Kathy Wheeler, PhD, RN, APRN, NP-C, FNAP, FAANP
Assistant Professor, University of Kentucky
College of Nursing

SWEET AS CAN BE: TRANSITIONING FROM ORAL TO INJECTABLE HYPOGLYCEMICS

The speaker has nothing to disclose regarding industry support
The speaker would like to thank colleagues Ellie Strock, Dixie Harms, Shannon Idzik, Angi Thompson and Kristy Umana for years of experience on the diabetes workshop trail, including adaptations of materials.

DISCLOSURES

1. Compare and contrast the non-insulin and insulin injectables that are available for the treatment of type 2 diabetes.
2. Describe starting and adjusting therapy for patients with type 2 diabetes in order to optimize patient outcomes.
3. Describe common patient scenarios (case studies) where injectables need to be started or adjusted to optimize patient outcomes.

OBJECTIVES

Over 100 million adult Americans have diabetes or prediabetes
9.4 percent of the population has diabetes
The south and Appalachia has even higher rates of diabetes

WE'RE IN AN EPIDEMIC !!!

Majority of patients with DM managed in primary care
NPs need to be proficient
- Understand and address metabolic defects
- Address lifestyle issues
- Advocate for glucose monitoring (SMBG), possibly continuous glucose monitoring (CGM)
- Modify strategies often

Primary Care and Diabetes
Clinical Realities
- Time limitations
- Referral limitations
- Limited skills and knowledge
- Accelerating medical change
- Clinical inertia
- Intensive glycemic control rarely achievable with only oral agents
PROGRESSION OF THERAPY IN T2DM

Single oral agent

Multiple agents

Multiple agents + insulin

GOALS OF CARE: A1C

ADA: <7

AACE: <6.5

CVD, elderly: <8

TARGETING THERAPY

Metformin

Secretagogues

Exercise

Medical Nutrition Therapy

Thiazolidinediones (TZD)

Insulin

GLP-1 Agonists

DPP-4 Inhibitors

α-Glucosidase Inhibitors

SGLT2 Inhibitors

Decision cycle for patient-centered glycemic management in type 2 diabetes.®2019 by American Diabetes Association

American Diabetes Association Dia Care 2019;42:S34-S45
Incretin mimetics are glucagon-like peptide-1 (GLP-1) agonists. Dipeptidyl peptidase-IV (DPP-IV) antagonists inhibit the breakdown of GLP-1.

GLP-1 Physiology

- Appetite
- Cardioprotection
- Cardiac Output
- Glucose production
- Glucose uptake
- Insulin secretion
- Glucagon secretion
- Beta cell neogenesis
- Beta cell apoptosis
- Gastric emptying
- Incretin based meds

Advantages

- Used with oral agents or basal insulin in T2DM
- QD, BID, or weekly
- Increase in glucose dependent insulin secretion
- Increase in glucagon production
- Increase in gastric emptying
- Increase in appetite/possible weight loss
- Lack of hypoglycemia if as monotherapy
- Weight loss
- Reduces post prandial glucose
- Combos of basal insulin and GLP-1 agonists are available

Disadvantages

- Injection
- H/A
- Nausea (usually transient)
- Diarrhea
- Dosage modification with renal dysfunction (albiglutide, dulaglutide)
- Avoid in severe renal impairment (exenatide)
- May be associated with pancreatitis
- Associated with thyroid cell cancer in rodents
- Associated with renal insufficiency

Srock, 2018
Medication Pen Delivery Device Frequency Dose Comments

**Exenatide (Byetta®)**
- $669/mo.
- Multi-dose pre-filled
- Twice daily 5 µg X 1 mo
  - then 10 µg
- Administer within 60 minutes of breakfast and dinner
- Monthly Rx: 1 pen
- Pen needles prescribed separately

**Liraglutide (Victoza®)**
- $750/mo.
- Multi-dose pre-filled
- Once daily 0.6 mg X 1 wk, 
  - then 1.2 mg or 1.8 mg as needed
- Administer anytime of day; same time each day
- Monthly Rx: 0.6 or 1.2 mg/day – 2 pen box; 1.8 mg/day – 3 pen box
- Pen needles prescribed separately

**Exenatide LA (Bydureon Bcise®)**
- $625/mo.
- Single dose pre-filled
- Once weekly 2 mg
- Administer same day of week anytime of day
- Monthly Rx: 1 box (4 pens)
- Pen needles supplied

**Albiglutide (Tanzeum®)**
- $525/mo.
- Single dose pre-filled
- (Needs to be reconstituted)
- Once weekly 30 mg; 
  - then 50 mg as needed
- Administer same day of week anytime of day
- Mixing: 15” for 30 mg & 30” for 50 mg doses
- Monthly Rx: 1 carton (4 pens)
- Pen needles supplied

**Dulaglutide (Trulicity®)**
- $660/mo.
- Single dose pre-filled
- Once weekly 0.75–1.5 mg
- No reconstitution needed
- Administer same day of week anytime of day
- Monthly Rx: 1 box (4 pens)
- Needle contained in pen device

**Lixisenatide (Adylixin®)**
- $560/mo.
- Multi-dose pre-filled
- Once daily 10 mcg X 14d
  - then 20 mcg
- Administer within 1 hour of first meal of day

**Semaglutide (Ozempic®)**
- $769/mo.
- Multi-dose pre-filled
- Once weekly 0.25 mg X 4 w,
  - then 0.5 mg x 4 wk
  - Max 1mg per week
- Administer with or without meals
- Comes with pen needles

---

**GLP-1 AGONIST OPTIONS**

**Short Acting**
- Exenatide (Byetta)
  - Initial: 5 mcg SC BID
- Liraglutide (Victoza)
  - Initial: 0.6 mg SC once daily x 1 week, then increase to 1.2 mg SC once daily
- Lixisenatide
  - Initial: 10 mcg SC once daily

**Long Acting**
- Exenatide extended-release (Bydurean or Bcise)
  - Initial: 2 mg SC once weekly
- Albiglutide (Tanzeum)
  - Initial: 0.6 mg SC once weekly
- Dulaglutide (Trulicity)
  - Initial: 0.75 mg SC once weekly
- Semaglutide (Ozempic)
  - Initial: 0.25mg SC once a week x 4 wk, then 0.5mg a week x 4 wk, max 1mg per week

---

**GLP-1/BASAL INSULIN COMBINATIONS**

- Insulin degludec U100/liraglutide
  - 3.6 mg/mL (Xultophy)
- Insuline glargine U100/lixisenatide
  - 33 mcg/mL (Soliqva)

---

**GLP-1/BASAL INSULIN COMBINATIONS**

- Basal insulin targets fasting glucose control
- GLP-1 RA will additionally improve postprandial control due to their glucose dependent action
- Reduce overall insulin requirements
- Less hypoglycemia
- Reduce weight gain from insulin therapy
- Adding GLP-1 RA to basal insulin
- Adding basal insulin to GLP-1 RA
- Start with GLP-1 RA /basal insulin combination

---

Idzik & Harms, 2018
• Indication: For patients with inadequately controlled type 2 diabetes treated with basal insulin (<50 units) or liraglutide (<1.8 mg)

• Administrator once daily at same time each day with or without food

• Maximum daily dosage is 30 units

• JULITOPI® 100/3.6 pen delivers doses from 10 to 50 units with each injection

• Each JULITOPI® 100/3.6 dosage unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide

Starting dose of 16 units

INSULIN DEGLUDEC U100/LIRAGLUTIDE 3.6 MG/ML (JULITOPI®)

Idzik & Harms, 2018

• Indication: For patients with type 2 diabetes uncontrolled on basal insulin OR lixisenatide therapy

• Administrator once daily within the hour prior to the first meal of the day

• Maximum daily dosage is 60 units

• Each Soliqua® dosage unit contains 1 unit of insulin glargine and 0.33 mcg lixisenatide

INSULIN GLARGINE U100/LIXISENATIDE 33 MG/ML (SOLIQUA)

Idzik & Harms, 2018

<table>
<thead>
<tr>
<th>GLP-1/BASAL INSULIN COMBINATIONS</th>
<th>Indication</th>
<th>Basal Insulin</th>
<th>Maximum Dose</th>
<th>Glucagon-like Peptide (GLP-1)</th>
<th>Administration</th>
<th>Glucose Response</th>
<th>Titration (based on FBG)</th>
<th>Titration Frequency</th>
<th>Minimum dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xultophy (iDegLira)</td>
<td>Current treatment with basal insulin OR liraglutide</td>
<td>Starting dose of 16 units</td>
<td>Maximum daily dosage is 50 units</td>
<td>Once daily at the same time of day</td>
<td>Glucose level at the same time of day</td>
<td>+2 units &gt; target</td>
<td>-2 units &lt; target</td>
<td>Every 3-4 days</td>
<td>&lt;16 units/day discontinue and use alternative therapy</td>
</tr>
</tbody>
</table>

Message: Stop taking other basal insulin or GLP-1 medications prior to starting

GLP-1/BASAL INSULIN COMBINATIONS

INSULIN DEGLUDEC U100/LIRAGLUTIDE 3.6 MG/ML (JULITOPI®)

Idzik & Harms, 2018

BASAL INSULIN: GLARGINE U300

Rendition per Toujeo PI, Sanofi, 2015

Wheeler, 2018

BASAL INSULIN: INSULIN DEGLUDEC

Rendition per Tresiba PI, NovoNordisk

Wheeler, 2018

<table>
<thead>
<tr>
<th>BASAL AND PRANDIAL INSULINS</th>
<th>Insulin Type</th>
<th>Onset of Action</th>
<th>Peak Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASAL INSULIN</td>
<td>Human NPH</td>
<td>Intermediate</td>
<td>1-2 hrs; 4-8 hours</td>
</tr>
<tr>
<td>Insulin glargine (Lantus and Basaglar)</td>
<td>Long-acting analog</td>
<td>1-2 hrs; No peak</td>
<td>24 hrs</td>
</tr>
<tr>
<td>Insulin detemir (Levemir)</td>
<td>Long-acting analog</td>
<td>1-2 hrs; No peak</td>
<td>22-24 hrs</td>
</tr>
<tr>
<td>Insulin glargine U300 (Toujeo)</td>
<td>Ultra long-acting analog</td>
<td>Over 6 hrs; No peak</td>
<td>36 hrs</td>
</tr>
<tr>
<td>Insulin degludec (Tresiba)</td>
<td>Ultra long-acting analog</td>
<td>30-90 minutes; No peak</td>
<td>42 hrs</td>
</tr>
</tbody>
</table>

PRANDIAL INSULINS

Rapid-acting analogs

Lispro (Humalog U100 and U200)

Aspart (NovoLog)

Glulisine (Apidra)

Fast acting aspart (Fiasp) | Ultra-fast acting analog | 2.5 min; 1-2 hours; 3-5 hrs |

Regular human | Short-acting | 30-60 min; 2-4 hours; 8-10 hrs |

New

BASAL INSULIN: GLARGINE U300

Rendition per Toujeo PI, Sanofi, 2015

Wheeler, 2018

BASAL INSULIN: INSULIN DEGLUDEC

Rendition per Tresiba PI, NovoNordisk

Wheeler, 2018

<table>
<thead>
<tr>
<th>BASAL INSULIN: GLARGINE U300</th>
<th>Type</th>
<th>Onset of Action</th>
<th>Peak Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human NPH</td>
<td>Intermediate</td>
<td>1-2 hrs; 4-8 hours</td>
<td>24 hrs</td>
</tr>
<tr>
<td>Insulin glargine (Lantus and Basaglar)</td>
<td>Long-acting analog</td>
<td>1-2 hrs; No peak</td>
<td>24 hrs</td>
</tr>
<tr>
<td>Insulin detemir (Levemir)</td>
<td>Long-acting analog</td>
<td>1-2 hrs; No peak</td>
<td>22-24 hrs</td>
</tr>
<tr>
<td>Insulin glargine U300 (Toujeo)</td>
<td>Ultra long-acting analog</td>
<td>Over 6 hrs; No peak</td>
<td>36 hrs</td>
</tr>
<tr>
<td>Insulin degludec (Tresiba)</td>
<td>Ultra long-acting analog</td>
<td>30-90 minutes; No peak</td>
<td>42 hrs</td>
</tr>
</tbody>
</table>

PRANDIAL INSULINS

Rapid-acting analogs

Lispro (Humalog U100 and U200)

Aspart (NovoLog)

Glulisine (Apidra)

Fast acting aspart (Fiasp) | Ultra-fast acting analog | 2.5 min; 1-2 hours; 3-5 hrs |

Regular human | Short-acting | 30-60 min; 2-4 hours; 8-10 hrs |

New

BASAL INSULIN: GLARGINE U300

Rendition per Toujeo PI, Sanofi, 2015

Wheeler, 2018

BASAL INSULIN: INSULIN DEGLUDEC

Rendition per Tresiba PI, NovoNordisk

Wheeler, 2018

Basal Insulin: Glargine U300

Basal Insulin Glargine U300

Basal Insulin: Glargine U300

Basal Insulin: Glargine U300

Basal Insulin: Glargine U300

Basal Insulin: Glargine U300

Basal Insulin: Glargine U300
PRE-MIXED INSULINS

<table>
<thead>
<tr>
<th>Pre-Mixed Insulin Analogs</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>75% NPL/25% lispro; (Humalog® Mix75/25)</td>
<td>15 min</td>
<td>Dual</td>
<td>10-16 hrs</td>
</tr>
<tr>
<td>70% aspart protamine/ 30% aspart</td>
<td>10-20 min</td>
<td>Dual</td>
<td>15-18 hrs</td>
</tr>
<tr>
<td>70% NPL/30% lispro</td>
<td>15 min</td>
<td>Dual</td>
<td>10-16 hrs</td>
</tr>
<tr>
<td>70% degludec/30% aspart</td>
<td>15 min</td>
<td>Dual</td>
<td>&gt;24 hrs</td>
</tr>
<tr>
<td>Pre-Mixed Human Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% NPH/30% Regular</td>
<td>30 min-1 hr</td>
<td>Dual</td>
<td>10-16 hrs</td>
</tr>
<tr>
<td>70% NPH/30% Regular; (NovoRapid 70/30)</td>
<td>30 min-1 hr</td>
<td>Dual</td>
<td>10-16 hrs</td>
</tr>
</tbody>
</table>

NEW GOAL WITH THERAPY: MIMIC NORMAL INSULIN SECRETION

Background (Basal) Insulin Needs ~ 50%
Mealtime (Bolus) Insulin Needs ~ 50%

Wheeler, 2018

INITIATING AND ADJUSTING INSULIN

CASE STUDIES

PERSONALIZED CARE

Consider human regular, NPH and pre-mixed insulin as an option for your patients who can’t afford insulin analogs.

Regular, NPH, 70/30 (Relion® Walmart) ~ $25/vial
Insulin Delivery

- Syringes
- Vials
- Pens
- Patch pumps
- Insulin pumps

Insulin Delivery Needles

**www.bddiabetes.com**

Products Features

<table>
<thead>
<tr>
<th>Insulin Delivery/Needles</th>
<th>ONE TOUCH VIA Thin, plastic delivery device worn on skin for 3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deliver fast acting analogs (Humalog or Novolog)</td>
</tr>
<tr>
<td></td>
<td>Dispenses in 2 unit increments, even through clothing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>V-Go Small delivery device worn on skin for 24 hours:</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 units/24 hour + Up to 36 units in 2 unit doses (56 total)</td>
</tr>
<tr>
<td>30 units/24 hour + Up to 36 units in 2 unit doses (66 total)</td>
</tr>
<tr>
<td>40 units/24 hour + Up to 36 units in 2 unit doses (76 total)</td>
</tr>
</tbody>
</table>

Delivers continuous basal insulin and as needed bolus insulin (Humalog or Novolog)

**NEW INSULIN DELIVERY SYSTEMS**

InPen Bluetooth enabled smart insulin pen paired with smartphone

Delivers fast acting analogs (Humalog or Novolog)

<table>
<thead>
<tr>
<th>Insulin Delivery Systems</th>
<th>ONE TOUCH VIA Thin, plastic delivery device worn on skin for 3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deliver fast acting analogs (Humalog or Novolog)</td>
</tr>
<tr>
<td></td>
<td>Dispenses in 2 unit increments, even through clothing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>V-Go Small delivery device worn on skin for 24 hours:</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 units/24 hour + Up to 36 units in 2 unit doses (56 total)</td>
</tr>
<tr>
<td>30 units/24 hour + Up to 36 units in 2 unit doses (66 total)</td>
</tr>
<tr>
<td>40 units/24 hour + Up to 36 units in 2 unit doses (76 total)</td>
</tr>
</tbody>
</table>

Delivers continuous basal insulin and as needed bolus insulin (Humalog or Novolog)

<table>
<thead>
<tr>
<th>InPen Bluetooth enabled smart insulin pen paired with smartphone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivers fast acting analogs (Humalog or Novolog)</td>
</tr>
<tr>
<td>Tracks injections, calculates doses</td>
</tr>
</tbody>
</table>

37 38