What’s New?
The 2016 Diabetes Pharmacotherapy Update

Susan Cornell, PharmD, CDE, FAPhA, FAADE
Associate Director of Experiential Education
Associate Professor of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Disclosure to Participants

• Susan Cornell, BS, PharmD, CDE, FAPhA, FAADE
  • Advanced Practitioner Advisory Board and Speaker bureau for:
    • Sanofi
    • Novo-Nordisk
Learning Objectives

• Summarize the 2016 changes to recent national guidelines for the care of patients with diabetes.

• Identify current and emerging pharmacotherapy treatments for type 2 diabetes.

• Relate common adverse drug effects of current diabetes pharmacotherapy to key side effects that should be minimized based on national guidelines.
Take Home Message

All of the Knowledge we have does no good if..........

......the patient does NOT take their medication or does NOT take it correctly
What questions do you have regarding the new/emerging therapies for diabetes?
The Diabesity Epidemic

> 29 million with Diabetes

86 million with Pre-diabetes

Centers for Disease Control and Prevention
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, etc.

The Ominous Octet: Circa 2008

HGP = hepatic glucose production
1) Pancreatic ß-cell ↓ ß-cell function ↓ ß-cell mass ↓ amylin

2) ↓ incretin effect

3) α-cell defect ↑ glucagon

Hyperglycemia

4) Adipose ↑ lipolysis

5) Muscle ↓ uptake

6) Liver ↑ glucose production

7) Brain ↑ appetite ↓ morning dopamine

10) ↓ immune dysregulation / inflammation

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

9) Stomach and small intestine ↑ glucose absorption

11) Kidney ↑ glucose reabsorption

By the time a person is diagnosed with T2DM, approximately how much β-cell function has been lost?

A. < 10%
B. 10 – 30%
C. 30 – 50%
D. 50 – 80%
E. 100%
Progressive Loss of β-Cell Function in Type 2 Diabetes

Progressive loss of β-cell function occurs prior to diagnosis

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

How many classes of drugs are currently available to treat type 2 diabetes?
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 glargine U100
  - Insulin glargine U300
  - Insulin degludec U100
  - Insulin degludec U200

**Oral Medications**
- Alpha-glucosidase inhibitors (AGIs)
- Biguanides
- Bile acid sequestrants (BAS)
- Dipeptidyl peptidase-4 inhibitors (DPP-4i or gliptins)
- Dopamine agonists
- Glitinides
- Sulfonylureas
- Sodium glucose cotransporter-2 inhibitors (SGLT-2i)
- Thiazolidinediones (TZDs or glitazones)

**Non-insulin injectable agents**
- Glucagon-like peptide-1 receptor agonists (GLP-1-RA)
- Amylinomimetic
Pharmacotherapy to “Fix” T2DM Dysfunctional Organs

- **Dopamine agonists** *(brain)*
- **Insulin Secretagogues** *(pancreas- β-cell)*
- **DPP-4i** *(liver, pancreas α & β-cells)*
- **Biguanides** *(liver, colon (?))*
- **AGI’s** *(GI tract- stomach/small intestine)*
- **Amylinomimetics** *(GI tract -stomach/small intestine, liver, pancreas - α & β-cells, brain)*
- **GLP-1 Agonists** *(GI tract -stomach/small intestine, Colon(?), liver, pancreas - α & β-cells, brain)*
- **TZD’s** *(Peripheral tissue, liver & fat)*
- **SGLT-2i** *(kidney)*

Schwartz SS, et al. Diabetes Care 2016;39(2)
## 2015 Management of T2DM Approach

### Monotherapy

<table>
<thead>
<tr>
<th>Efficacy (↓( \text{HbA1c} ))</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Major side effect(s)</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>Low risk</td>
<td>GI, lactic acidosis</td>
<td>Low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after ~3 months of monotherapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient – and disease specific factors):

### Dual Therapy

<table>
<thead>
<tr>
<th>Efficacy (↓( \text{HbA1c} ))</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Major side effect(s)</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Sulfanylurea</td>
<td>High</td>
<td>Moderate risk</td>
<td>GI, lactic acidosis</td>
<td>Low</td>
</tr>
<tr>
<td>Metformin + Thiazolidinedione</td>
<td>High</td>
<td>Gain</td>
<td>Edema, HF, fx's</td>
<td>High</td>
</tr>
<tr>
<td>Metformin + DPP-4 Inhibitor</td>
<td>High</td>
<td>Low risk</td>
<td>GI, lactic acidosis</td>
<td>Low</td>
</tr>
<tr>
<td>Metformin + SGLT2 Inhibitor</td>
<td>High</td>
<td>Low risk</td>
<td>GI, dehydration</td>
<td>High</td>
</tr>
<tr>
<td>Metformin + GLP-1 receptor agonist</td>
<td>High</td>
<td>High risk</td>
<td>GI, dehydration</td>
<td>High</td>
</tr>
</tbody>
</table>

If needed to reach individualized A1C target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):

### Triple Therapy

<table>
<thead>
<tr>
<th>Efficacy (↓( \text{HbA1c} ))</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Major side effect(s)</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Sulfanylurea + DPP-4-i</td>
<td>High</td>
<td>Moderate risk</td>
<td>GI, lactic acidosis</td>
<td>Low</td>
</tr>
<tr>
<td>Metformin + Thiazolidinedione + SLG2-I</td>
<td>High</td>
<td>Gain</td>
<td>Edema, HF, fx's</td>
<td>High</td>
</tr>
</tbody>
</table>
| Metformin + DPP-4 Inhibitor + SGLT2 Inhibitor | Intermediate | Low risk | GI, dehydration     | Neutral /

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1 RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. In refractory patients consider adding TZD or SGL2-I:

### Combinable Injectable Therapy

<table>
<thead>
<tr>
<th>Efficacy (↓( \text{HbA1c} ))</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Major side effect(s)</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin + Basal Insulin</td>
<td>High</td>
<td>High risk</td>
<td>GI, lactic acidosis</td>
<td>High</td>
</tr>
<tr>
<td>Metformin + Mealtime Insulin</td>
<td>High</td>
<td>High risk</td>
<td>GI, lactic acidosis</td>
<td>High</td>
</tr>
</tbody>
</table>

---

2016 AACE/ACE Glycemic Control Algorithm

**LIFESTYLE THERAPY**
(Including Medically Assisted Weight Loss)

**MONOTHERAPY**
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

**DUAL THERAPY**
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

**TRIPLE THERAPY**
- GLP-1 RA
- SGLT-2i
- TZD
- Basal Insulin
- DPP-4i
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

**SYMPTOMS**
- NO
- YES

**ADD OR INTENSIFY INSULIN**
Refer to Insulin Algorithm

**LEGEND**
- ✓ Few adverse events and/or possible benefits
- ❞ Use with caution

*Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation.

**PROGRESSION OF DISEASE**

Fasting vs. Postprandial Glucose Relationship to Complications

• Fasting Glucose
  • Microvascular complications
    • Retinopathy
    • Neuropathy
    • Nephropathy

• Postprandial Glucose
  • Macrovascular complications
    • Dyslipidemia
    • Hypertension
Take- Aways

• Take 60 seconds to share with your “neighbor” at least 2 “take-aways”
  • Write down your “take-aways”
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
### Pharmacotherapy Options

<table>
<thead>
<tr>
<th>Traditional Commonly Used</th>
<th>Traditional Not Commonly Used</th>
<th>Newer Commonly Used</th>
<th>Newer Not Commonly Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>AGIs</td>
<td>DPP-4 inhibitors</td>
<td>Dopamine agonists</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glinides</td>
<td>GLP-1 agonists</td>
<td>Amylinomimetic</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td></td>
<td>SGLT-2 inhibitors</td>
<td>Bile acid sequestrant</td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AGI = α-glucosidase inhibitors; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; SGLT-2 = sodium glucose cotransporters -2.
# Glucose Lowering Comparison

<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>
</tr>
<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>
</tr>
<tr>
<td>AGIs</td>
<td>Oral</td>
<td>No</td>
<td>GI tract</td>
<td>PPG</td>
<td>0.5-1.0</td>
</tr>
<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>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Oral</td>
<td>No</td>
<td>GI tract</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<tr>
<td>Dopamine agonists</td>
<td>Oral</td>
<td>No</td>
<td>Brain, possibly adipose fat</td>
<td>PPG</td>
<td>0.4</td>
</tr>
<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>
</tr>
<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><strong>Weight Effect</strong></th>
<th><strong>Hypoglycemia</strong></th>
<th><strong>β-Cell Protection</strong></th>
<th><strong>CVD Benefits</strong></th>
<th><strong>Cost</strong></th>
<th><strong>Other Considerations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AGIs</strong></td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
<td>Possible</td>
<td>$ to $$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GI adverse effects (gas), dose frequency</td>
</tr>
<tr>
<td><strong>Amylinomimetic</strong></td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GI adverse effects (nausea), injectable, dose frequency</td>
</tr>
<tr>
<td><strong>Bile acid sequestrant</strong></td>
<td>Neutral or loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GI adverse effects (constipation), dose frequency</td>
</tr>
<tr>
<td><strong>Biguanides</strong></td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GI adverse effects (diarrhea), renal and hepatic impairment</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors (gliptins)</strong></td>
<td>Neutral</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Minimal adverse effects</td>
</tr>
<tr>
<td><strong>Dopamine agonist</strong></td>
<td>Neutral or loss</td>
<td>Low risk</td>
<td>Unknown</td>
<td>Yes/no</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GI adverse effects (nausea), hypotension, dizziness</td>
</tr>
<tr>
<td><strong>GLP-1 agonists</strong></td>
<td>Loss</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GI adverse effects (nausea), injectable</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td>Gain or loss</td>
<td>Risk—bolus</td>
<td>Possible</td>
<td>Possible</td>
<td>$ to $$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low risk—basal</td>
<td></td>
<td></td>
<td>Injectable, dose frequency (bolus), increased SMBG</td>
</tr>
<tr>
<td><strong>Secretagogues sulfonylureas and glinides</strong></td>
<td>Gain</td>
<td>Risk</td>
<td>No</td>
<td>No</td>
<td>$ to $$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Immediate short-term response, increased SMBG, dose frequency (glinides)</td>
</tr>
<tr>
<td><strong>SGLT-2 inhibitors</strong></td>
<td>Loss</td>
<td>Low risk</td>
<td>??</td>
<td>Yes</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Urinary tract and urogenital infections</td>
</tr>
<tr>
<td><strong>TZDs (glitazones)</strong></td>
<td>Gain</td>
<td>Low risk</td>
<td>Possible</td>
<td>Yes/no</td>
<td>$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></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.
Newer Therapies

Tell me what you know about:

DPP-4i
GLP-1 RA
SGLT-2i
<table>
<thead>
<tr>
<th>GLP-1 Receptor Agonists</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>short-acting GLP-1 agonists</strong></td>
<td><strong>long-acting GLP-1 agonists</strong></td>
</tr>
<tr>
<td>Exenatide (Byetta®)</td>
<td>Liraglutide (Victoza®)</td>
</tr>
<tr>
<td>5 mcg &amp; 10 mcg</td>
<td>0.6 mg, 1.2 mg, &amp; 1.8 mg</td>
</tr>
<tr>
<td>Twice-daily dosing</td>
<td>Once-daily dosing</td>
</tr>
<tr>
<td>Lixisenatide (Lyxumia®) **</td>
<td>Exenatide (Bydureon®)</td>
</tr>
<tr>
<td>10 mcg &amp; 20 mcg</td>
<td>2 mg</td>
</tr>
<tr>
<td>once-daily dosing</td>
<td>Once-weekly dosing</td>
</tr>
<tr>
<td></td>
<td>Albiglutide (Tanzeum®)</td>
</tr>
<tr>
<td></td>
<td>30mg &amp; 50mg</td>
</tr>
<tr>
<td></td>
<td>Once-weekly dosing</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide (Trulicity®)</td>
</tr>
<tr>
<td></td>
<td>0.75 mg &amp; 1.5 mg</td>
</tr>
<tr>
<td></td>
<td>Once-weekly dosing</td>
</tr>
</tbody>
</table>

** Not FDA approved yet
GLP-1 Receptor 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% to 1.5% (~20-45 mg/dL; most postprandial)

• Long acting agonists lowers fasting and postprandial glucose
  • Decreases A1c by 0.8% to 1.8% (~20-50 mg/dL)

• Most common side effects
  • Weight loss
  • Stomach upset
  • Caution in patients at risk for pancreatitis

# Comparison of Short-Acting vs Long-Acting GLP-1 Receptor Agonists

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

HbA1c = glycated hemoglobin; SBP = systolic blood pressure
DPP-4 Inhibitors (Gliptins)

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

• Saxagliptin (Onglyza®)
  • 2.5 mg and 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, and 25 mg
  • Once-daily dosing
  • Dose adjustment in renal impairment
DPP-4 Inhibitors (Gliptins)

- Inhibits DPP-4 enzyme in the GI tract that breaks down GLP-1 resulting in ↑ endogenous GLP-1 (fixes 2 broken organs)
  - 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

Comparing Actions of DPP-4i and GLP-1 RAs

- **DPP-4 inhibitors**
  - Oral administration
  - Block DPP-4 degradation of GLP-1
  - Increase endogenous GLP-1 levels
    ≈ 2-fold

- **GLP-1 RAs**
  - Subcutaneous administration
  - Add exogenous GLP-1 activity
  - Increase GLP-1 activity ≈ 9-fold
  - Greater A1C and weight effects than DPP-4 inhibitors

SGLT-2 Inhibitors

• Canagliflozin (Invokana®)
  • FDA approved 2013

• Dapagliflozin (Farxiga®)
  • FDA approved 2014

• Empagliflozin (Jardiance®)
  • FDA approved 2014
SGLT-2 Inhibitors

• ↓ 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% to 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)

UTI = urinary tract infection.
Glucose Regulation by the Kidney

(180 L/day) (1000 mg/L) = 180 g/day

90% Glucose

SGLT-2

S1

SGLT-1

S3

10%

No Glucose
Mechanistic Differences in Weight Loss

• **SGLT-2 inhibitors**
  - Mechanism: glucose loss in urine
  - 1 g glucose = 4 kcal
  - Loss of potentially 200 to 300 kcal/day
  - Maximum weight loss at approximately 6 months
  - Weight loss is, in general, maintained

• **GLP-1 agonists**
  - Mechanism: central satiety, other mechanisms?
  - Direct stimulation of several areas of brain
  - Maximum weight loss at approximately 6 months
  - Weight loss is, in general, maintained

Clinical Pearls – Newer Non-Insulin Therapies

• New therapies have low risk of hypoglycemia, are weight neutral or promote weight loss and have CV benefit
  • SGLT-2i promotes most weight loss

• Incretin based therapies fix dysfunctional organs:
  • DPP-4i – fix liver and pancreas
  • GLP-1 agonists fix liver, pancreas, GI tract and brain

• DPP-4i, GLP-1 agonists and SGLT-2i are ideal second line (possibly first line) treatment options for many people with T2D.

• Metformin, GLP-1 agonists and SGLT-2i are in current clinical trials for T1D people with metabolic syndrome (insulin resistance)
Concentrated Insulin
Pharmacokinetic Profile of Currently Available Insulins

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
  • 10–20% of total daily insulin requirement at each meal

• Correction dose (sensitivity factor)
  • Correct hyperglycemia reactively
Rationale for “true” 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 SC administration
  • Multiple injections are required to deliver a single dose
  • Increased injections may lead to compliance issues and poor glycemic control
  • Discomfort
  • Unpredictable absorption (rate-limiting step in insulin activity)
U-100 Insulin vs U-500 Insulin

• Humulin R U-500 is highly concentrated and contains 5 times as much insulin in 1 mL as standard U-100 insulin
  • Truly used for patients on high doses of insulin (usually > 200 units daily)
• Both have onset of action at 30 minutes
  • U-500 insulin exhibits a delayed and lower peak effect relative to U-100
  • U-500 insulin typically has a longer duration of action compared with U-100 (up to 24 hours following a single dose)
• Clinical experience has shown that U-500 insulin frequently has time-action characteristics reflecting both prandial and basal activity

PK and PD profiles for U-500 vs. U-100 Human Insulin

Humulin R U-500 KwikPen

• Can deliver up to 300 units in a single injection
  • No dose conversion for pen
    • Vials/syringes will need dose conversion
  • Dials in 5-unit increments
  • Holds 1500 units of insulin in every pen
  • For severely insulin-resistant patients
    • When daily insulin requirements are in excess of 200 units/day
High-Concentration Glargine (U300)

• U300 insulin glargine offers a smaller depot surface area, leading to a reduced rate of absorption
• Provides flatter and prolonged pharmacokinetic and pharmacodynamic profiles and more consistency
• Half-life is ~23 hours
• Steady state in 4 days
• Duration of action ≤36 hours
  • FDA approved February 25, 2015 (Toujeo®)

Garber AJ. Diabetes Obesity Metab; [Epub ahead of print; published online 31 Oct 2013].
PK and PD of U300 Insulin Glargine vs U100 Insulin Glargine

U300 glargine displays a more even and prolonged PK/PD profile compared with U100 glargine, offering blood glucose control beyond 24 hours.

LLOQ = lower limit of quantification; GIR = glucose infusion rate; PK = pharmacokinetic; PD = pharmacodynamic.

U-100 and U-200 Insulin Degludec

• Approved Sept 2015—Tresiba®
  • Available only as FlexTouch pens
    • U-200: 600 units/pen, max 160 units/inj
    • U-100: 300 units/pen, max 80 units/inj
• Duration of action >42 hours
• Half-life ~25 hours
  • Detectable for at least 5 days
• Steady state in 3-4 days

Garber AJ. Diabetes Obesity Metab; [Epub ahead of print; published online 31 Oct 2013].
Basal Insulin Degludec

Flat, stable profile of both 100 unit/mL and 200 unit/mL formulations

Mean 24-Hour GIR Profile of the Two Insulin Degludec Formulations at Steady State

GIR = glucose infusion rate.

## Concentrated Basal Insulin Dosing Conversion Comparison

<table>
<thead>
<tr>
<th></th>
<th>Glargine U-300</th>
<th>Degludec U-200</th>
<th>Humulin R U-500</th>
</tr>
</thead>
<tbody>
<tr>
<td>True basal insulin</td>
<td>True basal insulin</td>
<td>Pseudo-basal insulin</td>
<td></td>
</tr>
<tr>
<td>1 daily injection</td>
<td>1 to 1</td>
<td>1 daily injection</td>
<td>1 to 1</td>
</tr>
<tr>
<td>2 daily injections</td>
<td>80% of total daily basal dose</td>
<td>2 daily injections</td>
<td>80% of total daily basal dose</td>
</tr>
<tr>
<td>Maximum single-dose injection</td>
<td>80 units</td>
<td>Maximum single-dose injection</td>
<td>160 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>
<td></td>
</tr>
<tr>
<td>240 units of insulin per pen</td>
<td>600 units of insulin per pen</td>
<td>1500 units of insulin per pen</td>
<td></td>
</tr>
<tr>
<td>Expect higher daily dose of Glargine U-300 to maintain glycemic control</td>
<td></td>
<td>Monitor for hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Products/Device</td>
<td>Refrigerated</td>
<td>Unrefrigerated</td>
<td>Once used (opened)</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>----------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Vials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro U-100</td>
<td>28 days</td>
<td>28 days</td>
<td></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>31 days</td>
<td>31 days</td>
<td></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>28 days</td>
<td>28 days</td>
<td><strong>Do not refrigerate</strong></td>
</tr>
<tr>
<td>Insulin aspart</td>
<td></td>
<td></td>
<td>Lispro, glargine, glulisine: 28 days</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td></td>
<td>Aspart: 14 days</td>
</tr>
<tr>
<td>Insulin glargine U-100</td>
<td></td>
<td>Glargine U-300: 42 days</td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vials &amp; pens: Insulin detemir</strong></td>
<td>42 days</td>
<td>42 days (pens should not be refrigerated)</td>
<td></td>
</tr>
<tr>
<td><strong>Pens: Insulin degludec</strong></td>
<td>56 days</td>
<td>56 days (pens should not be refrigerated)</td>
<td></td>
</tr>
<tr>
<td>U-100, U-200</td>
<td></td>
<td></td>
<td></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>
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
Importance of Patient Education
BG–Lowering Agents and the “Best” Time to Take Them

• **Agents to be taken before meals**
  - AGIs
  - Dopamine agonists
  - Glinides
  - Short-acting GLP-1 agonists
  - Bolus insulin

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

• **Agents that can be taken with or without food**
  - TZDs
  - DPP-4 inhibitors
  - Long-acting GLP-1 agonists
  - SGLT-2 inhibitors
  - Basal insulin

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?

Take- Aways

• Take 60 seconds to share with your “neighbor” at least 2 “take-aways”
  • Write down your “take-aways”
Take Home Message

• Diabetes management is constantly evolving
  • Clinicians must stay current with new therapies and trends

• The longer we wait—the more damage is done!
  • Earlier diagnosis and treatment is needed
  • Appropriate drug therapy plus lifestyle modification is needed
    • Monotherapy rarely works, and does so only on a short-term basis

• Newer and emerging therapies target key organ defects

• Individualize glycemic goals and therapy
  • One size does NOT fit all
  • Key considerations in therapy
    • Protect β-cell, minimize hypoglycemia, & minimize weight gain