td>
</tr>
</tbody>
</table>

*Do not refrigerate*
- Lispro, glargine, glulisine: 28 days
- Aspart: 14 days
Clinical Pearls – Concentrated Insulin

- Watch for over basalization
  - High basal dose with no or little bolus insulin

- Continually increasing insulin doses does not reduce insulin resistance

- Humulin R U-500 is useful for patients on very high total daily insulin doses (e.g. > 200 TDD/day)

- Ultra long acting basal insulins (Glargine U-300 and Degludec U-200) provide longer duration of action for better basal coverage with low nocturnal hypoglycemia
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 SMBG in order to know the medication is effective
  - What are common adverse effects
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?
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 that can be taken with or without food
  - TZDs
  - DPP-4 inhibitors
  - Long-acting GLP-1 agonists
  - SGLT-2 inhibitors
  - Basal insulin

- Agents to be taken with or after meals
  - SU
  - Metformin
  - Bolus insulin

Patient Adherence with Devices

- Always have patients demonstrate their technique for devices (syringes, pens, SMBG meters, etc.)
  - At first education of the device
  - At first follow-up visit
  - At frequent intervals thereafter
References

- Cornell S. The Continual Evolution of Type 2 Diabetes: An Update on Pathophysiology and Emerging Treatment Options. Therapeutics and Clinical Risk Management. 2015;11:621-632
- Food and Drug Administration. Humulin R-U-500 (concentrated) Insulin Human Injection. *Drugs@FDA.*
References