Beyond Basal Insulin: Intensification of Therapy
Jennifer D’Souza, PharmD, CDE, BC-ADM
Jennifer D’Souza has no conflicts of interest to disclose.
When Basal Insulin Is Not Enough  

*Learning Objectives*

- Categorize patient characteristics that would assist clinicians in identifying the appropriate management for intensification of insulin therapies in patients with type 2 diabetes
- Discuss the implications of adverse effects associated with various classes of antihyperglycemic medications
- Compare and contrast advantages and disadvantages of various strategies used for intensifying insulin therapy
- Employ clinical practice recommendations from practice guidelines toward the optimal use of different classes of drugs for intensification of insulin therapy in individuals with diabetes
Case Study: Introduction

- Mr. K, a 50-year-old Caucasian male, has had diabetes for 6 years
- He is concerned about his uncontrolled blood glucose level, a recent increase in weight (5 lbs), and that lately has been feeling anxious and sometimes confused

**Physical exam:**
- Height 5’9” (152 cm)
- Weight 198 lbs (90 kg)
- BMI 29.2 kg/m²
- BP 138/84 mmHg
Case Study: Introduction (cont’d)

- **Lab results (recent):**
  - A1C 8.1%
  - FPG <130 mg/dL
  - 2-hour postprandial (dinner) >180 mg/dL (~200 mg/dL)
- **Medication history:**
  - Metformin 500 mg/glipizide 5 mg: 2 tabs (1000/10) BID
  - Started on insulin glargine last year, titrating to a current dose of 50 units at bedtime (increased by 6 units in the past week)
- Consults with a registered dietitian and eats a healthy diet
- Exercises three times a week

Continued...
### ADA/EASD Medication Guideline for T2DM

**ADA/EASD Medication Guideline for T2DM**

**Monotherapy**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Hypoglycemia Risk</th>
<th>Weight Effect</th>
<th>Side Effects</th>
<th>Cost Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>Low</td>
<td>Neutral/loss</td>
<td>GI/lactic acidosis</td>
<td>Low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- & disease-specific factors):

<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
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<tr>
<td>Sulfonylurea</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>intermediate</td>
<td>low risk</td>
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If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- & disease-specific factors):

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### References


American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017;40(Suppl. 1):S64–S74.
US FDA-Approved Therapies To Be Combined with Basal Insulin

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents with FDA Approval for Use in Combination with Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (TZD)</td>
<td>• Pioglitazone</td>
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<tr>
<td></td>
<td>• Rosiglitazone</td>
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<tr>
<td>DPP-4 inhibitors</td>
<td>• Alogliptin</td>
</tr>
<tr>
<td></td>
<td>• Linagliptin</td>
</tr>
<tr>
<td></td>
<td>• Saxagliptin</td>
</tr>
<tr>
<td></td>
<td>• Sitagliptin</td>
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</table>

DPP-4 Inhibitors as Add-on Therapy to Basal Insulin (With or Without Oral Agents)

- Basal insulin, add DPP-4 inhibitor
  - Sitagliptin¹
  - Saxagliptin²
  - Linagliptin³
  - Alogliptin⁴

- Basal insulin, add placebo

Baseline A1C = 8.5%

- Δ 0.6%*
- Δ 0.41%†
- Δ 0.7%†
- Δ 0.61%*

A1C <7.0%.

* p < 0.001; † p < 0.0001
DPP-4 Inhibitors and Basal Insulin: Low Risk of Severe Hypoglycemia or Weight Gain

The proportion of patients attaining A1C <7% with sitagliptin, alogliptin, or linagliptin in combination with basal insulin ranged from 8% to 20%;¹ no data for saxagliptin

### US FDA-Approved Therapies To Be Combined with Basal Insulin

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<tr>
<th>Class</th>
<th>Agents with FDA approval for use in combination with insulin</th>
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<tr>
<td>SGLT2 inhibitors</td>
<td>• Canagliflozin</td>
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<tr>
<td></td>
<td>• Dapagliflozin</td>
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<td>• Empagliflozin</td>
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**US FDA. Drugs@FDA Web site.**
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/
SGLT2 Inhibitors and Basal Insulin: Impact on Hypoglycemia and Body Weight

Proportion of patients attaining A1C <7% with SGLT2 inhibitors, in combination with basal insulin, ranged from 11% to 25%¹-³

* p < 0.001 vs. placebo; † p < 0.01 vs. placebo

SGLT2 Inhibitors and Potential Risk of Diabetic Ketoacidosis

The EMA will review incidences of ketoacidosis in patients using SGLT2 inhibitors

• The focus will be on dapagliflozin, canagliflozin, empagliflozin, canagliflozin/metformin, and dapagliflozin/metformin

This follows a warning issued by the FDA on May 15, 2015 FDA regarding the potential risk of ketoacidosis with SGLT2 inhibitors

20 cases of diabetic acidosis, reported as diabetic ketoacidosis, ketoacidosis, or ketosis, were recorded in patients treated with SGLT2 inhibitors between March 2013 and June 2014

Mr. K had enjoyed good glucose control for 6 months with a metformin 500 mg/glipizide 5 mg: 2 tablets (1000/10) BID and a stable dose of basal insulin glargine 36 units at bedtime.

A few weeks ago, his post-dinner blood glucose levels increased, prompting him to increase in his basal insulin dose, which is now 50 units.

His blood glucose diary shows the following:

<table>
<thead>
<tr>
<th>Day</th>
<th>Pre-breakfast</th>
<th>Pre-dinner</th>
<th>2-hr post-dinner</th>
<th>Bedtime</th>
<th>Comments</th>
</tr>
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<tr>
<td>Sun</td>
<td>138</td>
<td>145</td>
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<td>188</td>
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<tr>
<td>Mon</td>
<td>132</td>
<td>205</td>
<td>196</td>
<td></td>
<td>Increased basal insulin dose by 4 units</td>
</tr>
<tr>
<td>Tues</td>
<td>120</td>
<td>135</td>
<td>182</td>
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</tr>
<tr>
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<td>145</td>
<td>168</td>
<td>198</td>
<td></td>
<td></td>
</tr>
<tr>
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Case Study: Introduction (cont’d)
From Mr. K’s diary, which plasma glucose patterns of hyperglycemia are present?

A. Fasting  
B. Preprandial  
C. Postprandial  
D. Nocturnal  
E. B and C above

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A drug from which of the following drug classes could you consider to intensify Mr. K’s treatment beyond basal insulin to manage his dysglycemia?

A. GLP-1 receptor agonist
B. DPP-4 inhibitor
C. SGLT2 inhibitor
D. Rapid-acting insulin before the main meal
E. A, B, C, or D above
When Basal Is Not Enough

- Initiate Basal Insulin
  Usually with metformin +/- other noninsulin agent

- If goals not met, consider changing to alternative insulin regimen.

Basal Insulin + GLP-1 Receptor Agonists
Scientific Rationale for Combining a GLP-1RA with Basal Insulin

GLP-1 receptor agonist¹,²
- Simple to initiate
- Pronounced PPG control
- Reduced risk of hypoglycemia
- Weight reduction
- Achieve A1C targets in 40-60%

Basal insulin analogs³,⁴
- Simple to initiate
- Control nocturnal and FPG
- Lower hypoglycemia risk vs NPH
- Modest weight gain (1-3 kg)
- Achieve A1C target in 40%

Additive effects

Complementary actions

PPG = postprandial
FPG = fasting plasma glucose

Basal (long-acting) insulin daily +
bolus (rapid-acting) insulin before meals
More Than 2 Daily Injections

As type 2 patients require larger doses of basal insulin (>0.5 units/kg)

- Temptation is to split basal dose and give it twice a day

If going to 2 injection insulin program

- Keep basal once daily, *and*
- Add a rapid acting insulin injection with largest meal
- Follow a dosing algorithm
- Follow the 90/10 rule

Adapted from:
American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017;40(Suppl. 1):S64-S74.
90/10 Rule for Basal+1

90% basal, 10% rapid-acting (bolus)

Start with largest meal of the day

When initiating rapid-acting insulin:
- Always stop the sulfonylurea
- Often stop thiazolidinedione
- Consider adjusting the doses of other antidiabetic medications

Adapted from:
American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017;40(Suppl. 1):S64-S74.
Dosing Algorithm for Basal+1

Add 1 rapid-acting insulin injection before largest meal

Start: 4 Units, 0.1 U/kg or 10% basal dose. If A1C < 8%, consider ↓ basal by same amount

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

For hypo: Determine & address causes; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

Adapted from:
American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017;40(Suppl. 1):S64-S74.
Example: 90/10 Rule for Initiating Basal+1

- Patient is administering basal insulin 50 units at bedtime
- Initiating the 90/10 Rule
  - Reduce basal insulin by 10% (i.e., 45 units)
  - Administer 5 units of bolus (rapid-acting) insulin before the largest meal

------------------------------------------
- 45 units basal insulin once daily (usually bedtime)
  - Glargine, detemir, degludec, or NPH
- 5 units bolus before the largest meal
  - Aspart, lispro, glulisine, or regular

Adapted from:
Timing of Bolus Insulin Injections

Based on preprandial levels:

↑ Pre-lunch: Add rapid-acting insulin at breakfast

↑ Pre-dinner: Add long-acting at breakfast or rapid-acting insulin at lunch

↑ Pre-bedtime: Add rapid-acting insulin at dinner

<table>
<thead>
<tr>
<th>Type of insulin</th>
<th>Onset of action</th>
<th>Peak of action</th>
<th>Duration of action</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting insulin analog</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro (U100, U200)</td>
<td>15 min</td>
<td>30-90 min</td>
<td>3-5 hour</td>
<td>Vial, pen/cartridge</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>15 min</td>
<td>30-90 min</td>
<td>3-5 hour</td>
<td>Vial, pen/cartridge</td>
</tr>
<tr>
<td>Insulin aspart</td>
<td>15 min</td>
<td>30-90 min</td>
<td>3-5 hour</td>
<td>Vial, pen</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>15 min</td>
<td>30-40 min</td>
<td>2-3 hour</td>
<td>Inhaler</td>
</tr>
<tr>
<td><strong>Short-acting insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular, human</td>
<td>30-60 min</td>
<td>120 min</td>
<td>5-8 hour</td>
<td>Vial</td>
</tr>
</tbody>
</table>

U-200 Lispro

- Pharmacokinetics
  - LIS 0.2 U/kg (n = 10)
  - Regular human insulin (n = 10); mean dose, 15.4 U

- Pharmacodynamics
  - LIS 0.2 U/kg (n = 10)
  - Regular human insulin (n = 10); mean dose, 15.4 U

Potential advantage: smaller injection volume for those with high prandial insulin requirements

PK/PD data generated from a study of 10 patients with T1DM

Inhaled Insulin (Technospheres) in T2DM

- Duration of action for inhaled insulin is much shorter than for RHI\(^1\)
- Almost complete PPG suppression has been observed in a double-blind, placebo-controlled trial in insulin-naive patients with T2DM using OADs\(^2\)

Premixed Insulins

• Contain both a basal and prandial component, allowing coverage of both basal and prandial needs with a single injection.

• Regular human insulin and human NPH/Regular premixed formulations (70/30) are less costly alternatives to rapid-acting insulin analogs and premixed insulin analogs, respectively
Types of Insulin: Premixed

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<tbody>
<tr>
<td>NPH/Regular 70/30 or 50/50</td>
<td>30-60 min</td>
<td>Dual</td>
<td>10-16 hour</td>
<td>Vial, pen/cartridge</td>
</tr>
<tr>
<td>Insulin Aspart Protamine/Insulin Aspart 70/30</td>
<td>10-20 min</td>
<td>Dual</td>
<td>15-18 hour</td>
<td>Vial, pen</td>
</tr>
<tr>
<td>Insulin Lispro Protamine/Insulin Lispro 75/25 or 50/50</td>
<td>5-15 min</td>
<td>Dual</td>
<td>16-18 hours</td>
<td>Vial, pen/cartridge</td>
</tr>
<tr>
<td>Insulin Degludec/Insulin Aspart 70/30</td>
<td>10-20 min</td>
<td>Dual</td>
<td>42 hours</td>
<td>Pen</td>
</tr>
</tbody>
</table>

When Basal Insulin Is Not Enough - SUMMARY

Know when additional therapy beyond basal insulin is needed

- Inadequate control despite effectively titrated basal insulin (FBG >130 mg/dL, A1C >7%)
  - Basal dose is ≥0.5 U/kg/day

Consider TZD, DPP-4 i, or GLP-1 RA as an additive to basal insulin

- Avoid hypoglycemia
- Therapies favorable to weight reduction and blood pressure
- Agents that specifically address post-prandial glucose excursions

Adding a rapid-acting insulin or premixed insulin in a step-wise method before meals
Thank You!