Clinical Case Studies: Effective Strategies for Improving Insulin Initiation and Overcoming Barriers to Insulin Therapy

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View faculty bios at www.ashpadvantage.com/startinsulin

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William H. Polonsky: Consultant-Eli Lilly and Company and Novo Nordisk, Inc.


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Learning Objectives

• Review interprofessional approaches that maximize patient engagement in the diabetes care plan and achieve individual treatment goals.
• Apply best practices that the interprofessional team should employ when initiating insulin therapies.
• Apply effective strategies for managing patients who exhibit psychological insulin resistance.
• Explain strategies for improving adherence to insulin therapy.
• Review effective techniques for overcoming therapeutic inertia.

Initiating and Titrating Insulin Therapy: Engaging the Patient to Achieve Therapeutic Goals

Curtis L. Triplitt, Pharm.D., CDCES
Greg
Age 67 y.o. Male with T2DM X16 years

- PMH
  - HTN
  - Dyslipidemia
  - Mild-NP DM Retinopathy
  - Obesity (100 kg)
- Current medications
  - Metformin 1 gram BID
  - Canagliflozin 300 mg daily
  - Lisinopril 40 mg PO daily
  - Atorvastatin 40 mg PO daily
- He follows a fairly healthy diet and takes his medications as prescribed
- Labs and BP are all normal except:
  - A1C 8.6% (3 days ago)
  - Was 8.2% 2 months ago

Long acting basal insulin daily
20 units at bedtime is started
Is this appropriate?

Progressive Beta-Cell Dysfunction in Prediabetes and T2DM*

IR = insulin resistance
NGT = normal glucose tolerance
IGT = impaired glucose tolerance
OGTT = oral glucose tolerance test

* OGGT Glucose values in mg/dL

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When is Insulin Appropriate?

- A1C>10% or blood glucose levels >300 mg/dL
- Any time glycemic control is inadequate on other therapies
- Type 1 DM is suspected
- Ongoing metabolic catabolism
  - Weight loss
  - Ketosis
  - Very high triglycerides
- Pregnancy

Type 2 DM: Building an Insulin Regimen

At Bedtime (NPH)
Or
Every 12-24 hours

- Fewer injections/day
- Easier to start versus more complex insulin regimens
- Improves FPG and glycemic control in majority of patients
- Similar long-term glycemic control with less initial hypoglycemia versus more complex insulin regimens


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Basal vs. Prandial vs. Premix Insulin
3-year Data


4T Trial: 3 Year Data
Insulin Dose and Hypoglycemia

Select Basal Insulin Choices

Basal Insulins Available*

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Time to Onset (hr)</th>
<th>Time to Peak Action (hr)</th>
<th>Duration of Action (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin human regular (U-500)</td>
<td>0.25</td>
<td>4-8</td>
<td>13-24</td>
</tr>
<tr>
<td>Intermediate-Acting Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human insulin isophane (NPH)</td>
<td>2-4</td>
<td>4-10</td>
<td>12-18</td>
</tr>
<tr>
<td>Long-Acting Insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>2-3</td>
<td>6-8</td>
<td>Up to 24</td>
</tr>
<tr>
<td>Giargline (U-100)</td>
<td>1-2</td>
<td>flat</td>
<td>20-24</td>
</tr>
<tr>
<td>Ultra-long Acting Insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giargline (U-300)</td>
<td>1-2</td>
<td>flat</td>
<td>up to 36</td>
</tr>
<tr>
<td>Degludec (U-100, U-200)</td>
<td>1</td>
<td>flat</td>
<td>&gt;42</td>
</tr>
<tr>
<td>GLP-1RA Mix with Basal Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Fixed Ratio Combinations”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lixisenatide and Giargline (U-100)</td>
<td>1-2</td>
<td>flat</td>
<td>20-24</td>
</tr>
<tr>
<td>Liraglutide and Degludec (U-100)</td>
<td>1</td>
<td>flat</td>
<td>&gt;42</td>
</tr>
</tbody>
</table>

Patient-specific onset, peak, and duration may vary from times listed in table. *Pre-mix products not depicted


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Starting and Titration of Basal Insulin

Every 24 hour long-acting insulin OR bedtime intermediate-acting insulin

**Daily dose:** 10 units or 0.1-0.2 units/kg/day

- Check FBG daily
- Increase dose by 2-3 units every 2-3 days until FPG at desired goal
- Check FBG daily
- In the event of hypoglycemia or FPG level <70 mg/dL:
  - Reduce insulin dose by 4 units, or by 10-20%

**Treat to Target**

<table>
<thead>
<tr>
<th>FPG over last 2-3 days</th>
<th>Basal Insulin Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;180 mg/dl</td>
<td>+8 units</td>
</tr>
<tr>
<td>140-180</td>
<td>+6 units</td>
</tr>
<tr>
<td>120-140</td>
<td>+4 units</td>
</tr>
<tr>
<td>100-120</td>
<td>+2 units</td>
</tr>
<tr>
<td>Below goal</td>
<td>-2 to -4 units</td>
</tr>
</tbody>
</table>

FPG = fasting plasma glucose


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**Are National Diabetes Organizations Recommendations in Line with This?**

ADA: Pharmacologic Approaches to Glycemic Treatment


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Greg

- Current medications
  - Metformin 1 gram BID
  - Canagliflozin 300 mg daily
  - Lisinopril 40 mg PO daily
  - Atorvastatin 40 mg PO daily
- Labs and BP are all normal except:
  - A1C 7.7% (1 day ago)
  - Was 8.1% 2 months ago

- Long-acting basal insulin 46 units at bedtime
- But 2X/week has awoken at 3AM “feeling funny”
- Self-monitored blood glucoses were 54 and 62 mg/dL
- Episodes were treated with orange juice

Long-acting basal insulin was discontinued:
Ultralong Acting Concentrated Insulin 40 units daily was started

Is this an appropriate change to address nocturnal hypoglycemia?
# Conversion Between Basal Insulins

<table>
<thead>
<tr>
<th>Conversion From:</th>
<th>To Other Basal Insulin</th>
<th>NOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>NPH Daily = Unit-per-Unit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NPH BID= Reduce dose 20%</td>
<td></td>
</tr>
<tr>
<td>U-100 Glargine</td>
<td>Unit-per-Unit</td>
<td></td>
</tr>
<tr>
<td>Detemir</td>
<td>Unit-per-Unit</td>
<td>Conversion to detemir- if &lt;0.3 units/kg, administer BID May need slightly higher dose</td>
</tr>
<tr>
<td>U-300 Glargine</td>
<td>Unit-per-Unit</td>
<td>May need slightly higher dose</td>
</tr>
<tr>
<td>U-100 or U-200 Degludec</td>
<td>Units-per-Unit</td>
<td></td>
</tr>
<tr>
<td>U-500 Regular</td>
<td>Conversion to U500 Regular (Split dose BID or TID) A1C&lt;8%= Lower Total Daily Dose of Insulin 20% A1C&gt;8%= Convert Total Daily Dose unit-per-unit</td>
<td></td>
</tr>
</tbody>
</table>

## Basal Insulins: Efficacy is “Similar,” but Hypoglycemia Risk Varies


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Insulin Degludec and Insulin Glargine: Phase 3 Trials

### BRIGHT (Sanofi)
- **Duration (weeks):** 24
- **A1C (%)**
  - Degludec: -1.64%
  - Glargine: -1.59%
- **Estimated RR (95% CI)**
  - Degludec: 0.88 (0.66-1.17)
  - Glargine: 0.99 (0.74-1.32)
- **Severe Hypo (95% CI):**
  - Degludec: 1 episode
  - Glargine: GLAR U300

### CONCLUDE (Novo Nordisk, Inc.)
- **Duration (weeks):** 88
- **A1C (%)**
  - Degludec: -0.1%
  - Glargine: -0.02%
- **Estimated RR (95% CI)**
  - Degludec: 0.88 (0.73-1.06)
  - Glargine: 0.63 (0.48-0.84)
- **Severe Hypo (95% CI):**
  - Degludec: 0.2
  - Glargine: 0.7 (0.57-1.03)

### DEVOTE (Novo Nordisk, Inc.)
- **Duration (years):** 2 years
- **A1C (%)**
  - Degludec: 0.01%
  - Glargine: -0.05%
- **Estimated RR (95% CI)**
  - Degludec: “Severe” 0.47 (0.31-0.73)
  - Glargine: 0.60 (0.48-0.76)

**Hypo:** hypoglycemia  
**Glar:** insulin glargine  
**Deg:** insulin degludec

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**ADA: Pharmacological Therapy Recommendations**

**Without Established ASCVD, CKD, or Heart Failure**

**Need to Minimize Hypoglycemia**
- SGLT2-i
- GLP-1 RA
- TZD
- DPP-4i

**Compelling Need to Minimize Weight Gain or Promote Weight Loss**
- SGLT2-i
- GLP-1 RA (good efficacy for weight loss)
- SU
- TZD

**Cost is a Major Issue**
- SU
- TZD

If A1C is above target:
- Continue addition of agents as listed above
- Later gen SU or basal insulin (w/ low hypo risk)

If quadruple therapy required or SGLT2-i or GLP-1 RA not tolerated then use regimen with lowest risk of weight gain

**Basal Insulin: ADA Pharmacologic Therapy Recommendations**

**Compelling Need to Minimize Hypoglycemia**
- DPP4i, SGLT2i, GLP-1RA, or TZD and Combination

If A1C above target:
- Consider addition of SU or basal insulin
- Consider basal insulin with lower risk of hypoglycemia*
  
*Degludec/U300 glargine<U100 glargine/detemir<NPH

**Compelling Reason to Minimize Weight Gain Or Lose Weight**
- GLP-1RA or SGLT2i

If A1C above target:
- Cautiously Add:
  - TZD
  - SU
  - Or Basal Insulin

**Cost is a Major Issue**
- SU then TZD
- Or TZD then SU

If A1C above target:
- **Basal Insulin with Lowest acquisition cost**
  - Or
    - Consider DPP4i or SGLT2i with lowest acquisition cost

**Basal Insulin: ADA Pharmacologic Therapy Recommendations for:**

**ASCVD PREDOMINATES**
- If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
  - For patients on a GLP-1 RA consider adding SGLT2i with proven CVD benefit
  - DPP-4i if not on GLP-1 RA
  - **Basal insulin**
  - TZD
  - SU

**HF or CKD PREDOMINATES**
- Avoid TZD in the setting of HF. Choose agents demonstrating CV safety:
  - For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1RA)
  - **Basal insulin**
  - SU

*Degludec or U100 Insulin Glargine have demonstrated CV safety*


---

**Cardiovascular Outcomes: Insulin Degludec vs. Glargine (U100)**

**DEVOTE CVOT Outcomes**

(n=7637)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint* Non-inferiority</td>
<td>0.91 (0.78-1.06)</td>
<td>&lt;0.001 (NI)*</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.92 (0.80-1.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.91 (0.76-1.11)</td>
<td>0.35</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>0.84 (0.60-1.16)</td>
<td>0.28</td>
</tr>
<tr>
<td>CV death</td>
<td>0.96 (0.76-1.21)</td>
<td>0.71</td>
</tr>
<tr>
<td>CV death excluding undetermined cause of death</td>
<td>0.91 (0.69-1.20)</td>
<td>0.52</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.85 (0.68-1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.65-1.23)</td>
<td>0.50</td>
</tr>
<tr>
<td>Unstable angina hospitalization</td>
<td>0.95 (0.68-1.31)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Median follow-up: 1.99 years

Favors degludec  Favors glargine

*CV death, nonfatal MI, or nonfatal stroke; †Confirmed noninferiority; superiority, P=0.21.

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Greg

- Current medications
  - Metformin 1 gram BID
  - Canagliflozin 300 mg daily
  - Lisinopril 40 mg PO daily
  - Atorvastatin 40 mg PO daily
- Labs and BP are all normal except:
  - A1C 7.5% (1 day ago)
- Has titrated to:
  - Ultra-long Acting Insulin 60 units (0.6 units/kg) daily

What would you recommend?
Titrate? Switch? Change regimen?

FPG and Bedtime Glucose (mg/dL) over last 7 days

<table>
<thead>
<tr>
<th></th>
<th>172</th>
<th>72</th>
<th>92</th>
<th>130</th>
<th>70</th>
<th>182</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>232</td>
<td>164</td>
<td>162</td>
<td>142</td>
<td>172</td>
<td>222</td>
</tr>
<tr>
<td>Bedtime</td>
<td>232</td>
<td>164</td>
<td>162</td>
<td>142</td>
<td>172</td>
<td>222</td>
</tr>
</tbody>
</table>

Basal Insulin and Overbasalization

Post-hoc analysis of 4, U-100 insulin glargine studies, ≥24 weeks in duration

- Hypoglycemia did not significantly increase with higher dose
- Weight DID increase above 0.5 units/kg

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Fasting Plasma Glucose Variability (FPGV)

- FPGV may be associated with higher risk of complications
  - Higher risk of proliferative retinopathy and macular edema¹
  - Associated with left ventricle wall thickness and LV ejection fraction²
  - FPGV associated with a 26% greater risk of CVD, and 46% higher risk of all-cause mortality in higher tertile³
- FPGV- limiting may negate risk
  - All-Cause Mortality no higher risk if mean/median variability <20%⁴

Fasting Glycemic Variability Associated Risks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hypoglycemia</td>
<td>3.37</td>
<td>2.52 to 4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3-Point MACE</td>
<td>1.21</td>
<td>0.98 to 1.49</td>
<td>0.08</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>1.33</td>
<td>1.01 to 1.75</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Basal Insulin Goals and Greg

1. **Control Fasting Plasma Glucose Levels**
   - Greg: Average FPG is 103 mg/dL
2. **Avoid overbasalization**
   - Reassess benefit if >0.5 units/kg
     - Greg: injects 0.6 units/kg of basal insulin
   - Bedtime SMBG to AM SMBG is a high number
     - Greg: Bedtime to AM glucose (BeAM) is 63 mg/dL
3. **Consistent FPG readings (Low Fasting Glucose Glycemic Variability)**
   - Greg: FPG is 103 on average, but 5 out of 6 of FPG vary by >20%

1. Greg States: “I didn’t think I would have to keep taking insulin”
2. Admits to omitting 2-3 injections per week
3. He feels hungry all the time, admits to overeating at times
SUMMARY: Basal Insulins

- Basal Insulin can help patients get to A1C goals
- Efficacy is similar between basal insulin options
- Be Patient Centered:
  - Understand the needs of your patient when starting and titrating basal insulin products
  - Ask about device options and cost
- Risk of hypoglycemia/nocturnal hypoglycemia may vary between basal insulin products
- Basal insulin has limitations:
  - Understand signs of need to intensify beyond basal insulin
  - Be cognizant of FPG variability- especially in CVD patients

Key Considerations in Initiating Insulin Therapy: Acknowledging and Overcoming Psychological Insulin Resistance

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### Reluctance to Initiate IT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polonsky, 2005</td>
<td>Survey ($n=708$)</td>
<td>28% “not willing”</td>
</tr>
<tr>
<td>Larkin, 2008</td>
<td>Survey ($n=100$)</td>
<td>33% “not willing”</td>
</tr>
<tr>
<td>Cefalu, 2008</td>
<td>Multinational survey ($n=975$)</td>
<td>46% would avoid insulin</td>
</tr>
<tr>
<td>Polonsky, 2011</td>
<td>Multinational survey ($n=1400$)</td>
<td>17% “not willing”; 35% “ambivalent”</td>
</tr>
</tbody>
</table>

IT = insulin therapy

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How Common is Initiation Delay?

- 3295 insulin-naïve T2Ds were identified who had been recommended insulin:
  - 984 (29.9%) declined
  - Of the 984 who declined, 374 (38%) eventually started insulin
  - Of the 374 who finally initiated, mean time to insulin initiation was 790 days

Obstacles to Insulin Initiation

<table>
<thead>
<tr>
<th>Started IT?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerned about “side effects”</td>
<td>12%</td>
<td>44%</td>
</tr>
<tr>
<td>Concerned about hypoglycemia</td>
<td>16%</td>
<td>43%</td>
</tr>
<tr>
<td>Risks/benefits not explained</td>
<td>39%</td>
<td>55%</td>
</tr>
<tr>
<td>Not confident re-adjusting dose</td>
<td>12%</td>
<td>41%</td>
</tr>
<tr>
<td>IT self-care training provided</td>
<td>100%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Seven Initiation Obstacles

1. Injection-related anxiety
   – Discomfort with injections
   – Needle phobia

2. Perceived lack of control
   – “If I start taking insulin, I’ll never be able to stop.”
   – “Taking insulin means no more spontaneity. It would restrict my life, making it too hard to travel, or eat out, or even have a life!”
Seven Initiation Obstacles

3. Low self-efficacy
   – “I’m just not confident I could handle the demands of insulin, like deciding how much to take and when to take it.”
   – “It’s just too complicated; it’s too much for me to do.”

Seven Initiation Obstacles

4. Personal failure
   – “If I take insulin, it means I have failed, that I haven’t done a good enough job taking care of my T2D.”

Seven Initiation Obstacles

5. Positive gain is not expected (DAWN)
   – 41% did not believe that IT might help to better glycemic control
   – 53% did not believe that IT might improve their health


Seven Initiation Obstacles

6. Concerns about adverse effects
   – Negative influence on work/social life
     • “My friendships may suffer (46%).”
   – Will lead to poorer health
     • IT “may cause hypo’s, weight gain, or perhaps serious problems with my eyes or kidneys.”
   – Represents sickness
     • “Starting insulin means I’m sicker, and my diabetes will become a more serious disease.”


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Seven Initiation Obstacles

1. Injection-related anxiety
2. Perceived lack of control
3. Low self-efficacy
4. A sense of personal failure
5. Positive gain is not expected
6. Concerns about adverse effects
7. COST!
Why Such Negative Attitudes About Insulin?

• Observation of others with diabetes
  – “... all expressed deep-seated fears regarding side effects and the long-term health prognosis of insulin users, often citing poor health of family and friends who had used insulin.” (n = 96)

Krall J et al. Diabetes Technol Ther. 2015; 17:268-74
• Threatening patients with insulin
  – “If you can’t make some positive changes in how you eat and exercise, then we’ll have no choice but to start insulin.”
• Underlying messages
  – Insulin should be avoided at all costs
  – You have failed
  – You are to be punished
“It’s our job to help patients live as long as possible free of CVD complications. Although most patients share that goal, we don’t always see the same pathways to get there. I want to believe that if patients knew what I know, they would take their medicine. What I’ve learned is that if I felt what they feel, I’d understand why they don’t.”


Physician Resistance to Initiation

1. Lack of confidence
2. Presumption that patient will be unwilling and/or not compliant
3. Hypoglycemia and weight gain
4. No beneficial outcomes
5. Competing clinical demands

So What To Do?

- Retrospective survey, $n = 594$ T2Ds:
  - US, Germany, Canada, UK, Spain, Brazil, Japan
- All subjects indicated an initial unwillingness to start insulin, but had eventually done so.


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Identifying Solutions to Psychological Insulin Resistance

- 38-item scale listed HCP statements/actions regarding IT initiation that may have occurred at medical visits.
- Each item rated on degree of helpfulness.
- EFAs then used to determine the key HCP action themes.

HCP = healthcare practitioner


Five Key HCP Action Themes

<table>
<thead>
<tr>
<th>Action Theme</th>
<th>Percent with &gt; 1 item occurring</th>
<th>Helpfulness (Mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrated the Injection Process</td>
<td>94%</td>
<td>3.07 (0.74)</td>
</tr>
<tr>
<td>Explaned Insulin Benefits</td>
<td>97%</td>
<td>2.97 (0.74)</td>
</tr>
<tr>
<td>Collaborative Style</td>
<td>95%</td>
<td>2.92 (0.78)</td>
</tr>
<tr>
<td>Dispelled Insulin Myths</td>
<td>89%</td>
<td>2.77 (0.72)</td>
</tr>
<tr>
<td>Authoritarian Style</td>
<td>54%</td>
<td>2.63 (0.85)</td>
</tr>
</tbody>
</table>

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Impact of HCP Action Themes

Table 4: Multivariate associations between perceived helpfulness of PAS Dimensions (participant-reported HCP actions) and insulin initiation and discontinuation behaviors

<table>
<thead>
<tr>
<th>Perceived Helpfulness of HCP Actions</th>
<th>Odds Ratio (OR)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demonstrated the Injection Process</td>
<td>0.67</td>
<td>0.17</td>
</tr>
<tr>
<td>Explained Insulin Benefits</td>
<td>0.51</td>
<td>0.01</td>
</tr>
<tr>
<td>Collaborative Style</td>
<td>0.55</td>
<td>0.01</td>
</tr>
<tr>
<td>Dispelled Insulin Myths</td>
<td>0.67</td>
<td>0.07</td>
</tr>
<tr>
<td>Authoritarian Style</td>
<td>0.95</td>
<td>0.85</td>
</tr>
</tbody>
</table>

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1. Encourage an Immediate Injection

• “Patients \( n = 96 \)… found that giving an injection when insulin was introduced to be very helpful, yet in-office demonstration was reported by only one-half of the PCPs.”

PCPs=primary care physicians


2. Provide a Sense of Control

• The Insulin Challenge:

  I’d like you to try insulin for just a month. At the end of the month, if you don’t think it’s been worthwhile, or if it still seems as awful as you’re imagining it might be, I promise to help you stop.”
3. Ask/Address Personal Obstacles and Misbeliefs

“What are some of the reasons why taking insulin seems so bad to you?”

| PROS | CONS |
Addressing Insulin Misbeliefs

<table>
<thead>
<tr>
<th>Obstacles</th>
<th>Discuss</th>
</tr>
</thead>
<tbody>
<tr>
<td>It means I have failed</td>
<td>• No matter what you do, you may need IT, because diabetes is “progressive”</td>
</tr>
<tr>
<td>I will get complications</td>
<td>• Review those old family stories</td>
</tr>
<tr>
<td></td>
<td>• Insulin is much more likely to reduce than raise complications risk</td>
</tr>
<tr>
<td>It means my diabetes is getting worse</td>
<td>• Insulin helps control BG levels and thus keeps the disease from getting worse</td>
</tr>
<tr>
<td>Insulin won’t help</td>
<td>• List long-term benefits of good control</td>
</tr>
<tr>
<td></td>
<td>• Nobel Prize not given for drugs that suck</td>
</tr>
</tbody>
</table>
• Psychological Insulin Resistance is common
• Reluctant individuals have good reasons
• Four solutions:
  – Encourage an immediate injection
  – Provide a sense of control regarding IT
  – Ask/address personal obstacles and misbeliefs
  – And be collaborative!

Therapeutic Inertia in Diabetes Care: A Call for Action in Clinical Practice

Lawrence Blonde, M.D., FACP, MACE

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Therapeutic Inertia in Diabetes Care:
A Call for Action in Clinical Practice - Outline

- Prevalence of diabetes
- State of Diabetes Health Care Quality
- Clinical Inertia – Therapeutic Inertia
- Relationship of Hypoglycemia to Decreased Adherence in Insulin Treated Individuals with Diabetes
- Reduced hypoglycemia with longer acting basal insulin analogues
- Reduced hypoglycemia for those with T2D combining basal insulin analogues with GLP‐1 receptor agonists vs. basal bolus insulin
- Need for timely intensification and deintensification of diabetes medications
- Some strategies to address Therapeutic Inertia


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2018 Estimates of Prevalence of Diabetes Mellitus

• 34.2 million people of all ages (10.5% of the US population) had diabetes
• 34.1 million adults (13% of all US adults) had diabetes
• 7.3 million (21.4% of all US adults with diabetes) who met laboratory criteria for diabetes were not aware of or did not report having diabetes
• The percentage of adults with diabetes increased with age, reaching 26.8% among those aged 65 years or older


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Achievement of Target A1C <7.0% by U.S. T2D Pts Treated With Basal Insulin in Both RCTs and Clinical Practice

**FIGURE 1.** Proportion of patients stratiﬁed by achieved A1C and FPG targets at 6 and 12 months. The graph represents data from pooled RCTs from 11 24-week studies of patients initiating basal insulin between 2000 and 2005 and from outpatient EMR data from the GE Centricity database for insulin-naïve patients initiating basal insulin between 2005 and 2012.

Proposed that the term “therapeutic inertia” is more appropriate to describe failure to advance or deintensify treatment, whereas broader concept of clinical inertia includes not only escalation or deintensification of therapy but also issues such as failure to screen, make appropriate referrals, and manage risk factors and complications.
Why does clinical inertia occur?

- **Clinician-level barriers**¹
  - Inertia related to clinicians including time constraints, suboptimal knowledge/training, concern re potential risks of hypoglycemia/weight gain etc., variations in guideline recommendations and overestimating adherence to guidelines

- **Patient-level barriers**¹
  - Inadequate adherence related to concerns including hypoglycemia, weight gain, other side effects and costs

- **Discontinuity of care**²
  - Failure of continuity of care i.e. the process by which the patient and their physician-led care team are cooperatively involved in ongoing health care management toward the shared goal of high quality, cost-effective medical care

- **System-level barriers**¹
  - Due to issues in healthcare, including costs of care

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### Systematic Review of Therapeutic Inertia in Patients with Type 2 Diabetes

- 53 papers from January 2004 to August 2016
- In most, median time to treatment intensification after above target HbA1c was more than 1 year
- Therapeutic inertia increased as number of antihyperglycemic drugs rose and decreased with increasing HbA1c
- Authors concluded that therapeutic inertia in management of hyperglycemia in people with type 2 diabetes is major concern

**Khunti K et al. Diabetes Obes Metab. 2018; 20(2):427-37.**

### Gap Between Efficacy in RCTs and Effectiveness in Real-World Use of GLP-1 RA and DPP-4 Therapies

- Retrospective claims (Optum/Humedica) analysis to compare change in A1C of Real-World (RW) T2D pts 12 months after starting GLP-1 RA or DPP-4 inhibitor with published findings from RCTs.
- Selected RW pts were similar to RCT pts, and regression analysis was used in RW data to adjust for differences between poorly adherent and adherent patients to explain why RCT and RW findings may differ.
- Poor medication adherence accounted for ~ 3/4 of gap between RW and expected RCT results (gap = 0.51% [6 mmol/mol] GLP-1 RA; 0.18% [3 mmol/mol] DPP-4).


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Poor Adherence Associated with Increased Hospitalization & Mortality

- Systematic review of 8 observational studies (318,125 patients with T2DM)
- Poor adherence was 37.8% (95% CI 37.6, 38.0)
- Good adherence associated with reduced:

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hong et al 2011</td>
<td>0.75 (0.59, 0.95)</td>
<td>33.23</td>
</tr>
<tr>
<td>Zhu et al 2015</td>
<td>0.82 (0.54, 1.23)</td>
<td>11.72</td>
</tr>
<tr>
<td>Ho et al 2006</td>
<td>0.68 (0.55, 0.82)</td>
<td>55.05</td>
</tr>
<tr>
<td></td>
<td>0.72 (0.62, 0.82)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

*P=0.0%, p=0.648*  
Favours good adherence  
Favours poor adherence

All-cause mortality 0.72 (95% CI 0.62–0.82)  
All-cause hospitalization 0.90 (95% CI 0.87–0.94)


Hypoglycemia and Insulin Adherence

- Single hypoglycemic event
- Fear of hypoglycemia
- Patient chooses a higher BG range to minimize the risk of hypoglycemia
- Decreased medication adherence


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Early Hypoglycemia & Adherence After Basal Insulin Initiation in Nationally Representative Sample of Medicare Beneficiaries With T2D

- Retrospective analysis of 5% sample of Medicare files identifying beneficiaries with T2D initiating BI from 1 January 2008 to 31 December 2012.
- Early hypoglycemia defined as ≥1 hypoglycemic event ≤6 months postindex. Outcomes included medication adherence and persistence over 12- and 36-month follow-up.
- Of 14,466 patients, 1315 (9.1%) experienced hypoglycemia ≤6 months after initiating BI.
- At 12 months, patients with early hypoglycemia were less likely to be adherent to (OR 0.81 [95% CI 0.70–0.93]) and more likely to discontinue (OR 1.33 [95% CI 1.07–1.66]) their insulin therapy. Results similar at 36 months.


Benefits of Ultra-Long-Acting Basal Insulins
Insulin Degludec and Insulin Glargine U-300

- Longer duration, Consistent once-daily dosing
- Less glycemic variability = Less hypoglycemia, especially nocturnal\(^1,\(^2,\(^3,\(^4\)
- May provide less weight gain\(^4,\(^5\)
- May lead to improved adherence\(^3\)

Real-world data from large IBM Watson Health™ Explorys database suggested that among T2D patients initiating BI after OADs, likelihood of reaching glycemic control diminished over time, and remained low from 12 months onwards.

Additional treatment options should be considered if patients do not reach glycemic control within 12 months of BI initiation.


Post-insulin Intensification Inertia

- Retrospective cohort study of T2D in UK Clinical Practice Research Datalink database between January 2004 and December 2011, with follow-up until December 2013.
- Of 11,696 patients, 36.5% had treatment intensified during study period; 50.0, 42.5 and 7.4% intensified with bolus or premix insulin or GLP1-RA, respectively.
  - Median time from initiation of BI to intensification was 4.3 years [95% (CI) 4.1, 4.6].
- Among those with A1C ≥ 7.5%, 30.9% had regimen intensified.
  - Median time to intensification was 3.7 years (95% CI 3.4, 4.0).
  - 32.1% stopped basal insulin therapy.

Antihyperglycemic Management in Older Adults at Hospital Discharge

• Retrospective cohort study of diabetes individuals ≥65 years not previously requiring insulin hospitalized in a Veterans Health Administration hospital for common medical conditions between 2012 and 2013
• 1 in 10 hospitalized older adults with diabetes was discharged with intensifications to their outpatient antihyperglycemic regimens
• Most intensifications were new initiations of insulins and sulfonylureas in response to increased inpatient BG levels
• 49% had limited life expectancy or had already achieved an outpatient A1C < 7.5% & not likely to benefit
• Only 20% of those with potential to benefit from stricter glycemic control, received intensifications
• Authors stated need to move toward more patient-centered decision-making considering long-term benefits and risks

Continuous Glucose Monitoring vs. Usual Care in Participants with T2D Receiving Multiple Daily Insulin Injections

**Background**
Continuous glucose monitoring (CGM) beneficial for adults with T1D but not well-evaluated in insulin treated T2D individuals

**Patients/Intervention**
158 adults; T2D for a median of 17 years. Random assignment to CGM or usual care for 24 weeks

**Results**
Mean HbA1c levels decreased from 8.5% to 7.7% in CGM group vs. 8.0% in controls


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**Effects of Smart Connected Insulin Pen**

- Observational study of effect of connected insulin pen on insulin regimen adherence and glycemic control
- 94 individuals with T1D on BBI regimen and CGM from 12 Swedish diabetes clinics downloaded pen data at each visit
- TIR significantly increased (+1.9 [0.8;3.0]95%CI hours/day; p<0.001) from baseline to follow-up
- Corresponding decreased time in hyperglycemia (-1.8 [-3.0;‐0.6]95%CI hours/day; p=0.003)
- Decreased L2 hypoglycemia (-0.3 [-0.6;‐0.1]95%CI hours/day; p=0.005), and no change in time in L1 hypoglycemia.
- Meals without bolus insulin within -15 and +60 minutes from meal start decreased by 30% over study (p=0.002).
- Study showed potential benefit on glycemic control and dosing behavior with reliable insulin dose data from connected pen in those with T1D.


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**CGM & Insulin-dosing Algorithms**

- Hybrid closed loop systems combining CGM data, insulin-dosing algorithms and insulin pumps have demonstrated improved time in range and reduced hypoglycemia
- CGM also associated with improved A1C in T2D MDI pts
- Smart connected pens associated with increased time in range and decreased missed bolus insulin injections in MDI T1D pts
- In future “smart insulin pen or cap for pen” combined with CGM data and insulin dosing algorithm will provide dosing recommendations to MDI treated patients on their smartphone.

Prevalence of diabetes continues to increase
State of diabetes health care quality needs improvement
Therapeutic Inertia - Clinical Inertia contribute to suboptimal diabetes care
Decreased adherence is component of therapeutic inertia and hypoglycemia in insulin treated individuals is a significant contributor
Reduced hypoglycemia is seen with longer acting basal insulin analogues and in those with T2D when BI is combined with GLP-1 receptor agonists vs. basal bolus therapy
Strategies to address Therapeutic Inertia may include
- Timely intensification of and deintensification of diabetes medications
- Increased use of CGM improve time in range and decrease hypoglycemia
- Targeted intensive insulin-adherence interventions
Clinicians, patients, health systems, payers, and industry entities developing diabetes medications, devices, and other products all can play a role in reducing Therapeutic Inertia

Consider these practice changes. Which ones will you make?
Select insulin therapies taking into account patient-specific characteristics.
Actively engage patients in ongoing discussions about the benefits of insulin therapies.
Educate team members about the clinical profiles of currently available insulin products with respect to dosing, variability, volume, and safety.
Educate team members about best practices in initiating insulin therapy.
Educate team members on strategies for managing patients who exhibit psychological insulin resistance.
Consider dose adjustments in patients who are non-adherent or are prone to clinical inertia.