Basal Insulin Therapy in the Treatment of Insulin Resistant Type 2 Diabetes: The Role of the Pharmacist in Ensuring Their Safe and Effective Use in Patients

Susan Cornell, BS, Pharm.D., CDE, FAPhA, FAADE
Midwestern University Chicago College of Pharmacy
Objectives

1. Describe the reasons for the use of high concentration insulin formulations in the treatment of type 2 diabetes

2. Discuss the clinical, pharmacokinetic and pharmacodynamic profiles for current and emerging basal insulins

3. Implement strategies for safely converting between U-100 and concentrated insulin formulations using different syringes and pen devices in patients with type 2 diabetes

4. Review currently available insulin pens and syringes used for the administration of insulin

5. Explain and apply strategies to overcome the barriers to insulin-mediated glucose control
Disclosures

- Susan Cornell, Pharm.D., CDE, FAPhA, FAADE has no real or potential conflicts of interest to report.
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Pre-Activity Questions 1-4
Pre-test Question #1

Which of the following does NOT represent a reason for using high concentration insulin formulations in the treatment of type 2 diabetes?

1. Volume of insulin dose is physically too large for a single SC administration
2. Patient cannot manipulate vials and syringes
3. Multiple injections are required to deliver a single insulin dose
4. Discomfort
5. Unpredictable insulin absorption
A 55 year old female, high school teacher with Type 2 diabetes is referred to you for dosing of U500 insulin. Her current meds are NPH 100 units twice daily, lispro 10-30 units with meals plus correction, and metformin 1000mg daily. Her A1C is 7.1% and Scr is 1.1. How would you instruct the patient to draw up 110 units of U500 insulin?

1) Using a U100 syringe, draw to the 50 units marking
2) Using a U100 syringe, draw to the 25 units marking
3) Using a tuberculin syringe, draw 0.2 mL
4) Using a tuberculin syringe, draw 0.4 mL
Pre-test Question #3

Which of the following is NOT a strategy to overcome the barriers to insulin therapy?

1. Avoid using insulin as a “threat” and discuss it as an option early
2. Dose NPH insulin twice daily to minimize hypoglycemia
3. Use insulin pens and regimens that offer maximum flexibility
4. Give a “limited” trial of insulin
Pre-test Question #4

Which of the following statements is **INCORRECT** regarding the new basal insulin U300 glargine?

1. It is associated with less nocturnal hypoglycemia
2. It has a flatter PK profile and a duration of action \(\leq 36\) hrs
3. It is only available in a pen with 1.5 mL of U300 glargine
4. Current pen allows for a max of 240 units of insulin per shot
5. Patients switching from twice daily NPH to U300 glargine should start with 80% of total daily NPH dosage
The Diabetes Epidemic
Diabetes in the United States

- 29.1 million people (9.3% of the population) have diabetes
- 8.1 million are undiagnosed
- CDC estimates that 1 in 3 adult Americans will have diabetes by 2050
- Type 2 Diabetes (T2DM)
  - Associated with obesity, older age, decreased physical activity, and race/ethnicity
  - Incidence in children and adolescents is increasing
- Estimated total costs in 2012: $245 billion
Type 2 Diabetes

- Characterized by chronic hyperglycemia
- Associated with microvascular and macrovascular complications
- Generally arises from a combination of insulin resistance and β-cell dysfunction

By the time a person is diagnosed with type 2 diabetes, approximately how much β-cell function has been lost?

1. <10%
2. 10–30%
3. 30–50%
4. 50–80%
5. 100%
Progressive Deterioration in β-Cell Function Over Time

HOMA = homeostasis model assessment.
Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet

- Decreased Incretin Effect
- Impaired Insulin Secretion
- Islet β-cell
- Increased Glucagon Secretion
- Islet α-cell
- Increased Glucose Reabsorption
- Increased Lipolysis
- Increased Glucose Uptake
- Neurotransmitter Dysfunction

Insulin Resistance
~90% of People with Type 2 Diabetes are Overweight or Obese

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...

More than 80% of Patients Progressing to Type 2 Diabetes are Insulin Resistant

Insulin Resistance Reduces Response to Circulating Insulin

- **Insulin resistance**
  - **Liver**: ↑ Glucose output
  - **Muscle**: ↓ Glucose uptake
  - **Adipose tissue**: ↓ Glucose uptake

- **Hyperglycemia**: ↑ Insulin/medication requirements needed to maintain glycemic control
Treatment Options for Type 2 Diabetes
12 Pharmacotherapy Options

**Insulin**
- **Bolus insulin**
  - Insulin lispro (Humalog)
  - Insulin aspart (NovoLog)
  - Insulin glulisine (Apidra)
  - Insulin human inhaled (Afrezza)
  - Regular human insulin
    - (Humulin R)
    - (Novolin R)
- **Basal insulin**
  - Insulin NPH
    - (Humulin N)
    - (Novolin N)
  - Insulin detemir (Levemir)
  - Insulin glargine U-100 (Lantus)
  - Insulin glargine U-300 (Toujeo)

**Oral Medications**
- $\alpha$-glucosidase inhibitors (AGI)
- Biguanides
- Bile acid sequestrants (BAS)
- Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins)
- Dopamine agonists
- Glitiniides
- Sulfonylureas
- Sodium glucose co-transporter-2 inhibitors
- Thiazolidinediones (TZDs or glitazones)

**Non-insulin injectable agents**
- Glucagon-like peptide-1 (GLP-1) agonists
- Amylinomimetics

## Glucose-Lowering Comparison

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Route of Administration</th>
<th>Targets Insulin Resistance</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>Both</td>
<td>1.5–2.0</td>
</tr>
<tr>
<td>Metformin</td>
<td>Oral</td>
<td>Yes</td>
<td>FPG</td>
<td>1.5</td>
</tr>
<tr>
<td>Glitazones</td>
<td>Oral</td>
<td>Yes</td>
<td>Both</td>
<td>1.0–1.5</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.5–2.0</td>
</tr>
<tr>
<td>AGIs</td>
<td>Oral</td>
<td>No</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>PPG</td>
<td>0.5–0.7</td>
</tr>
<tr>
<td>Bile acid sequestrant</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.4</td>
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<tr>
<td>Dopamine agonists</td>
<td>Oral</td>
<td>No</td>
<td>PPG</td>
<td>0.4</td>
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<tr>
<td>SGLT-2 inhibitors</td>
<td>Oral</td>
<td>↓ glucose toxicity</td>
<td>FPG</td>
<td>0.7–1.1</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Injectable</td>
<td>No</td>
<td>Short-acting – PPG</td>
<td>0.8–1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Long-acting – Both</td>
<td></td>
</tr>
<tr>
<td>Amylin analogs</td>
<td>Injectable</td>
<td>No</td>
<td>PPG</td>
<td>0.6</td>
</tr>
<tr>
<td>Insulin</td>
<td>Injectable</td>
<td>↓ glucose toxicity</td>
<td>Basal – FPG Bolus – PPG</td>
<td>↓ as much as needed</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose; PPG = postprandial glucose.

Basal Insulin Therapy: Concept and Physiology
UKPDS: Progressive Deterioration in Glycemic Control Over Time

HbA1C Level

<table>
<thead>
<tr>
<th>Time from Randomization (y)</th>
<th>Median A1C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7.0</td>
</tr>
<tr>
<td>3</td>
<td>7.1</td>
</tr>
<tr>
<td>6</td>
<td>7.2</td>
</tr>
<tr>
<td>9</td>
<td>7.4</td>
</tr>
<tr>
<td>12</td>
<td>7.6</td>
</tr>
<tr>
<td>15</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Conventional

Intensive

## Currently Available Insulins

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Onset</th>
<th>Peak, h</th>
<th>Duration of Action, h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting analogs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro, aspart,</td>
<td>15 min</td>
<td>0.5–1.5</td>
<td>3–5</td>
</tr>
<tr>
<td>glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin human inhaled</td>
<td>12–15 min</td>
<td>~1.0</td>
<td>2.5–3.0</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular human (U-100)</td>
<td>30–60 min</td>
<td>2–4</td>
<td>5–8</td>
</tr>
<tr>
<td>Regular human (U-500)</td>
<td>30–60 min</td>
<td>4–8</td>
<td>14–15</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human NPH insulin</td>
<td>1–3 h</td>
<td>6–12</td>
<td>12–24</td>
</tr>
<tr>
<td><strong>Long-acting (basal)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>2–4 h</td>
<td>No pronounced peak</td>
<td>20–24</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>1–3 h</td>
<td></td>
<td>18–20</td>
</tr>
<tr>
<td><strong>Ultralong-acting (basal)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td>6 h</td>
<td>No pronounced peak</td>
<td>≤36</td>
</tr>
</tbody>
</table>

Thinking Like a Pancreas

- No food
- Meals
- More for “waking up”
- Less overnight

Time:
- 8 AM
- 12 NOON
- 3 PM
- 6 PM
- 9 PM
- 3 AM
- 7 AM
PK Profile of Currently Available Insulins

PK = pharmacokinetic; NPH = neutral protamine Hagedorn.

Insulin Regimens Used in T2DM

- **Basal only**
  - 1 injection
  - Added to oral agents

- **Basal plus**
  - 2 injections or 1 injection + 1 inhalation
  - Adding one rapid-acting analog sequentially starting with largest meal

- **Basal bolus**
  - 4 injections or 1 injection + 3 inhalations
  - Rapid-acting analog before each meal

- **Pre-mixed**
  - 2 injections

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

Insulin Therapy in Patients with Insulin Resistance

• Insulin, insulin, and yet more insulin!
  – Causes weight gain and fluid retention
  – Increased risk of hypoglycemia
  – Expensive at high volumes (especially the pens)
  – Multiple injections per day often needed

• Pumps not practical with high volume insulin usage
High Doses of Insulin

• Concerns:
  – Hypoglycemia
  – Medication errors in dosing
  – Absorption issues

• Problems:
  – Over-basalization
  – Failure to treat the physiological defects
    • Insulin resistance
    • Decrease satiety
Concentrated Insulin
Why Concentrated Insulin?

• When daily insulin requirements are in excess of 200 units/day, the volume of U-100 injected insulin becomes a challenge:
  – Physically too large for a single SC administration
  – Multiple injections are required to deliver a single dose
  – Increased injections may lead to adherence issues and poor glycemic control
  – Discomfort
  – Unpredictable absorption (rate-limiting step in insulin activity)

Patients Who May Require Concentrated Insulin

- **Patients with insulin resistance**
  - Patients with inherited insulin receptor abnormalities or presence of autoantibodies to insulin receptor
  - Diabetes patients with insulin antibodies
  - Type 2 diabetes patients
  - Overweight/obese Type 1 diabetes patients

- **Other patients**
  - Obstetrics patients
  - Patients receiving high-dose glucocorticoid therapy

Currently Available Concentrated Insulins

Regular human insulin U-500 (Humulin R U-500)

Insulin glargine U-300 (Toujeo)

U-500 Regular Human Insulin

• U-500 is highly concentrated and contains five times as much insulin in 1 mL as standard U-100 insulin

• U-500 vial
  – U-500 : contains 20 mL
  – U-100: contains 10 mL

• U-500 vial
  – Marked with a band of diagonal brown stripes to distinguish it from the U-100 vial, which has no stripes
  – “U-500” is also highlighted in red on the label

U-100 Insulin vs U-500 Insulin

• Both have onset of action of 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 to 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

**IRI = immunoreactive insulin.**

Safety Concerns with Concentrated Insulin
Medication Errors Associated with U-500 Insulin

• Some health care professionals may not be aware of U-500 insulin, increasing the chance of dispensing errors
  – From the shelf during dispensing
  – From the computer screen when prescribing
  – Communication errors during medication reconciliation

• Dosing errors
  – No insulin syringe designed to measure U-500 insulin

• Due to increasing medication errors with U-500 insulin and the lack of a U-500 specific syringe, The Institute for Safe Medication Practices suggests “It’s time to rethink safe use of strengths above U-100”

U-500 Insulin Dosing Conversion

<table>
<thead>
<tr>
<th>U-500 Insulin Dose (Actual units)</th>
<th>U-100 Syringe (Unit markings)</th>
<th>Volume for Tuberculin Syringe (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>75</td>
<td>15</td>
<td>0.15</td>
</tr>
<tr>
<td>100</td>
<td>20</td>
<td>0.20</td>
</tr>
<tr>
<td>125</td>
<td>25</td>
<td>0.25</td>
</tr>
<tr>
<td>150</td>
<td>30</td>
<td>0.30</td>
</tr>
<tr>
<td>175</td>
<td>35</td>
<td>0.35</td>
</tr>
<tr>
<td>200</td>
<td>40</td>
<td>0.40</td>
</tr>
<tr>
<td>225</td>
<td>45</td>
<td>0.45</td>
</tr>
<tr>
<td>250</td>
<td>50</td>
<td>0.50</td>
</tr>
<tr>
<td>275</td>
<td>55</td>
<td>0.55</td>
</tr>
<tr>
<td>300</td>
<td>60</td>
<td>0.60</td>
</tr>
<tr>
<td>325</td>
<td>65</td>
<td>0.65</td>
</tr>
<tr>
<td>350</td>
<td>70</td>
<td>0.70</td>
</tr>
<tr>
<td>375</td>
<td>75</td>
<td>0.75</td>
</tr>
<tr>
<td>400</td>
<td>80</td>
<td>0.80</td>
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<tr>
<td>425</td>
<td>85</td>
<td>0.85</td>
</tr>
<tr>
<td>450</td>
<td>90</td>
<td>0.90</td>
</tr>
<tr>
<td>475</td>
<td>95</td>
<td>0.95</td>
</tr>
<tr>
<td>500</td>
<td>100</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*The following dosing formulas may also be used: dose (actual units) × 0.2 = unit markings in a U-100 insulin syringe, dose (actual units) × 0.002 = volume (mL) in a tuberculin syringe.

Food and Drug Administration. Humulin R-U-500 (concentrated) Insulin Human Injection. Drugs@FDA .gov.
New and Emerging Basal Insulins
Quest for Better Insulin Products

1. Efficacy
   - Reductions in A1C
   - Reductions in FBG and PPG

2. Convenience
   - Pen dosing
   - Flexible dosing (any time of day)
   - Different concentrations
   - Ability to mix with other insulin and non-insulin agents

3. Safety
   - Low incidence of hypoglycemia
   - Low incidence of nocturnal hypoglycemia
   - Less individual variability
   - Less weight gain
Newly Approved U-300 Insulin Glargine

- U-300 insulin glargine offers a smaller depot surface area leading to a reduced rate of absorption
- Provides a 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
- Associated with less hypoglycemia especially nocturnal hypoglycemia
- FDA approved February 25, 2015

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


U-300 glargine displays a more even and prolonged PK/PD profile compared with U-100 glargine, offering blood glucose control beyond 24 hours.
## U-300 Glargine vs U-100 Glargine in T2DM: Meta-Analysis of Phase III Trials EDITION 1, 2, & 3

Baseline to Month 6

<table>
<thead>
<tr>
<th></th>
<th>Glar U-300 (N=1247)</th>
<th>Glar U-100 (N=1249)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C (%)</strong>, LS mean</td>
<td>−1.02</td>
<td>−1.02</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong>, LS mean</td>
<td>0.49</td>
<td>0.75</td>
<td><em>P</em> = 0.058</td>
</tr>
<tr>
<td><strong>Any hypo in 24 hr</strong>*</td>
<td>67.8</td>
<td>73.8</td>
<td>0.92 (0.87–0.96)</td>
</tr>
<tr>
<td><strong>Any nocturnal hypo</strong>*</td>
<td>31.7</td>
<td>41.3</td>
<td>0.77 (0.69–0.85)</td>
</tr>
<tr>
<td><strong>Confirmed BG &lt;54 mg/dl or severe hypo</strong>*</td>
<td>26.9</td>
<td>33.3</td>
<td>0.81 (0.72–0.90)</td>
</tr>
<tr>
<td><strong>Confirmed nocturnal BG &lt;54 mg/dl or severe hypo</strong>*</td>
<td>9.7</td>
<td>13.2</td>
<td>0.73 (0.59–0.91)</td>
</tr>
</tbody>
</table>

*% people ≥1 event.

LS = least squares; RR = relative risk; BG = blood glucose; CI = confidence interval.

Flexible vs Fixed Dosing U-300 Glargine: Sub-Studies of Phase III Trials

- No difference in A1C between flexible- vs fixed-dosing
- No difference in severe or nocturnal hypoglycemia within each sub-study

Edition 1 Sub-Study
N = 109

Edition 2 Sub-Study
N = 89

U-300 Insulin Glargine

• Only available in pens
  – 300 U/mL, 1.5 mL
  – Max dose per shot is 80 units with current pen
  – New pen in development will allow a max dose of 240 units
  – Just dial the prescribed dose; no conversion needed like U-500

• U-300 glargine pen is white and green with the concentration highlighted in orange to distinguish it from U-100 glargine

U-300 Insulin Glargine Dosing

• Insulin-Naive Patients:
  – Type 1 Diabetes – Start with 1/3 to 1/2 of the total daily insulin dose calculated by using 0.2-0.4 U/kg/day; give the remainder of the total daily insulin dose as a short-acting insulin and divide between each daily meal
  – Type 2 Diabetes – Start with 0.2 U/kg/day

• Type 1 or Type 2 Diabetes:
  – Changing from once daily long-acting or intermediate-acting insulin:
    • Initial dose can be the same as the once daily long-acting dose; for patients controlled on U-100 insulin glargine, expect that a higher daily dose of U-300 glargine will be needed to maintain the same level of glycemic control
  – Changing from twice daily NPH insulin:
    • Initial dose is 80% of the total daily NPH dosage

Insulin Degludec*

- Duration of action >42 hours
- Half-life ~25 hours
  - Detectable for at least 5 days
- Steady state in 2–3 days
- FDA denied approval in 2013, research continues
  - Approved in EU

*Not FDA approved.

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.

Pharmacodynamic Variability with Insulin Degludec vs Insulin Glargine

Subjects listed in increasing order of individual coefficient of variation

U-200 Insulin Degludec: Safety and Efficacy

26-week Open-label, Randomized Study of 457 Patients with Type 2 Diabetes

No difference in hypoglycemia between the two treatment groups

PEGylated Insulin Lispro*

- Polyethylene glycol polymer covalently attached to lispro
- Half-life 2–3 days
- Steady state in 7–10 days
- Duration of action >36 hours
- Phase II–III clinical trials

*Not FDA-approved.

PEGylated Insulin Lispro (LY2605541) Pharmacodynamics

Glucose clamp study in 32 patients, 8 per study arm

Mean GIR (mg/min/kg)

Time (hours)

GIR = glucose infusion rate.

PEGylated Insulin Lispro (LY2605541) vs Glargine U-100 in T1DM

LY2605541 Treatment at 8 weeks

- Significantly lowered A1C vs glargine
- Significantly reduced weight (1.2 kg)
- Increased overall hypos ($p = 0.04$) but less nocturnal hypos ($p = 0.01$)
- Lowered prandial insulin dose
- Significantly increased liver enzymes

Is there an alternative to concentrated insulin for patients on high doses of insulin?
Combination Basal Insulin and GLP-1 RAs

- **Basal Bolus**: Add Prandial Insulin before Each Meal
- **Basal Plus**: Add Prandial Insulin at Main Meal
- **Basal**: Add Basal Insulin and Titrate
- **Basal** plus **GLP-1 RAs**
- **Lifestyle Changes plus Metformin** (± other agents)
Barriers to Insulin-Mediated Glucose Control
Significant Delay in Insulin Initiation

The reason for delay in starting insulin in diabetes management is:

a. Provider reluctance (clinical inertia)
b. Patient reluctance
c. Lack of time
d. Fear of hypoglycemia
e. All of the above
### Key Barriers to Insulin Therapy

<table>
<thead>
<tr>
<th>Patient Barriers</th>
<th>Provider Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient reluctance</td>
<td>Clinical inertia</td>
</tr>
<tr>
<td>Sense of failure</td>
<td>Lack of insulin training, time, and/or support</td>
</tr>
<tr>
<td>Loss of independence</td>
<td>Fear of hypoglycemia</td>
</tr>
<tr>
<td>Belief that insulin is ineffective</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Fear of injections</td>
<td></td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
</tr>
</tbody>
</table>

Overcoming the Barriers to Insulin Therapy

• Avoid using insulin as a “threat,” but a solution and discuss it as an option early

• Use insulin pens and regimens that offer maximum flexibility

• Give a “limited” trial of insulin

• Tell patient injection is less painful than finger stick and give an injection in the office

• Teach patient to recognize and treat hypoglycemia, and use basal analog insulins to minimize hypoglycemia risk

• Meet with dietitian before initiation of insulin

Insulin Administration
Insulin Titration and Education

• First, do no harm
  – Halt the hypoglycemia

• Fix the fastings

• Pare the postprandials
Patient Education

• Equipment and supplies patients need to effectively manage their insulin therapy at home
  – Insulin
  – Syringes or pen needles
  – Blood glucose meter and strips
  – Lancets and lancing device
  – Glucagon emergency kit
  – Contact information of diabetes care provider(s)
# Expiration of Products

<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</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>
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<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>
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<td></td>
<td>Do not refrigerate</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Expiration Date</td>
<td>28 days</td>
<td>(lispro, glargine) – 28 days,</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td></td>
<td></td>
<td>(aspart) – 14 days</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-100</td>
<td></td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U-300</td>
<td></td>
<td>28 days</td>
<td></td>
</tr>
<tr>
<td><strong>Vials and pens</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Insulin detemir</td>
<td>Expiration Date</td>
<td>42 days</td>
<td>42 days</td>
</tr>
<tr>
<td><strong>Inhaled:</strong> Insulin human</td>
<td>—</td>
<td>Expiration Date</td>
<td>15 days for device</td>
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</tbody>
</table>

## Basal Insulin Delivery Options

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Concentration</th>
<th>Vial</th>
<th>Pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glargine</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glargine</td>
<td>U-300</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Detemir</td>
<td>U-100</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Regular Human</td>
<td>U-500</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Source: Food and Drug Administration. Drugs@FDA FDA Approved Drug Products. http://www.accessdata.fda.gov
Vial and Syringe

• Some patients still use vials and syringes
  – Wipe the rubber stopper (on vial) with alcohol swab
  – Put equivalent amount of air into the vial before drawing up the insulin (based on insulin dose)

• When mixing insulin:
  – Clear before cloudy
  – Pre-drawn N + R = stable for 30 days refrigerated
Needles and Syringes

- Needle (cannula)
- Needle hub
- Inner protective cap
- Peel foil
- Outer protective cap
- Plunger
- Barrel

Dimensions:
- 12.7 mm (1/2"
- 8 mm (5/16"
- 5 mm (3/16"

Insulin Pens

How to Use an Insulin Pen
Patient Cases
Case 1

• 67-year-old male, retired engineer
  – BMI 45
  – A1c = 8.5%
  – SrCr = 1.2

• Medications:
  – Glargine (pen) 80 units twice per day
  – Aspart (pen) 30–60 units per meal + correction
  – Lisinopril 10 mg daily
  – Atorvastatin 10mg daily

• Total daily dose (TDD) insulin: ~300 units per day
• Largest meal is supper and snacks at night
Case #1 – Question #1

- The physician recently became aware of concentrated insulin and would like to switch the patient to U-500. For a total daily dose of 300 units to be given twice daily, how would you instruct the patient to draw up 150 units of U-500 insulin?

1) Using a U-100 syringe, draw to the 60 units marking
2) Using a U-100 syringe, draw to the 30 units marking
3) Using a tuberculin syringe, draw 0.2 mL
4) Using a tuberculin syringe, draw 0.4 mL
Case 1 Continued

- First assess patient current insulin injection technique
  - If technique is appropriate then.....

- Start U-500 insulin:
  - 300 units divided into two doses = 150 units twice daily
  - 150 units of U-500 insulin is equal to 30 units on a U-100 syringe
  - 30 units x 5 (5 times concentration) = 150 units of actual insulin
  - If using tuberculin syringe, 150 units = 0.3 mL

- U-300 insulin glargine is not a substitute for U-500 insulin because the current U-300 pen delivers only up to 80 units per injection
Case 2

- 56 year old female, high school principal
  - BMI 32
  - A1c = 8.9%
  - SrCr = 1.1
- Patient did report occasional episodes nocturnal hypoglycemia
  - ~ 3–5 per month
- Medications:
  - NPH (pen) 63 units twice per day
    - Morning (7 AM) and 2 hours before bed (9 PM)
  - Metformin 1000 mg daily
  - Sitagliptin 100 mg daily
  - Lisinopril 10 mg daily
  - Simvastatin 20 mg daily
- Total daily dose (TDD) insulin: ~126 units per day
- Patient does not want to start bolus insulin due to erratic meal and work schedules
Case #2 – Question #1

• The physician wants to switch the patient to U-300 insulin glargine. What would be your recommendation for switching from 63 units twice daily (126 units/day) NPH to U-300 insulin glargine?

1) Using a U-100 syringe, draw to 21 units marking (63 units) and inject twice daily

2) Using a U-100 syringe, draw to 49 units marking (126 units) and inject once daily

3) Using the U-300 pen, dial to 126 units and inject once daily

4) Using the U-300 pen, dial to 51 units and inject twice daily
Case 2

- Switching to U-300 insulin glargine
  - Determine starting dose:

<table>
<thead>
<tr>
<th>Prior treatment</th>
<th>Start with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily long-acting or intermediate acting insulin</td>
<td>1:1</td>
</tr>
<tr>
<td>Twice-daily NPH</td>
<td>80% total daily basal dose</td>
</tr>
<tr>
<td>No current basal insulin</td>
<td>0.2 U/kg/day</td>
</tr>
</tbody>
</table>

- 126 units x 0.80 = 100.8 units U-300 glargine
  - 101 units/2 = 51 units given twice daily; current U-300 pen has max dose of 80 units per injection

- To minimize hypoglycemia risk, titrate the dose no more frequently than every 3–4 days
Summary

• Type 2 diabetes is a growing epidemic with an ever-growing number of patients requiring high doses of insulin to maintain glycemic control.

• Insulin resistance is a MAJOR problem among patients with type 2 diabetes, and combination therapy is often needed to improve insulin sensitivity.

• A basal-bolus insulin regimen is best to mimic natural insulin physiology but requires frequent BG monitoring and provider/patient education.

• Concentrated insulin is ideal for patients with insulin doses >200 U/day due to the large volume associated with U-100 insulin.
Summary Continued

• U-500 regular human insulin is associated with a high incidence of dosing errors due to the lack of a U-500 specific insulin syringe

• Newly approved U-300 insulin glargine is available in a pen, avoiding the need for conversion using U-100 or tuberculin syringes needed with U-500 insulin

• Insulin in T2DM is often delayed, but in order to optimize glycemic control, it is important that clinicians recognize and address the barriers to insulin therapy

• U-300 insulin glargine and emerging basal insulins have improved PK/PD profiles compared to current insulins
  – Flatter time–action profiles with less variability
  – Less hypoglycemia, particularly nocturnal hypoglycemia
Post-Activity Questions 1-4
Post-test Question #1

Which of the following does **NOT** represent a reason for using high concentration insulin formulations in the treatment of type 2 diabetes?

1. Volume of insulin dose is physically too large for a single SC administration
2. Patient cannot manipulate vials and syringes
3. Multiple injections are required to deliver a single insulin dose
4. Discomfort
5. Unpredictable insulin absorption
A 55 year old female, high school teacher with Type 2 diabetes is referred to you for dosing of U500 insulin. Her current meds are NPH 100 units twice daily, lispro 10-30 units with meals plus correction, and metformin 1000mg daily. Her A1C is 7.1% and Scr is 1.1. How would you instruct the patient to draw up 110 units of U500 insulin?

1) Using a U100 syringe, draw to the 50 units marking
2) Using a U100 syringe, draw to the 25 units marking
3) Using a tuberculin syringe, draw 0.2 mL
4) Using a tuberculin syringe, draw 0.4 mL
Post-test Question #3

Which of the following is NOT a strategy to overcome the barriers to insulin therapy?

1. Avoid using insulin as a “threat” and discuss it as an option early
2. Dose NPH insulin twice daily to minimize hypoglycemia
3. Use insulin pens and regimens that offer maximum flexibility
4. Give a “limited” trial of insulin
Post-test Question #4

Which of the following statements is **INCORRECT** regarding the new basal insulin U300 glargine?

1. It is associated with less nocturnal hypoglycemia
2. It has a flatter PK profile and a duration of action ≤36 hrs
3. It is only available in a pen with 1.5 mL of U300 glargine
4. Current pen allows for a max of 240 units of insulin per shot
5. Patients switching from twice daily NPH to U300 glargine should start with 80% of total daily NPH dosage
Backup Slides
In what year was insulin made available to treat humans?

1) 1898
2) 1922
3) 1937
4) 1948
5) 1956
BANTING (1891–1941) & BEST (1899–1978)

First Commercial Insulin
Milestones in Insulin Development

First Time Preparation

• Check the pen
  – Make sure liquid is clear, colorless, particle-free (N insulin and mixed insulin will be cloudy)
  – Wipe the rubber stopper with alcohol

• Attach the needle

• Prime the needle
  – Dial 2 to 3 units, hold up and depress the button
    • Repeat the process until a drop of insulin appears at the tip of the needle

• Dial up the dose
Insulin Injection

• Inject straight into the skin
  – Depress the button to release insulin into SC tissue

• Hold for 5 to 10 seconds before removing the needle from skin

• Remove needle and dispose into sharps container

• Always have the patient demonstrate their technique
  – At first education of the device
  – At first follow-up visit
  – At frequent intervals thereafter
Improper Insulin Injection Technique

• The patient did not tip and roll insulin suspension pen injector to ensure proper mixing

• The patient put a needle on the pen, dialed to 10 units, pushed the needle into the injection pad, and then proceeded to dial back to zero

• The patient omitted the 2-unit air shot prior to each dose

• The patient injected his insulin into the orange (as he was taught) and then ate the orange
Insulin Resistance: Patient Risk Factors

• Medical conditions associated with risk:
  – History of gestational diabetes (GDM)
  – Lipodystrophy and other inherited disorders
  – Fatty liver disease
  – Metabolic syndrome (obesity, HTN, mixed hyperlipidemia)
  – Polycystic ovarian syndrome (PCOS)

• Physical exam/historical markers associated with risk:
  – Obesity
  – Increased waist-to-hip ratio (visceral adiposity)
  – Certain ethnic groups have increased risk
  – Acanthosis nigricans