Optimizing Insulin Therapy for Patients with Type 2 Diabetes: Existing Challenges and New Opportunities for Improved Care

SPEAKERS
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Frank Lavernia, MD

Learning Objectives
• Better identify and understand the pathophysiologic defects contributing to postprandial hyperglycemia and its impact on managing the glycemic burden in patients with type 2 diabetes mellitus
• Overcome both clinician and patient resistance to appropriate initiation and intensification of insulin therapy to best manage postprandial hyperglycemia, while lowering risk for adverse events
• Incorporate assessment of postprandial glucose as part of diagnostic and treatment plan so as to target therapy to better manage hyperglycemia and prevent potential complications in patients with type 2 diabetes mellitus
• Better distinguish conventional, new, and emerging prandial insulin therapies for appropriate treatment selection in patients with T2DM so as to properly integrate in to care and improve outcomes

The History of Diabetes Survival

Photographs courtesy of the National Library of Medicine

Presenter Disclosure Information
The following relationships exist related to this presentation:
► Dr. Blonde receives honorarium from AstraZeneca, Janssen Pharmaceuticals, Inc., Merck & Co., Novo Nordisk, Sanofi, GlaxoSmithKline, and Quest Diagnostics. Dr. Blonde’s institution receives grant/research support from Eli Lilly and Company, Novo Nordisk, and Sanofi.
► Dr. Lavernia serves on the Speakers Bureau and Medical Advisory Board for Janssen, as well as the Medical Advisory Board for Eli Lilly.

Off-Label/Investigational Discussion
► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
**Typical Diagnosis of Diabetes**

- Normal Blood Glucose
- IGT
- Frank Diabetes
- Insulin Resistance
- Insulin Secretion
- Postprandial Glucose
- Fasting Blood Glucose
- Risk of Macular Degeneration
- Risk of Macrovascular Complications
- Years to Decades
- Typical Diagnosis of Diabetes

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**Natural History of Type 2 Diabetes**

- NGT
- IGT
- Frank Diabetes
- Insulin Resistance
- Insulin Secretion
- Postprandial Glucose
- Fasting Blood Glucose
- HbA1C is “gold standard” measure of diabetes control over previous 2–3 months

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**ADA/EASD: Approach to the Management of Hyperglycemia**

- More stringent
  - More motivated, adherent, excellent self-care capacities
  - More severe disease
  - Life expectancy
  - More important comorbidities
  - Established vascular complications
    - Limited or absent support system

- Less stringent
  - Less motivated, non-adherent, poor self-care capacities
  - Less severe disease
  - Life expectancy
  - Less important comorbidities
  - Established vascular complications
    - Adequate support system

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**T2DM Patients Can Spend More Than 12 Hrs/day in the Postprandial State**

- Postprandial
- Postabsorptive
- Fasting

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**Glycemic Target Goals for Patients with Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Treatment Goal</th>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C (%)</td>
<td>&lt; 7</td>
<td>≤ 6.5</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>80–130</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>Preprandial glucose (mg/dL)</td>
<td>80–130</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>Postprandial glucose (mg/dL)</td>
<td>&lt; 180*</td>
<td>&lt; 140**</td>
</tr>
</tbody>
</table>

*Peak PPG, **2 Hr PPG

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**Fasting vs Postprandial Glucose: Relationship to A1C Level**

- PPG contribution to HbA1c is greater when HbA1c is lower

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**To achieve a normal or near normal HbA1c, both FPG and PPG levels must be normal or near normal.**

Thus both FPG and PPG must be targets for therapy.
Case: Poorly Controlled T2DM Patient on OAD meds

- 55-yr old African American male with T2DM diagnosis since age 45 on OADs and poorly controlled T2DM
- Hx: HTN, mixed dyslipidemia adequately controlled with medications
  - Employed as heavy machine operator, married with 2 children in college
  - Relatively active with exercise 3 times per week for 30 minutes daily. Tennis occasionally.
  - EtoH & tobacco (negative)

Current Exam & Treatment

Current exam:
- Wt 208 lbs, Ht 68”, BMI 31.6
- A1C 8.2%, Cr 0.9 mg/dL
- eGFR: 90 mL/min/1.73 m²

Current treatment:
- Metformin 1000 mg BID
- Glimepiride 4 mg QD
- Sitagliptin 50 mg QD
- Atorvastatin 20 mg QD
- Lisinopril 10 mg QD

Current Presentation, cont.

- A1C is 8.2% and FPG averages ~ 182 mg/dL
- Random BG after breakfast ~ 210 mg/dL
- He has a fear of needles and dreads having to inject himself, particularly at work where he is employed as a heavy machine operator.
- He mentions his concern about his increase in weight in light of his fairly strict diet and exercise. He has gained 10 lbs since his last visit 6 months ago.

When to Consider Insulin in a Person with Type 2 Diabetes

- When a combination of non-insulin antihyperglycemic medications are unable to achieve HbA1c target
- High fasting (FPG) or postprandial (PPG)
- Unacceptable side effects of other medications
- Advanced hepatic or renal disease
- Special considerations (steroids, infection, pregnancy)
- Hyperglycemia in a hospitalized patient
- “Severely” uncontrolled diabetes*

Physiologic Insulin Secretion

- Adapted from Krasowska Y, et al. Diabetologia. 1987; 30(1).


Random Glucose > 300 mg/dL, A1C > 10%, Ketonuria, Symptomatic polyuria/polydipsia, weight loss
Types of Insulin

Ultra-Rapid-acting:
- Inhaled human insulin

Rapid-acting analogs:
- Aspart, Lispro, Glulisine

Short-acting insulin: Regular (soluble)

Intermediate-acting insulin: NPH

Long-acting insulin:
- Detemir, Glargine

Human insulin 70/30:
- Premix NPH/regular

Premixed Analogs:
- Insulin lispro mix 75/25, 50/50
- Biphasic insulin aspart 70/30

Advantages of Basal Insulin Analogs Over Human Insulin

- Longer-acting (up to 24 hours)
  - Once-daily administration
  - Less variability from day to day
- Flatter biological activity (less peak)
  - Lower risk of nocturnal and overall hypoglycemia
- Less weight gain (insulin detemir)

Basal Insulin Analogs in Development

- Insulin Degludec U100 & U200
- Insulin Glargine U300
- PEGylated insulin lispro

Currently Available Insulin Products

<table>
<thead>
<tr>
<th>Insulin*</th>
<th>Onset</th>
<th>Peak</th>
<th>Effective Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra-Rapid Acting</td>
<td>Insulin lispro inhaled (TI)</td>
<td>7.5-15 minutes</td>
<td>12-15 minutes</td>
</tr>
<tr>
<td>Rapid Acting</td>
<td>Aspart, lispro, Lispro</td>
<td>5-15 minutes</td>
<td>15-30 minutes</td>
</tr>
<tr>
<td>Short Acting</td>
<td>Regular, Aspart</td>
<td>2-3 hours</td>
<td>2-4 hours</td>
</tr>
<tr>
<td>Intermediate (basal)</td>
<td>NPH</td>
<td>2-3 hours</td>
<td>4-12 hours</td>
</tr>
<tr>
<td>Long Acting (basal)</td>
<td>Glargine, Detemir</td>
<td>2-3 hours</td>
<td>24-36 hours</td>
</tr>
</tbody>
</table>

* Assumes 0.1-0.2 units/kg/Injection. Onset and duration may vary significantly by injection site.
** Time to steady state


Addition of Basal Insulin to Oral Therapy: Treat-to-Target Trial

756 Patients with Type 2 Diabetes on 1 or 2 Oral Agents

<table>
<thead>
<tr>
<th>A1C</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.0%</td>
<td>8.5%</td>
<td>8.0%</td>
<td>7.5%</td>
<td>7.0%</td>
<td>6.5%</td>
<td>6.0%</td>
<td></td>
</tr>
</tbody>
</table>


What to Do When OADs and Basal Insulin Are Not Enough?

Individualize treatment to patient’s needs:
- Add GLP-1 RA or DPP-4 inhibitor
- Substitute premix insulin
- Add bolus insulin analogue
- Add inhaled human insulin


Non-insulin Approaches

- **GLP-1 RA:** (exenatide, liraglutide, albiglutide, dulaglutide, lixisenatide*)
  - Injectable class that improves glycemic control through multiple mechanisms
  - Enhance insulin secretion & inhibit glucagon release in a glucose dependent manner
  - Longer acting GLP-1 RAs have greater impact on FPG & less effect on PPG levels
  - Weight loss & improved CV risk profile

- **DPP-4 Inhibitors:** (sitagliptin, linagliptin, saxagliptin, alogliptin)
  - Oral agents with moderate A1C improvement, esp. when combined with metformin
  - Weight neutral & improved CV risk profile
  - Adjustments for renal impairment except linagliptin

- **SGLT2 Inhibitors:** (canagliflozin, dapagliflozin, empagliflozin)
  - Oral agents with A1C improvement
  - Reduced SBP / DBP and weight loss
  - Limited use in renal impaired patients

*lixisenatide – not FDA approved

When Is It Time to Initiate Prandial Insulin Therapy in T2DM?

- **Individual is not meeting glycemic targets on basal insulin**
  - A1C still not at goal with ≈ 0.5 U/kg/day of daily basal insulin
  - Elevated A1C despite normal FPG (in the absence of available PPG readings) with basal insulin
  - FPG with basal insulin is within targeted range, but PPG is persistently above goal
    - Based on individualised glucose target
      - (eg. AM fasting FPG < 100 mg/dL or fasting FPG 100-130 mg/dL)
  - **Nocturnal hypoglycemia**
    - Large glucose drops overnight or between meals (possible over-basalization)
    - Further increases in basal insulin result in hypoglycemia

Advantages of Rapid-Acting Insulin Analogs Over Human Insulin

- More rapid onset of action
  - Convenient mealtime administration
  - Better PPG control
- More rapid return to basal levels
  - Potentially less hypoglycemia
- Greater predictability

Role for Premixed Insulin

- **Advantages**
  - Easy (no mixing, single product, pens available)
  - Covers insulin requirements through most of day
- **Disadvantages**
  - Not physiologic
  - Less flexible: requires consistent meal and exercise pattern, and cannot titrate individual insulin components unless custom-mixed insulin is used
  - ↑ Nocturnal hypoglycemia (presupper NPH)
  - ↑ Fasting hyperglycemia (presupper NPH wears off)
  - Higher A1C (realistic goal of ≤ 8%)
Patient Concerns About Insulin

- Self-blame due to perception that adherence to therapy could have been better.
- Avoidance/fear of injections
- Concerns of risk
  - Hypoglycemic effects
  - Complexity of regimens
  - Misconceptions about complications
  - Weight gain
- Skepticism of need for insulin or its’ efficacy
- Negative impact on social life


SOLVE: Baseline A1C Distribution at Insulin Initiation

How Often Does Hypoglycemia Occur in Diabetes?

How Often Does Hypoglycemia Occur With Diabetes?

Severe Hypoglycemia Increases the Risk of Mortality and CV Events

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Hazard Ratio (95% CI)</th>
<th>ADVANCE Trial Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovascular events</td>
<td></td>
<td>3.49 (2.54-4.88); P &lt; .001</td>
</tr>
<tr>
<td>Death—any cause</td>
<td></td>
<td>3.30 (2.31-4.71); P &lt; .001</td>
</tr>
<tr>
<td>Death—CV cause</td>
<td></td>
<td>3.19 (2.34-4.35); P &lt; .001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Hazard Ratio (95% CI)</th>
<th>VADT Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovascular events</td>
<td></td>
<td>2.06 (1.67-4.86); P = .001</td>
</tr>
</tbody>
</table>

When Does Hypoglycemia Occur With Diabetes?

When Does Hypoglycemia Occur With Diabetes?

All Hypoglycemia Negatively Affects Quality of Life in Patients With T2DM

Severe Hypoglycemia Increases the Risk of Mortality and CV Events

Hypoglycemia Severity

Hypoglycemia is also associated with lower treatment satisfaction, poorer adherence, and greater resource utilization

Practical Tips for Treating Hypoglycemia

- Patient, family, and friends should be aware of hypoglycemia signs and symptoms
- Have a plan to manage hypoglycemia (eg, Rule of 15)
  - Test BG, if possible
  - Treat hypoglycemia with 15 grams of sugar or carbohydrates (eg, ½ cup juice, 2-3 glucose tablets)
  - Wait 15 minutes and test BG again
  - Take additional 15 grams if necessary
  - Follow treatment of hypoglycemia with protein
  - Resume activity when feeling better and BG > 100 mg/dL

Guidelines for Preventing Hypoglycemia

AACE1-4
- Address in each patient contact
- If problematic, adjust regimen by:
  - Reviewing/applying diabetes self-management
  - Frequent SMBG
  - Flexible, appropriate insulin regimens
  - Individualized glycemic goals
  - Ongoing professional guidance and support
  - Consider each of the known risk factors for hypoglycemia

ADA5
- Reevaluate SMBG skills periodically
- Avoid aggressive targets in advanced disease
- Limit alcohol intake
  - ≤ 1 drink/day in adult women
  - ≤ 2 drinks/day in adult men
  - Add carbohydrate before exercising if BG < 100 mg/dL
- Strict avoidance of hypoglycemia for several weeks partly resolves repeated severe hypoglycemia, hypoglycemia unawareness

SMBG, self-monitoring of blood glucose.

Summary

- Many type 2 diabetes patients will require insulin for glycemic control
- Whether basal insulin or a GLP-1 receptor agonist should be the 1st injectable should be individualized
- Insulin analogs have several advantages over human insulin products
- When FPG is at goal but A1C is elevated, PPG needs to be assessed
- Multiple options for addressing elevated PPG but ultimately many patients may require prandial insulin

Therapeutic Approaches to the Management of Postprandial Hyperglycemia

Frank Lavernia, MD
Founder, The North Broward Diabetes Center
Pompano Beach, Florida
Controlling Glucose is Difficult

- Self-monitoring of blood glucose > 4 times daily
- Measurement of A1C every 3-4 months
- Dietary modification
- Rigorous diet / exercise program
- No existing drug that consistently controls blood glucose levels
- Mealtime glucose excursions are poorly controlled

Case: Poorly Controlled T2DM Patient on Basal Insulin at HS

- 58-yr old African American male with T2DM diagnosis since age 45, now on basal insulin at HS for past 3 yrs returns for follow-up.
- Hx: HTN, mixed dyslipidemia adequately controlled with medications
  - Recently widowed, but children live nearby
  - Physically active with regular exercise 4 X/wk for 30-45 minutes daily. Tennis at least once each week
- EtoH & tobacco (negative)

Current Exam & Treatment

**Current exam:**
- Wt 228 lbs, Ht 68”, BMI 34.7
- A1C 8.2%, Cr 1.2, C-peptide 2.9 ng/mL
- eGFR: 50 mL/min/1.73 m²

**Current treatment:**
- Metformin 1000 mg BID
- Sitagliptin 100 mg QD
- Glargine insulin 47 U HS
- Atorvastatin 20 mg QD
- Lisinopril 10 mg QD

Current Presentation, cont.

- A1C is 8.2% and FPG averages ~ 119 mg/dL.
- At his physician’s request he recorded his glucose values which showed modestly increased post-lunch and pre-bedtime glucose values.
- He is concerned about hypoglycemia, especially since he lives alone and has had 3 documented instances of hypoglycemia over past year.
- Also concerned about recent weight gain (8 lbs), which seems to have also worsened over time.

Need for Better Coverage?

![Diagram of plasma insulin levels with time]


Limitations of Human Regular Insulin

- **Slow onset of action**
  - Requires inconvenient administration:
    - 20 to 40 minutes prior to meal
  - Risk of hypoglycemia if meal is further delayed
  - Mismatch with postprandial hyperglycemic peak
- **Long duration of activity**
  - Up to 12 hours’ duration
  - Increased at higher dosages
  - Potential for late postprandial hypoglycemia
**Prandial Insulins: Rapid-Acting Analogues vs. Regular Human Insulin**

- **Rapid-acting analogues** have more rapid onset and shorter time to peak than regular human insulin.

**Clinical features of Rapid-acting Analogues**

- Insulin profile more closely mimics normal physiology
- Convenient administration immediately prior to meals
- Faster onset of action
- Limit postprandial hyperglycemic peaks
- Shorter duration of activity
  - Reduced late postprandial and nocturnal hypoglycemia
  - But more frequent late postprandial hyperglycemia
- Need for basal insulin replacement revealed

**Comparing 2 Methods of Stepwise Prandial Insulin Intensification**

<table>
<thead>
<tr>
<th>Parameter/ Characteristic</th>
<th>SimpleSTEP</th>
<th>ExtraSTEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal insulin titration</td>
<td>Based on average of 3 pre-breakfast plasma glucose readings</td>
<td></td>
</tr>
<tr>
<td>Prandial dose addition</td>
<td>Added to perceived largest meal</td>
<td>Added to meal with highest postmeal plasma glucose increase</td>
</tr>
<tr>
<td>(every 12 weeks, if needed)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prandial insulin titration</td>
<td>Based on PREMEAL plasma glucose</td>
<td>Based on POSTMEAL plasma glucose</td>
</tr>
<tr>
<td>SMBG</td>
<td>3 × 4-point profiles</td>
<td>3 × 6-point profiles</td>
</tr>
<tr>
<td></td>
<td>• Before each meal</td>
<td>• Before each meal</td>
</tr>
<tr>
<td></td>
<td>• Bedtime</td>
<td>• 2 h after each meal</td>
</tr>
</tbody>
</table>

**STEPwise Study Conclusions**

- Overall reduction in A1C of 1.2% was achieved with the addition of prandial insulin.
- Greatest A1C reductions were achieved with the first and second bolus injections.
- Improvement in glycemic control was comparable in both groups.
- Number of hypoglycemic episodes increased with increasing number of prandial injections.
- Basal-bolus treatment can be introduced in a more patient-friendly approach, using simple stepwise addition of prandial insulin.

**Physicians Confirm Need for a Faster Insulin**

"We need insulins that work faster than current rapid-acting analogs."

**Ideal Prandial Insulin**

<table>
<thead>
<tr>
<th>Desirable Characteristics</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precise dosing</td>
<td>Precise dosing</td>
</tr>
<tr>
<td>Improve post-meal profile</td>
<td>Improved post-meal profile</td>
</tr>
<tr>
<td>Rapid onset of action</td>
<td>Reduced risk of hypoglycemia</td>
</tr>
<tr>
<td>Short duration of action</td>
<td>Day &amp; night</td>
</tr>
<tr>
<td></td>
<td>Less weight gain</td>
</tr>
</tbody>
</table>
Approaches to Accelerate the Time Action Profiles of Fast-Acting Insulins

- Faster insulins
  - Linjeta - Biodel (Phase 3)
  - Adocia – Biochaperone (Phase 2)
  - Faster-acting Aspart - Novo Nordisk (Phase 3)

- Co-formulate with hyaluronidase
  - Halozyme (Phase 4)

- Warming the infusion site
  - InsuPad- InsuLine Medical

- Alternate Routes
  - Inhaled Insulin: Afrezza-MannKind (FDA Approved)
  - Intra-dermal: Micro-needle infusion sets-BD
  - Intra-peritoneal: DiaPort-Roche

Challenges of Previous Inhaled Human Insulin

- Challenges
  - Size of device
  - Difficult dose adjustment
  - Dosage form inconsistencies
  - Risk of lung disease
  - Insurance barriers
  - Withdrawn from the market in 2007

Novel Delivery of Insulin

Human insulin produced by recombinant DNA technology

Technosphere insulin consists of fumaryl diketopiperazine (FDKP)
  - Biologically inert excipient
  - Self-assembles into microcrystals
  - 2-4 µm (~ 2.5µm in diameter)
  - Ideal size for inhalation into the deep lung
  - FDKP has no metabolic activity in man
  - FDKP excreted intact in the urine

Inhaled Insulin Delivery

- pH < 6
  - FDKP particle formation
  - Insulin absorption onto particle

- pH > 6
  - rapid dissolution the lungs

Rapid Absorption and Short Duration of Action

Compared to subcutaneous rapid acting insulin analog (RAA), TI shows:
- More rapid absorption:
  - Time to peak serum insulin conc. (T_{max})
    - ~ 14 min after TI inhalation
    - ~ 40 minutes after SC RAA
- Faster elimination
  - ~ 180 minutes for TI
  - ~ 300 minutes for RAA

Clinical Application of Inhaled human Insulin

- Indications:
  - A rapid-acting, pre-meal time insulin for patients with Type 1 and 2 diabetes.

- Place in therapy:
  - An inhaled alternative to vial and syringe for meal-time insulins. Type 1 diabetes patients will need a long-acting insulin in addition to prandial insulin.
Non-Inferior Glycemic Control
A1C Change - Baseline to Week 52

<table>
<thead>
<tr>
<th>Study Week</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.5</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>26</td>
<td>7.5</td>
</tr>
<tr>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>52</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Rosenstock J, Lancet, 2010

Inhaled Insulin + Glargine
PreMix 70/30

T2DM Trial Design (Trial 175)

Randomization
- Inhaled human insulin (TI) + OADs (n = 177)
- Inhaled placebo + OADs (n = 176)

Pre-randomization: Start on 10 U TI or TP
Dose titration: Dosing adjusted via 90 minute PPG values to range of ≥ 110 to < 160 mg/dL
Stable dosing: Rescue therapy was available if PPG exceeded certain thresholds
4-Week follow-up: Return to usual care

Insulin-naive patients with inadequate glycemic control (HbA1c 7.5% to 10%) on optimal or maximally-tolerated doses of either metformin monotherapy or ≥ 2 OADs

Primary Endpoint: HbA1c Change from Baseline to Week 24

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>Baseline</th>
<th>Week 24</th>
<th>Change</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TI + OAD</td>
<td>177</td>
<td>8.25%</td>
<td>7.43%</td>
<td>-0.82%</td>
<td>-0.40% p&lt;0.0001</td>
</tr>
<tr>
<td>TP + OAD</td>
<td>176</td>
<td>8.27%</td>
<td>7.85%</td>
<td>-0.42%</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Difference 95% CI: (-0.57, -0.23)

Adverse Effects

<table>
<thead>
<tr>
<th>Inhaled Insulin vs. Placebo in Type 2 DM patients</th>
<th>Inhaled Insulin vs SC insulin in Type 1 DM patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache: 3.1% (2.8%)</td>
<td>Headache: 4.7% (2.8%)</td>
</tr>
<tr>
<td>Cough: 25.6% (19.7%)</td>
<td>Cough: 29.4% (4.9%)</td>
</tr>
<tr>
<td>Throat pain / irritation: 4.4% (3.8%)</td>
<td>Death pain / irritation: 5.5% (1.9%)</td>
</tr>
<tr>
<td>Severe hypoglycemia: 5.1% (1.7%)</td>
<td>Bronchitis: 2.9% (2.0%)</td>
</tr>
<tr>
<td>Hypoglycemia: 67% (30%)</td>
<td>Urinary tract infection: 2.3% (1.9%)</td>
</tr>
<tr>
<td>FEV1 decline &gt;15%: 6% (3%)</td>
<td></td>
</tr>
</tbody>
</table>

Safety

- Well tolerated
- Most common adverse events were cough and hypoglycemia
- Small non-progressive, clinically insignificant changes in pulmonary function
- Significant reduction in the risk of mild, moderate and severe hypoglycemia compared with SC insulins
- No increased cardiovascular risk
- No increased cancer risk observed
Limitations / Contraindications

- **Limitations:**
  - Inhaled insulin is not a substitute for long-acting insulin.
  - Not recommended for the treatment of diabetic ketoacidosis.
  - Not recommended in patients who smoke or who have stopped smoking in last 6 months.

- **Contraindications:**
  - During episodes of hypoglycemia.
  - In patients who have chronic lung disease such as COPD or asthma.

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Warnings and Precautions

- Decline in pulmonary function observed over time.
- Incidence of lung cancer was observed in controlled and uncontrolled trials.
- More patients using inhaled insulin experienced ketoacidosis.
- Life-threatening hypokalemia.

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Monitoring Parameters

- **Efficacy Monitoring:**
  - Blood glucose, A1C.

- **Toxicity Monitoring:**
  - Pulmonary function tests before initiating, after 6 months of therapy and annually, even in absence of pulmonary symptoms.
  - Fluid retention and heart failure with concomitant use of thiazolidinediones.
  - Hypokalemia.

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Insulin Naïve & Conversion Dosing

**Insulin Naïve Individuals:** Start on 4 units of inhaled insulin at each meal.

**Individuals Using Subcutaneous Mealtime (Prandial) Insulin:** Determine the appropriate inhaled dose for each meal by converting from the injected dose using table.
Mealtime Dose Adjustment

• Adjust the dosage of inhaled insulin based on the individual's metabolic needs, blood glucose monitoring results and glycemic control goal.

• Dosage adjustments may be needed with changes in physical activity, changes in meal patterns, changes in renal or hepatic function or during acute illness.

• Carefully monitor blood glucose control in patients requiring high doses of inhaled insulin. If blood glucose control is not achieved with increased inhaled doses, consider use of subcutaneous mealtime insulin.

Switching from SC Pre-mixed Insulin:

• Estimate the mealtime injected dose by dividing half of the total daily injected pre-mixed insulin dose equally among the three meals of the day.

• Convert each estimated injected mealtime dose to an appropriate inhaled dose using chart.

• Administer half of the total daily injected pre-mixed dose as an injected basal insulin dose.

Clinical Case Scenario

• A 58 y/o man with T2DM of 6 yrs duration presents to his primary care provider for follow-up.
  • History of HTN, mixed dyslipidemia, obesity
  • Recently widowed, but children live nearby
  • Physically active with regular exercise at least 4 times/week for 30-45 minutes daily. Tennis at least once each week

• He is currently taking metformin, sitagliptin and insulin glargine and not at goal

Clinical Case Scenario, cont.

• A1C is 8.2% and FPG averages ~ 119 mg/dL

• At his physician’s request he recorded his glucose values which showed modestly increased post lunch and pre-bedtime glucose values.

• He is concerned about hypoglycemia, especially since he lives alone and has had 3 documented instances of hypoglycemia over past year.

• Also concerned about recent weight gain (8 lbs), which seems to have also worsened over time.

Current Labs & Medications

Labs:
• Blood pressure: 136/85 mmHg
• BMI: 33.5
• LDL-C: 80 mg/dL
• TC: 182 mg/dL
• eGFR: 50 mL/min/1.73 m²

Medications
• metformin 1,000 mg BID
• sitagliptin 100mg QD
• glargine insulin 47 U SC
• atorvastatin 20 mg QD

Conclusions

• Many type 2 diabetes patients will require insulin for glycemic control

• When FPG is at goal, but A1C is elevated, PPG needs to be assessed

• Multiple options for addressing elevated PPG but ultimately many patients may require prandial insulin

• Wide range of prandial insulins are available for both SC and inhaled delivery

• Hypoglycemia can be minimized and treated
More Conclusions

- Inhaled insulin is indicated for use as meal time insulin in patients with type 1 and type 2 diabetes.
- Inhaled insulin has quicker onset and shorter duration than other rapid-acting insulins resulting in improved postprandial control with less risk of hypoglycemia and weight gain.
- Adding 3 x daily inhaled insulin to existing oral therapy is generally more effective over a 12-24 week period than adding a second oral agent taken once or twice a day.
- Should be avoided in smokers, patients with chronic pulmonary disease and patients with bronchospasm or asthma.
- Most suitable for patients with A1C levels that remain elevated after FPG have been controlled with a basal insulin.

### Drug List (Generic: Brand)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
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<tbody>
<tr>
<td>Metformin</td>
<td>Glucophage</td>
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<tr>
<td>Glimepiride</td>
<td>Amaryl</td>
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<tr>
<td>Canagliflozin</td>
<td>Invokana</td>
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<tr>
<td>Empagliflozin</td>
<td>Jardiance</td>
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<tr>
<td>Dapagliflozin</td>
<td>Farxiga</td>
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<td>Albiglutide</td>
<td>Tanzeum</td>
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<td>Liraglutide</td>
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<td>Dulaglutide</td>
<td>Trulicity</td>
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<tr>
<td>Exenatide BID</td>
<td>Byetta</td>
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<tr>
<td>Exenatide QW</td>
<td>Hydreaon</td>
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<tr>
<td>Lixisenatide</td>
<td>Lyxumia*</td>
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<tr>
<td>Pioglitazone</td>
<td>Actos</td>
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<td>Pramlintide</td>
<td>Symlin</td>
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<td>Januvia</td>
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<td>Levemir</td>
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<td>Insulin glargine</td>
<td>Lantus</td>
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<td>Humalog Mix 75/25</td>
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<td>Afrezza</td>
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<td>Humalog</td>
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<td>Insulin aspart</td>
<td>Novolog</td>
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<tr>
<td>Insulin glulisine</td>
<td>Apidra</td>
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</tbody>
</table>

*pending FDA approval