Intensifying Therapy After Basal Insulin Optimization in Type 2 Diabetes

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Accreditation Statement

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Type of Activity: Knowledge
Media: Internet
New Horizons in Diabetes Care: Reducing Cardiovascular Risks Through Advances in Pharmacotherapy

This valuable and engaging 3-part webinar series was designed to inform and educate pharmacists in all practice settings who are involved in the care of patients with T2DM, bridging the gap of learning about the new classes of medications for T2DM, including their pathophysiologic basis of action across the continuum of care for patients with T2DM, while keeping in mind the cardiovascular safety of these glucose-lowering medications.

Attend one, two, or all three webinars and gain confidence in applying the results of recent studies to clinical practice.

Part 1 - “Type 2 Diabetes—Pathophysiology and Pharmacology Review”
Wednesday, March 22, 2017 at 1:00 PM EDT

Part 2 – “Intensifying Therapy after Basal Insulin Optimization in Type 2 Diabetes—Options for Targeting Postprandial Control”
Thursday, March 30, 2017 at 1:00 PM EDT

Part 3 – “Cardiovascular Outcome Trials (CVOTs): Practical Considerations for your Type 2 Diabetes Patients”
Wednesday, April 5, 2017 at 1:00 PM EDT

Disclosures to Participants

Conflicts of Interest and Financial Relationships

**Presenter**
Susan Cornell, BS, PharmD, CDE, FAPhA, FAADE
- **Speakers Bureau:** Novo Nordisk and Sanofi US

**Program Chair:**
Joshua J. Neumiller, PharmD, CDE, FASCP
- **Advisory Board/Consultant:** Eli Lilly & Boehringer Ingelheim
- **Research Grant Support to WSU:** Novo Nordisk

**Content Reviewer:**
*Tricia Russell, PharmD, BCPS, CDE* has nothing to disclose.
Objectives

After completing this webinar, participants will be able to:

• Select pharmacotherapeutic agents for use as add-ons to optimized basal insulin to improve postprandial glycemic control on the basis of patient-specific considerations

• Describe expected treatment outcomes for patients treated with prandial insulin or other medications when used as add-on therapy to optimized basal insulin

Need for Improved Glycemic Control in the United States (U.S.)

• Glycemic targets must be individualized

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

• Many adults in the U.S. with diagnosed diabetes do not have an A1C < 7%


Why is Glucose Control Important?

• 60% of people with type 2 diabetes (T2DM) have at least 1 complication because of diabetes
  • Complications are often present at time of diagnosis


WUZZLE #1
Natural History of T2DM

Decline in β-cell Function in Pre-diabetes and T2DM

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?

![Graph showing A1C Range (%) vs % Contribution to complications]

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 of amount of side effects, especially undesirable side
effects
  • Hypoglycemia
  • Weight gain
• Consider cardiovascular safety
  • Benefit
  • Neutral

Key Points to Consider When Selecting Pharmacotherapy for T2DM

• Other considerations include:
  • How long the patient has had T2DM
    • Duration of disease and preservation of β-cell function
  • Which blood glucose level is not at target
    • FPG, PPG, or both
  • The degree of A1C-lowering effect required to achieve goal
  • Co-existing conditions
    • depression, osteoporosis

Pathophysiologic Defects in T2DM: The Ominous Octet

- Islet β-cell: Impaired insulin secretion
- Islet α-cell: Increased glucagon secretion
- Decreased glucose uptake
- Decreased hepatic glucose production
- Increased glucose reabsorption
- Increased lipolysis
- Decreased incretin effect (gastrointestinal tract)

Take-aways

- Take 60 seconds to share with your “neighbor” at least 2 informational medication “take-aways”
- Write down your “take-aways”
Which pharmacotherapies should be used as add-ons to basal insulin to improve postprandial hyperglycemia?

WUZZLE #2
ADA Standards of Medical Care (2017)

Effects of Insulin

Decreased incretin effect (gastrointestinal tract)

Increased lipolysis

Islet β-cell

Impaired insulin secretion

Islet α-cell

Increased glucagon secretion

Increased hepatic glucose production

Neurotransmitter dysfunction

Hyperglycemia

Increased glucose reabsorption

Decreased glucose uptake

Pharmacokinetic Profiles of Currently Available Insulin Products

Comparison of Insulin Products

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Duration (h)</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>Insulin, regular U100</td>
<td>0.5 - 1</td>
<td>2 - 4</td>
<td>5 - 8</td>
<td>Clear</td>
</tr>
<tr>
<td>Insulin, regular (inhaled)</td>
<td>Within 5 min</td>
<td>20 - 40 min</td>
<td>3</td>
<td>Powder</td>
</tr>
<tr>
<td>Insulin, regular U500</td>
<td>30 min</td>
<td>2 - 4</td>
<td>Up to 24 hr</td>
<td>Clear</td>
</tr>
<tr>
<td>NPH insulin</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>5 - 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>Insulin 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>Insulin 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>Insulin 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>Insulin 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, and duration may vary from times listed in table. Peak and duration are often dose dependent: smaller doses have lower peaks and shorter durations of action and larger doses have higher peaks and longer durations of action.
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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**Add 1 rapid-acting insulin injection before largest meal**

**Start:** 4 units, 0.1 U/kg, or 10% basal dose

**Adjust:** ↑ 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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**Add 2 rapid-acting insulin injections before meals (basal-bolus)**

**Start:** 4 units, 0.1 U/kg, or 10% basal dose

**Adjust:** ↑ 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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**Add GLP-1 receptor agonist**

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

**Adjust:** ↑ 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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**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:** ↑ 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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**Change to premixed insulin analog 3 times daily (breakfast, lunch, supper)**

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

**Adjust:** ↑ 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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**If A1C not controlled, consider**

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GLP-1 = glucagon-like peptide-1; SMBG = self-monitoring of blood glucose.

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


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: ↑ 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%

If A1C not controlled, consider

Change to premixed insulin twice daily (before breakfast and supper)
Mark: divide current basal dose into 2/3 AM & 1/3 PM 4 U/kg or 1/2 AM & 1/2 PM 2 U/kg
Target: For hypoglycemia: identify/fix cause; can ↓ dose by 2 - 4 units or 10% - 20%
If A1C not controlled, consider

Change to premixed insulin 3 times daily (breakfast, lunch, supper)
Mark: add additional injection before lunch
Adjust: ↑ 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%
If A1C not controlled, consider

Pharmacokinetic Profiles of Currently Available Bolus (Prandial) Insulin Products

![Graph showing plasma insulin levels over time for rapid-acting and regular insulin.]

Insulin Strategies in T2DM
Basal insulin + bolus insulin (with or without metformin)

- Fasting coverage from basal and 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

Dosing Options

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

Basal insulin

Bolus insulin

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

Dosing Options

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

Basal insulin

Bolus insulin

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

When 2-bolus regimen is not enough, increase to:
Basal + 3 bolus injections (MDI)
(with breakfast, lunch, & supper)

The Basal-bolus Concept

- Basal insulin: 50% of daily need
  - Controls night-time and between-meal glucose at a nearly constant level

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

- Correction dose (sensitivity factor)
  - Corrects hyperglycemia reactively

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

MDI = multiple daily injections.

**Insulin Resistance**

- Major defect in individuals with T2DM
  - Reduced biological response to insulin
  - Closely associated with obesity
  - Associated with cardiovascular risk
- Patients with type 1 diabetes can also have insulin resistance
- Adding more insulin (e.g., increasing dose) does not fix insulin resistance

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

<table>
<thead>
<tr>
<th>Initial Insulin</th>
<th>Usual with metformin or other oral agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start insulin</td>
<td>10 U/day or 0.1-0.2 U/kg/day</td>
</tr>
</tbody>
</table>

**If A1C not controlled, consider**

**Add GLP-1 receptor agonist**

If not tolerated or A1C target not reached, change to 2-injection insulin regimen

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Effects of GLP-1 Receptor Agonists

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

• GLP-1 receptor agonists “fix” 6 dysfunctional defects in T2DM
  • Suppress glucagon production
    • Results in decreased glucose production in the liver
  • Enhance appropriate insulin and amylin secretions from the pancreas
    • Results in brain satiety
  • Regulate the gastrointestinal tract to slow gastric emptying time
  • Improve insulin uptake in peripheral tissue via weight 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

<table>
<thead>
<tr>
<th></th>
<th>Exenatide</th>
<th>Lixisenatide</th>
<th>Liraglutide</th>
<th>Exenatide</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>5 or 10 mcg BID (within 30-60 min of morning and evening meals)</td>
<td>10 or 20 mcg (within 60 min of same meal once daily)</td>
<td>Initiate at 0.6 mg initial daily, then ↑ to 1.2 &amp; 1.8 mg; can be taken any time of the day</td>
<td>2 mg weekly</td>
<td>30 mg or 50 mg once weekly</td>
<td>0.75 mg or 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>2 mg 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</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
</tbody>
</table>

BID = twice daily.
Results of Cardiovascular 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-4 inhibitors</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>16,500</td>
<td>Neutral (2013)</td>
</tr>
<tr>
<td></td>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>14,000</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 receptor agonists</td>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>14,000</td>
<td>Neutral (2015)</td>
</tr>
<tr>
<td></td>
<td>LEADER</td>
<td>Liraglutide</td>
<td>16,500</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></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>22,200</td>
<td>Expected (2019)</td>
</tr>
</tbody>
</table>

DPP-4 = dipeptidyl peptidase-4; SGLT-2 = sodium glucose cotransporter-2.

Adapted from Handelsman Y. Endocrine Today. 2016.

GLP-1 Receptor Agonist vs. Bolus Insulin in Patients with T2DM and Optimized Basal Insulin

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

Insulin Glargine/lixisenatide Fixed-ratio Combination (24-week Data)

<table>
<thead>
<tr>
<th></th>
<th>iGlarLixi (lixisenatide/insulin glargine) (n = 161)</th>
<th>U100 insulin glargine (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in A1C from baseline*</td>
<td>-1.8%</td>
<td>-1.5%</td>
</tr>
<tr>
<td>Participants achieving A1C &lt; 7.0%</td>
<td>84%</td>
<td>78%</td>
</tr>
<tr>
<td>Change in body weight from baseline</td>
<td>-1 kg</td>
<td>+0.5 kg</td>
</tr>
<tr>
<td>Participants with documented symptomatic hypoglycemia</td>
<td>21.7%</td>
<td>22.8%</td>
</tr>
<tr>
<td>Gastrointestinal treatment-emergent adverse events</td>
<td>15.5%</td>
<td>9.3%</td>
</tr>
</tbody>
</table>

*Mean baseline A1C was 8.1% in the iGlarLixi (lixisenatide/insulin glargine) group and 8.0% in the U100 glargine group.


Insulin Degludec/Liraglutide Fixed-ratio Combination (DUAL I Trial, 52-week Data)

<table>
<thead>
<tr>
<th>Baseline A1C category(%)</th>
<th>5 - 6.4</th>
<th>6.5 - 7.4</th>
<th>7.5 - 8.4</th>
<th>8.5 - 9.4</th>
<th>9.5 - 10.0</th>
<th>Total trial population</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>208</td>
<td>124</td>
<td>117</td>
<td>299</td>
<td>139</td>
<td>833</td>
</tr>
</tbody>
</table>

IDegLira = insulin degludec + liraglutide; IDeg = insulin degludec alone; Lira = liraglutide alone.

Insulin Degludec/Liraglutide Fixed-ratio Combination (DUAL I Trial, 52-week Data)

Compared to the Lira group, fewer participants in the IDegLira group reported adverse gastrointestinal events (19.7% vs. 8.8%)

GLP-1 Receptor Agonist/Basal Insulin Combinations

Soliqua 100/30

- Fixed-dose combination
  - Insulin glargine U100
  - Lixisenatide (short-acting GLP-1 receptor agonist)

- Starting dose
  - For patients on < 30 units basal insulin:
    - 15 units insulin glargine U100 (5 mcg lixisenatide)
  - For patients on 30 - 60 units basal insulin:
    - 30 units insulin glargine U100 (10 mcg lixisenatide)

- Max dose is 60 units insulin glargine U100/20 mcg lixisenatide
- Titrate 2 - 4 units (insulin glargine U100) once weekly on the basis of FPG
- Dose 1 hour before the first meal of the day
GLP-1 Receptor Agonist/Basal Insulin Combinations

**Xultophy 100/3.6**

- Fixed-dose combination
  - Insulin degludec U100
  - Liraglutide (long-acting GLP-1 receptor agonist)
- Starting dose
  - 16 units insulin degludec (0.58 mg liraglutide) once daily
  - Max dose is 50 units insulin degludec/1.8 mg liraglutide
  - Titrate 2 units (insulin degludec) every 3-4 days on the basis of FPG
- Dose at same time every day (with or without food)

### Approach To Starting and Adjusting Insulin in T2DM

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**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:** ↑ 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%

---

**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 ↓ by 4 units or 20%

---

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

**Start:** 4 units, 0.1 U/kg, or initial dose at lowest amount

Adjust: ↑ 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%

---

**Add GLP-1 receptor agonist**

If A1C not controlled, consider:

- Add ≥ 2 rapid-acting insulin injections before meals (basal-bolus)
  - Adjust: ↑ 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%

---

**Add 1 rapid-acting insulin injection before largest meal (basal-bolus)**

Mark: ↑ 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

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

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.

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.
What about oral agents for prandial coverage?

ADA Standards of Medical Care (2017)
Effects of DPP-4 Inhibitors

- Impaired insulin secretion
- Increased glucagon secretion
- Increased hepatic glucose production
- Decreased glucose reabsorption
- Decreased glucose uptake
- Increased lipolysis
- Decreased incretin effect (gastrointestinal tract)

DPP-4 Inhibitors

- Inhibit DPP-4 enzyme in the gastrointestinal tract
  - *DPP-4 breaks down GLP-1, resulting in increased endogenous GLP-1*
  - Suppress glucagon production, resulting in decreased glucose production in the liver
  - Enhance appropriate insulin and amylin secretions from the pancreas
- Lower PPG
  - Decrease A1C by 0.5% - 0.7% (~15 - 20 mg/dL; mostly postprandial)
- Most common side effects
  - Stuffy, runny nose
  - Headache
  - Upper respiratory tract infection
- Can be used thru duration provided insulin is present
  - Promising durability

ADA Standards of Medical Care (2017)

Effects of SGLT-2 Inhibitors

Decreased incretin effect (gastrointestinal tract)

Increased lipolysis

Impaired insulin secretion

Increased glucagon secretion

Increased hepatic glucose production

Neurotransmitter dysfunction

Hyperglycemia

Increased glucose reabsorption

Decreased glucose uptake

SGLT-2 Inhibitors

- Decrease renal glucose reabsorption in the early proximal tubule of the kidney
  - Decrease body fat, possibly due to increased water and fat urination (elimination)
- Lower FPG & PPG
  - Decrease A1C by 0.7% - 1% (~20 - 30 mg/dL)
- Most common side effects
  - Weight loss
  - Vaginal and male genital infections
  - Rash
  - Urinary tract infection
  - Frequent urination
  - Increased thirst
  - Gastrointestinal problems (when combined with metformin)


WUZZLE #3

W O L O F

Take-aways

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

Intensifying Therapy After Basal Insulin Optimization in Type 2 Diabetes

Questions and Answer Session

- To ask a question please type it into the Ask A Question Tab
Don’t Miss the Upcoming Webinars in This Series!

• Cardiovascular Outcome Trials (CVOTs): Practical Considerations for Your Type 2 Diabetes Patients

Presenter: Dr. Curtis Triplitt