The New Age of Insulin: Exploring the Latest Trends in Insulin Therapy

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Disclosure
Conflicts of Interest and Financial Relationships Disclosures:

Susan Cornell, PharmD, CDE, FAPhA, FAADE
• Advanced Practitioner Advisory Board and Speaker’s Bureau:
  • Novo Nordisk.

Objectives
At the conclusion of this knowledge-based educational activity, participants will be able to:

• Describe the use of individualized insulin therapy in current treatment guidelines for type 2 diabetes mellitus.

• Compare the pharmacokinetic and pharmacodynamic parameters of insulin formulations and delivery methods.

• Explain appropriate insulin preparation and injection techniques for at least 3 different products.
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29.1 million with Diabetes

86 million with Prediabetes


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


β-cell Decline in Prediabetes and T2DM


IR = insulin resistance

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Relationship Between FPG and PPG Levels and Complications

- **FPG**
  - Microvascular complications
  - Retinopathy
  - Neuropathy
  - Nephropathy
- **PPG**
  - Macrovascular complications
  - Dyslipidemia
  - Hypertension

Which Blood Glucose Values Are Causing the Problem: FPG or PPG?

<table>
<thead>
<tr>
<th>% Contribution</th>
<th>A1C Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FPG</td>
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<td>8.5 - 9.2</td>
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<tr>
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</tr>
</tbody>
</table>


Key Points to Consider When Selecting Pharmacotherapy for T2DM

- Utilize a treatment regimen that will fix as many of the diabetes defects as possible
- Choose a therapy that is safe and effective with the least amount of side effects, especially undesirable side effects
  - Hypoglycemia
  - Weight gain
- Consider cardiovascular safety
- Benefit
- Neutral
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The Ominous Octet: Circa 2008

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 have insulin resistance as well
- Adding more insulin (eg, high doses) does not fix insulin resistance

ADA Standards of Medical Care (2017)
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Insulin “fixes 5 defects

Thinking like a Pancreas

The Basal-Bolus Concept

• “Components” of Insulin Replacement
  • 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)
    • Additional insulin needed (usually pre-meal)
      • Often to correct for fasting hyperglycemia

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### Insulin Options

- **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

**NPH = neutral protamine Hagedorn**

* Can be purchased without prescription

### Pharmacokinetic Profile of Currently Available Insulins

![Pharmacokinetic Profile](image)

**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>Regular U100 &amp; U200</td>
<td>within 15 min</td>
<td>0.5-1.5</td>
<td>3-6</td>
<td>Clear</td>
</tr>
<tr>
<td>NPH</td>
<td>within 15 min</td>
<td>0-18</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>90-120</td>
<td>2-4</td>
<td>24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Regular hum insulin</td>
<td>90-120</td>
<td>0-40 min</td>
<td>9 hr</td>
<td>Powder</td>
</tr>
<tr>
<td>Regular U200</td>
<td>20 min</td>
<td>2-4</td>
<td>up to 24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>NPH</td>
<td>2-8</td>
<td>2-4</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>0-4</td>
<td>0-20 min</td>
<td>24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>Insulin glargine U100</td>
<td>2</td>
<td>0-24</td>
<td>Clear</td>
<td></td>
</tr>
<tr>
<td>Insulin glargine U300</td>
<td>6</td>
<td>24</td>
<td>Clear</td>
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<td>Insulin glargine U300</td>
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<td>24</td>
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<tr>
<td>Lantus</td>
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<td>Clear</td>
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<td>Lantus Lente</td>
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<td>0-24</td>
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<td>Clear</td>
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<tr>
<td>Lantus Lente 7200</td>
<td>0-12</td>
<td>0-24</td>
<td>Clear</td>
<td></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.

**References**


Flood TM. *J Fam Pract*. 2007; 56(suppl 1):S1-S12.

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Approach To Starting and Adjusting Insulin in T2DM

- **Initiate basal insulin**
  - Usually with metformin +/- other non-insulin agent

- **Start:** 10 U/day or 0.1 - 0.2 U/kg/day
- **Adjust:** 10% - 15% or 2 - 4 units once/twice weekly to reach FPG target
- **For hypoglycemia:** identify/fix cause; can decrease dose by 10% - 20% or 4 units

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**Insulin Strategies in T2DM**

Metformin + basal insulin

- **Fasting coverage**
- **Minimal postprandial coverage**
- **Hypoglycemic risk**
  - Insulins glargine, detemir, degludec — lower risk
  - Cost is higher
  - Requires prescription
  - **Human insulin isophane (NPH) — higher risk**
  - Cost is lower
  - **Can be purchased without a prescription**
- **Weight gain/neutral**

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Let’s Look at Basal Insulin options

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Pharmacokinetic Profile of Currently Available “Basal” Insulins

Plasma Insulin Levels

Intermediate (NPH)
Long (detemir)
Long (U-100 glargine)
Ultra-long (degludec: U-100 & U-200) (glargine U-300)

Basal: NPH
twice daily injections (with breakfast & supper)

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


Basal: NPH
twice daily injections (with breakfast & bedtime)

If Somogyi effect (Nocturnal Hypoglycemia):
Move supper time dose to bedtime.

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

Concentrated Insulin Glargine (U-300)

- “Ultra long-acting” basal insulin
  - 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 pen
  - 450 units/pen (1.5 mL)
  - Maximum 80 units/injection
  - 3 pens per box

PK and PD of U-300 Insulin Glargine vs U-100 Insulin Glargine

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
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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

U-100, U-200 Insulin Degludec

- Only available in pens
  - 100 units/mL, 3 mL
    - Max 80 units per injection
    - Dose in 1 unit increments
  - 200 units/mL, 3 mL
    - Max dose per injection is 160 units
    - Dose in 2 unit increments
  - Just dial the dose-no need to worry about concentration
- Conversion to or from U-100 TO U-200 insulin degludec is 1:1
  - However, in clinical practice, when converting from degludec to a “not as long”-acting basal insulin, a 20% reduction may be prudent (pending on the insulin dose)
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Basal Insulin Degludex

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.


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

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
Which pharmacotherapies should be used as add-ons to basal insulin to improve postprandial hyperglycemia?

**Approach To Starting and Adjusting Insulin in T2DM**

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

- **Start:** 4 units, 0.1 U/kg, or 10% basal dose
  - If A1C < 8%, can ↓ basal dose by same amount
- **Adjust:** 1 dose by 1 - 2 units or 10% - 15% once/twice weekly until reach SMBG target
- **For hypoglycemia:** identify/fix cause; can ↓ dose by 2 - 4 units or 10% - 20%

**Pharmacokinetic Profiles of Currently Available Bolus (Prandial) Insulin Products**
Insulin Strategies in T2DM
Basal insulin + bolus insulin (with or without metformin)

- Fasting coverage from basal
- Postprandial coverage from bolus
  - Hypoglycemic risk
  - Insulins aspart, lispro, glulisine – high risk
  - Cost is higher
  - Requires prescription
  - Human insulin, regular – very high risk
  - Cost is lower
  - Can be purchased OTC
- Weight gain

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Dosing Options
Basal + 1 bolus injection (with largest meal – usually dinner)

Basal insulin

Bolus insulin

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Dosing Options
When 1 bolus is not enough, increase to:
Basal + 2 bolus injections (with breakfast & supper)

Basal insulin

Bolus insulin

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*Insulin effect images are theoretical representations and are not derived from clinical trial data.
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Dosing Options
When 2-bolus regimen is not enough, increase to:
Basal + 3 bolus injections (MDI)
(with breakfast, lunch, & supper)

Basal insulin
Bolus insulin

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

MDI = multiple daily injections.


Approach To Starting and Adjusting Insulin in T2DM

If A1C not controlled, consider

Add GLP-1 receptor agonist
If not tolerated or A1C target not reached, change to 2-injection insulin regimen

Insulin + GLP-1 agonist


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GLP-1 Receptor Agonists

- Short-acting GLP-1 receptor agonists
  - Exenatide (Byetta)
    - 5 mcg & 10 mcg
    - twice-daily dosing
  - Lixisenatide (Lyxumia, Adlyxin)
    - 10 mcg & 20 mcg
    - once-daily dosing
- Long-acting GLP-1 receptor agonists
  - Liraglutide (Victoza)
    - 0.6 mg, 1.2 mg, & 1.8 mg
    - once-daily dosing
  - Exenatide (Bydureon)
    - 2 mg
    - once-weekly dosing
  - Albiglutide (Tanzeum)
    - 30 mg & 50 mg
    - once-weekly dosing
  - Dulaglutide (Trulicity)
    - 0.75 mg & 1.5 mg
    - once-weekly dosing

Insulin Strategies in T2DM

Basal insulin + GLP-1 receptor agonist (with or without metformin)

- Fasting coverage from:
  - Basal insulin
  - Long-acting GLP-1 receptor agonist
  - Some postprandial coverage
- Postprandial coverage from:
  - Short-acting GLP-1 receptor agonist
  - Minimal fasting coverage
- Low risk of hypoglycemia
- Weight neutral/loss

GLP-1 Receptor Agonists

- Short-acting GLP-1 receptor agonists lower PPG
  - Decrease A1C by 0.8% - 1.5% (~20 - 45 mg/dL; mostly PPG)
- Long-acting GLP-1 receptor agonists lower FPG and PPG
  - Decrease 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
  - Can be used for duration of disease provided insulin is present
  - Promising durability
Comparison of GLP-1 Receptor Agonists

| GLP-1 Receptor Agonist | Dose | Half-life | Homology to GLP-1 | Antibodies | FPG or PPG effects | ΔA1C (%)
|------------------------|------|----------|-----------------|------------|-------------------|--------
| Exenatide             | 5 or 10 mcg BID (within 30-60 min of morning and evening meals) | 2-4 hours | 53% | 44% | PPG | -1.5
| Lixisenatide          | 5-10 mcg daily (within 60 min of same meal once daily) | 2-4 hours | 50% | 69.8% | PPG | -1.0
| Liraglutide           | 1-2 mg daily | 13 hours | 97% | 8.6% | Both | -0.5
| Exenatide             | 2 mg once weekly | 5 days | 44% | 44% | Both | 0.0
| Albiglutide           | 50 mcg once weekly | 5 days | 57% | 2.5% | Both | 0.5
| Dulaglutide           | 1.8 mcg once daily | 5 days | 97% | 2% | Both | 1.0

Max dose: 10 mcg BID

Half-life: 2-4 hours

Homology to GLP-1: 53%

Antibodies: 44%

FPG or PPG effects: PPG

ΔA1C (%): -1.5 to -1.0

Exenatide caused more gastrointestinal issues (47% vs. 13%) but fewer nonnocurnal episodes of hypoglycemia (15% vs. 34%) than insulin lispro.

Fixed Combination Products

- Insulin glargine + lixisenatide (Soliqua™) – iGlarLixi
- Insulin degludec + liraglutide (Xultophy®) – iDegLira
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Fixed Combination Products

**iGlarLixi**
- Concentration: 100 units/33mcg
- Max dose: 60 units/20mcg
- Administer within 1 hour before breakfast
- Expiration: 14 days after first use

**iDegLira**
- Concentration: 100 units/3.6mcg
- Max dose: 50 units/1.8mcg
- Administer once daily regardless of meals
- Expiration: 21 days after first use

---

**Fixed Combination Products**

**iGlarLixi**
- Prime dose before every use (2 units)
  - Starting dose
    - 15 units/5 mcg – previously treated with GLP-1RA or <30 units basal insulin
    - 30 units/10 mcg – previously treated with 30-60 units basal insulin
  - Titrate by 2-4 units every week

**iDegLira**
- Prime dose before every use (priming symbol)
  - Starting dose
    - 16 units/0.58 mcg
  - May be down titrated to 10 units/0.36 mcg
  - Titrate by 2 units every 3-4 days

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**Approach To Starting and Adjusting Insulin in T2DM**

Change to premixed insulin twice daily (before breakfast and supper)

Start: Divide current basal dose into 2/3 AM & 1/3 PM or 1/2 AM & 1/2 PM

Adjust: 1 dose by 1 - 2 units or 10% - 15% once/twice weekly until reach SMBG target

For hypoglycemia: identify/fix cause; can ↓ dose by 2 - 4 units or 10% - 20%

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Premixed Insulin Products

- Pre-mixed combinations of short-acting and intermediate-acting insulins (biphasic)
- Usually given twice daily
- Convenient but not flexible
- Cloudy (require resuspension)
- Short-acting + NPH = Humulin or Novolin 70/30
- 70/30 mixtures = 70% NPH + 30% regular insulin
- Humulin 50/50 = 50% NPH + 50% regular insulin
- Rapid-acting + NPH analog
  - Humalog 75/25 = 75% NPH analog + 25% insulin lispro
  - Novolog 70/30 = 70% NPH analog + 30% insulin aspart
- Caution: potential for error!!

Dosing Option:
Twice-daily Split-mixed Insulin Regimen

Basal needs: NPH
Bolus needs: regular or rapid-acting

Must watch for HYPOGLYCEMIA – especially when meals are skipped and during the overnight hours

Dosing Option:
Three-injection Regimen

Basal needs: NPH
Bolus needs: regular or rapid-acting

Consider moving evening NPH dose to bedtime to avoid episodes of HYPOGLYCEMIA in the middle of the night

*Insulin effect images are theoretical representations and are not derived from clinical trial data.
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Dosing Option:
Three-times-daily Split-mixed Insulin Regimen

- Basal needs: NPH
- Bolus needs: regular or rapid-acting

Must watch for HYPOGLYCEMIA – especially when meals are skipped and during the overnight hours

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

Concentrated Insulin

• Why Do We Need Concentrated Basal Insulin?
  • Currently U-100 insulin pens deliver a maximum of 80 units per injection, and a U-100 syringe will deliver up to 100 units/injection
  • There is some evidence that large insulin volumes are poorly inconsistently absorbed, leading to suboptimal glycemic control
  • Obesity/Insulin resistance continues, increasing the likelihood of the need for larger doses to control the blood glucose

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
**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

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**PK and PD profiles for U-500 vs U-100 Regular Insulin**

**Pharmacokinetic Profile: Regular U-500 vs. NPH U-100**

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Regular Insulin U-500 Pen

- U-500 has dedicated pen and syringe delivery devices.
- Do NOT promote Dose Conversion in U-100 syringe
  - Use pen – Dosed by 5 unit increments;
  - Max dose=300 units/injection
- U-500 Insulin Syringe – 5 unit increments to 250 units

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

Concentrated Basal Insulin Dosing Conversion Comparison

<table>
<thead>
<tr>
<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>Mixed basal/bolus insulin</td>
</tr>
<tr>
<td>1 daily injection</td>
<td>1 to 1</td>
<td>1 to 1</td>
</tr>
<tr>
<td>2 daily injections</td>
<td>80% of total daily basal-dose</td>
<td>1 daily injections</td>
</tr>
<tr>
<td>Maximum single-dose injection</td>
<td>80 units</td>
<td>Maximum single-dose injection</td>
</tr>
<tr>
<td>Maximum single-dose injection</td>
<td>300 units</td>
<td></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>Monitor for hypoglycemia; administer with meals</td>
<td></td>
</tr>
</tbody>
</table>
Patient Education

• Equipment and supplies needed to effectively manage 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)

What Patients Need to Know About Insulin AND Delivery Devices

• Storage and expiration
  • When it should be refrigerated
  • When it can be at room temperature
  • When medication expires after first use
  • How to prepare product for first use
  • How to properly use the device
  • How to dispose of the device

Product Expiration

<table>
<thead>
<tr>
<th>Product/Device</th>
<th>Refrigerated</th>
<th>Unrefrigerated</th>
<th>Once used (opened)</th>
</tr>
</thead>
</table>
| Vials:
  • Insulin lispro U-100
  • Insulin aspart
  • Insulin glargine
| Expiration Date | 28 days | 28 days |
| Vials:
  • Insulin human
  • Insulin human R | Expiration Date | 31 days | 31 days |
| Pens:
  • Insulin lispro U-100, U-200
  • Insulin aspart
  • Insulin glargine
  • Insulin detemir Expiration Date | 28 days | 42 days | 28 days |
| Pens:
  • Insulin degludec U-100, U-200 | Expiration Date | 56 days | 56 days |
| Vials & pens: Insulin alone | Expiration Date | 42 days | 42 days (pens should not be refrigerated) |

First-Time Preparation

• Check the pen
  • Make sure liquid is clear, colorless, and particle-free (N insulin and mixed insulin will be cloudy)
  • Wipe the rubber stopper with alcohol
• Attach the needle
• Prime the needle
  • Dial 2-3 units; hold up, depress the button
  • Repeat process until a drop of insulin appears at tip of the needle
• Dial up the dose

Injection

• Inject straight into the skin
  • Depress button to release insulin into subcutaneous tissue
• Hold for 5 to 10 seconds before removing needle from skin
• Remove needle and dispose into sharps container

Take Home Messages

• Diabetes management and care has significantly evolved over the past few decades
  • There are currently 12 classes of drugs available for the treatment of T2DM
    • No single agent fixes all 8+ defects
  • Use of combination drug therapy that addresses all 8+ diabetes defects provides optimal results
• There are several non-insulin options for prandial control available as add-ons to basal insulin for T2DM
  • Lower risk of hypoglycemia
  • Weight benefits/neutral
Clinical Pearls/Take-Aways

- Watch for over-basalization
  - High basal dose with no or little bolus insulin
- Continually increasing insulin doses does not reduce insulin resistance
- New, long-acting basal insulin analogs may provide benefit compared to "older" basal insulins
  - Flatter time-action profiles with less variability
  - Less hypoglycemia, particularly nocturnal hypoglycemia
- Patients/Caregivers need to know how to properly use insulin devices
  - Injection technique should be reviewed at initiation and periodically thereafter