Main Pathophysiological Defects in T2DM
“The Ominous Octet”

- **Islet β-cell**
  - Impaired Insulin Secretion

- **Islet α-cell**
  - Increased Glucagon Secretion

- Decreased Incretin Effect

- Increased Lipolysis

- Increased Glucose Reabsorption

- Decreased Glucose Uptake

- Increased HGP

- Neurotransmitter Dysfunction

Injectable Therapies for T2DM and Obesity

This presentation will:

• Explain the pathophysiological aspects of T2DM, and how defects can be addressed with injectable therapies

• Outline incretin-based injectable therapies for T2DM and obesity management and discuss evidence from clinical trials

• Describe established and newly available insulin therapies for treatment of type 2 diabetes.

• Describe how to intensify insulin regimens to achieve glycemic targets
Abnormal Insulin and Glucagon Responses Contribute to Hyperglycemia in Type 2 Diabetes

Mean ± SE
The Incretin Effect

Control Subjects (n=8)

Incretin Effect

Type 2 Diabetes (n=14)

GLP-1 Modulates Numerous Functions in Humans

- **GLP-1:** Secreted upon the ingestion of food
- **Beta cells:** Enhances glucose-dependent insulin secretion
- **Alpha cells:** Glucose-dependent postprandial glucagon secretion
- **Liver:** Glucagon reduces hepatic glucose output
- **Stomach:** Helps regulate gastric emptying
- **Brain:** Promotes satiety and reduces appetite

Glucose-Dependent Actions of GLP-1: Effect in Subjects With Type 2 Diabetes

Data are mean ± SE. *P<0.05

Strategies for Enhancing GLP-1 Action

- **GLP-1 receptor agonists** (injectable therapies)
  - Exenatide
  - Liraglutide
  - Albiglutide
  - Dulaglutide

- **DPP-4 inhibitors** (oral therapies)
  - Inhibit actions of DPP-4
  - Sitagliptin, Saxagliptin, Linagliptin, Alogliptin
**Characteristics of GLP-1 Agonists**

*Exenatide, Liraglutide, Albiglutide, Dulaglutide*

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mimic prolonged action of GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Decrease A1C levels 0.5%-2.0%</td>
</tr>
<tr>
<td></td>
<td>(depends on entry of glucose into bloodstream from gut)</td>
</tr>
<tr>
<td>Dosing</td>
<td>Once- or twice-daily injection, weekly *</td>
</tr>
<tr>
<td>Side effects</td>
<td>Nausea, vomiting, weight loss</td>
</tr>
<tr>
<td>Main risk</td>
<td>C-cell thyroid tumors**, long-term safety unknown</td>
</tr>
<tr>
<td>Associated with</td>
<td>Pancreatitis possible</td>
</tr>
</tbody>
</table>

* Dosing depends on GLP-1 agonist  
** With liraglutide, in rodents only  

A1C = glycated hemoglobin; GLP-1 = glucagon-like peptide-1

Exenatide [package insert]. San Diego, CA; Amylin Pharmaceuticals; 2010.; Tanzeum (albiglutide) [prescribing information].
# Marketed GLP-1 RAs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exenatide BID</th>
<th>Liraglutide</th>
<th>Exenatide ER</th>
<th>Albiglutide</th>
<th>Dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Byetta</td>
<td>Victoza</td>
<td>Bydureon</td>
<td>Tanzeum (U.S.)</td>
<td>Eperzan (Europe)</td>
</tr>
<tr>
<td>Description</td>
<td>Synthetic exendin-4, a peptide identified in H. suspectum that activates the GLP-1 R and is resistant to DPP-4 degradation</td>
<td>GLP-1 modified to be resistant to DPP-4 degradation</td>
<td>Exenatide contained in a hydrolyzable polymer microspheres for extended release</td>
<td>An albumin fusion protein made of 2 copies of modified human GLP-1</td>
<td>A fusion protein with 2 disulfide-linked human GLP-1 analog sequence chains, connected by a small peptide linker to human immunoglobulin G4 (IgG4)</td>
</tr>
<tr>
<td>Administration</td>
<td>Subcutaneous injection</td>
<td>Subcutaneous injection</td>
<td>Subcutaneous injection</td>
<td>Subcutaneous injection</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.4 hours</td>
<td>13 hours</td>
<td>&gt; 1 week</td>
<td>5 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Dosing</td>
<td>2 × daily, before meals</td>
<td>1 × daily, any time</td>
<td>1 × weekly</td>
<td>1 × weekly</td>
<td>1 × weekly</td>
</tr>
</tbody>
</table>

a Amino acid substitution and addition of acyl chain.

Liraglutide

- Liraglutide: 0.6 mg sc QD x 1 week then 1.2 mg sc QD increase to 1.8 mg sc QD if needed
- Supplied in a pen
- Use: 2-3 pens per month
### Glucose Control With Liraglutide With/Without Oral Agents

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy vs Glimepiride 52 Weeks&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Add-on to Metformin 26 Weeks&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Add-on to Metformin 26 Weeks&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Add-on to Sulfonylurea 26 Weeks&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Add-on to Met + TZD 26 Weeks&lt;sup&gt;5&lt;/sup&gt;</th>
<th>Add-on to Met + SU 26 Weeks&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>746</td>
<td>1091</td>
<td>665</td>
<td>1041</td>
<td>821</td>
<td>581</td>
</tr>
<tr>
<td>Treatment</td>
<td>Gli</td>
<td>Met</td>
<td>Glim + Lira + Met</td>
<td>SU + Rosi + Lira + Met</td>
<td>Rosi + Lira + Met</td>
<td>Met + Glar + Lira + Met</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.4</td>
<td>8.3</td>
<td>8.4</td>
<td>8.4</td>
<td>8.4</td>
<td>8.3</td>
</tr>
<tr>
<td>ΔA1C (%)</td>
<td>-1.14</td>
<td>-0.98-1.00</td>
<td>-0.9</td>
<td>*</td>
<td>**</td>
<td>-1.09</td>
</tr>
</tbody>
</table>

*P<0.0001 vs monotherapy. **P<0.0001 vs dual therapy. ***P=0.0015 vs glargine.

<sup>1</sup>All liraglutide dosages shown are 1.8 mg QD.

**Weight Reduction With Liraglutide: Mono and Dual Combination Therapy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Δ Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy vs Glimepiride 52 Weeks</td>
<td>Gli</td>
</tr>
<tr>
<td>746</td>
<td>1.10</td>
</tr>
<tr>
<td>Add-on to Metformin 26 Weeks</td>
<td>Met</td>
</tr>
<tr>
<td>1091</td>
<td>1.00</td>
</tr>
<tr>
<td>665</td>
<td>2.10</td>
</tr>
<tr>
<td>1041</td>
<td>-0.10</td>
</tr>
<tr>
<td>821</td>
<td>0.60</td>
</tr>
<tr>
<td>581</td>
<td>1.60</td>
</tr>
</tbody>
</table>

*P<0.0001 vs glargine, rosiglitazone, sitagliptin, or SU. **P<0.01 vs metformin. ***P<0.05 vs SU.

†All liraglutide dosages shown are 1.8 mg QD.

Hypoglycemia With Liraglutide: Mono and Dual Combination Therapy

<table>
<thead>
<tr>
<th>Treatment†</th>
<th>Monotherapy 52 Weeks¹</th>
<th>Add-on to Metformin 26 Weeks²</th>
<th>Add-on to Metformin 26 Weeks³</th>
<th>Add-on to Sulfonylurea 26 Weeks⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Glim</td>
<td>746</td>
<td>1091</td>
<td>665</td>
<td>1041</td>
</tr>
<tr>
<td>Lira</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Met</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glim + Met</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lira + Met</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sit + Met</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lira + SU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosi + SU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patients Reporting Hypoglycemia (%)**

- Monotherapy 52 Weeks: 24%
- Add-on to Metformin 26 Weeks: 17%
- Add-on to Sulfonylurea 26 Weeks: 8%

*P<0.01 vs active comparator.
†All liraglutide dosages shown are 1.8 mg QD.

## Blood Pressure Changes With Liraglutide

### Δ Systolic BP (mmHg)

<table>
<thead>
<tr>
<th>N</th>
<th>Treatment</th>
<th>Gli</th>
<th>Lir</th>
<th>Monotherapy vs Glimepiride 52 Weeks&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Add-on to Metformin 26 Weeks&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Add-on to Metformin 26 Weeks&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Add-on to Sulfonylurea 26 Weeks&lt;sup&gt;4,5&lt;/sup&gt;</th>
<th>Add-on to Met + TZD 26 Weeks&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Add-on to Met + SU 26 Weeks&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>746</td>
<td>Gli</td>
<td>Met</td>
<td>-0.7</td>
<td>0.4</td>
<td>-0.9</td>
<td>-1.1</td>
<td>-5.6</td>
<td>-4.0</td>
<td></td>
</tr>
<tr>
<td>1091</td>
<td>Lir</td>
<td>Glim + Met</td>
<td>-3.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>665</td>
<td>Met</td>
<td>Lira + Met</td>
<td></td>
<td></td>
<td>-0.7</td>
<td>-2.3</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1041</td>
<td>SU</td>
<td>Rosi + SU</td>
<td></td>
<td></td>
<td>-0.9</td>
<td>-2.8</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>821</td>
<td>Rosi</td>
<td>Lira + Met</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>581</td>
<td>Met</td>
<td>Glar + Met + SU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 vs comparator.

†All liraglutide dosages shown are 1.8 mg OD.

# Liraglutide: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events*</th>
<th>Monotherapy</th>
<th>+ Met</th>
<th>+ Glim</th>
<th>+ Met + TZD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lir (n=497)</td>
<td>Glim (n=248)</td>
<td>Lir (n=724)</td>
<td>PBO (n=121)</td>
</tr>
<tr>
<td>Nausea</td>
<td>28.4</td>
<td>8.5</td>
<td>15.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17.1</td>
<td>8.9</td>
<td>10.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10.9</td>
<td>3.6</td>
<td>6.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>9.9</td>
<td>4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9.1</td>
<td>9.3</td>
<td>9.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adverse events of interest occurring in ≥5% of patients receiving liraglutide.

Nausea Declined Over Time with Liraglutide Monotherapy

Patients (%)

Time (weeks)

Liraglutide Monotherapy vs SU

Liraglutide 1.2 mg (n=251)
Liraglutide 1.8 mg (n=246)
Glimepiride 8 mg (n=248)

Liraglutide 3mg

- Approved December 2014 for treatment of overweight/obesity
- Indications: adults with BMI $\geq 30$ or BMI $\geq 27$ with one CV risk factor: hypertension, type 2 diabetes, hypercholesterolemia
- Approved with REMS: follow up and registry for MTC, breast cancer, CV safety
- Supplied as 3 mL pen, 6mg/mL (5 pens/mo.)
- Dose titration: 0.6mg daily sc x 7 d; 1.2mg daily x 7 d; 1.6mg daily x 7 d; 1.8mg daily x 7 d; 2.4mg daily x 7 d; 3mg daily maintenance
Liraglutide 3mg QD

• Phase 3 - 56-week trials:
• Proportion of patients achieving weight loss:

<table>
<thead>
<tr>
<th></th>
<th>≥ 5%</th>
<th>≥ 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 3mg</td>
<td>60.3</td>
<td>31.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>24.4</td>
<td>8.7</td>
</tr>
</tbody>
</table>
Glucose Control With Exenatide ER

<table>
<thead>
<tr>
<th></th>
<th>Add-on to OAs* 30 Weeks¹</th>
<th>Monotherapy vs OAs 26 Weeks²</th>
<th>Add-on to Metformin 26 Weeks³</th>
<th>Add-on to Met +/- SU 26 Weeks⁴</th>
<th>Add-on to OAs† 26 Weeks⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>258</td>
<td>820</td>
<td>514</td>
<td>456</td>
<td>911</td>
</tr>
<tr>
<td>Treatment</td>
<td>Exe BID</td>
<td>Exe ER</td>
<td>Sit Pio Met Exe ER</td>
<td>Glar + OAs + OAs</td>
<td>Lira + Exe ER + OAs</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.3</td>
<td>8.5</td>
<td>8.5</td>
<td>8.3</td>
<td>8.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Δ A1C (%)</th>
<th>0</th>
<th>-0.475</th>
<th>-0.95</th>
<th>-1.425</th>
<th>-1.9</th>
<th>-1.5</th>
<th>-1.28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P&lt;0.01</td>
<td>P&lt;0.001</td>
<td>P&lt;0.0001</td>
<td>P=0.017</td>
<td>P&lt;0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.

†Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.

Exenatide ER

- 2 mg sc every 7 days, w/ or w/o meals
- 23G x 5/16” needle
- Microsphere release; steady state: 6-7 wks
- Not recom. as 1st line Rx or use w/insulin
- Add on to metformin, SU, TZD, or combination
- Less nausea vs exenatide BID
- ↑ weight loss vs exenatide BID: 5.1 lb vs 3.1 lb @24 wks
# Weight Reduction With Exenatide ER

<table>
<thead>
<tr>
<th>Add-on to OAs* 30 Weeks¹</th>
<th>Monotherapy vs OAs 26 Weeks²</th>
<th>Add-on to Metformin 26 Weeks³</th>
<th>Add-on to Met +/- SU 26 Weeks⁴</th>
<th>Add-on to OAs† 26 Weeks⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>258</td>
<td>820</td>
<td>514</td>
<td>456</td>
</tr>
<tr>
<td>Treatment (mg/day)</td>
<td>Exe BID</td>
<td>Exe ER</td>
<td>Exe ER</td>
<td>Exe ER + OAs</td>
</tr>
<tr>
<td>Δ Weight (kg)</td>
<td>-3.6 -3.7</td>
<td>-2.0 -2.0</td>
<td>-2.3</td>
<td>-2.6</td>
</tr>
<tr>
<td></td>
<td>*P&lt;0.001</td>
<td>*P&lt;0.001</td>
<td>*P&lt;0.001</td>
<td>*P&lt;0.0001</td>
</tr>
</tbody>
</table>

*Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.
†Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.

Hypoglycemia With Exenatide ER

*Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.
†Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.

# Exenatide Extended Release: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events*</th>
<th>Patients (%)</th>
<th>Monotherapy</th>
<th>+ Met</th>
<th>+ Met +/- SU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exe ER (n=248)</td>
<td>Sit (n=163)</td>
<td>Pio (n=163)</td>
<td>Met (n=246)</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.3</td>
<td>3.7</td>
<td>4.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.9</td>
<td>5.5</td>
<td>3.7</td>
<td>12.6</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>10.5</td>
<td>6.7</td>
<td>3.7</td>
<td>10.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.5</td>
<td>2.5</td>
<td>1.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Headache</td>
<td>8.1</td>
<td>9.2</td>
<td>8.0</td>
<td>12.2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7.3</td>
<td>1.8</td>
<td>4.9</td>
<td>3.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adverse events of interest occurring in ≥5% of patients receiving exenatide extended release.
More Weekly GLP-1 Receptor Agonists

- Albiglutide (modified GLP-1 fused to albumin)
- Dulaglutide (GLP-1 analog fused to IgG4)
- Resistant to DPP-4 degradation
- Similar efficacy as exenatide ER
- A1c reduction 0.8 - 1.0%
- Studied with metformin, SU, pioglitazone, basal insulin
- Not recommended as first-line therapy
Albiglutide

• 30 mg sc Qwk
• Increase to 50 mg sc Qwk if needed
• Supplied as single-dose prefilled pen
Dulaglutide

- 0.75 mg sc Qwk
- Increase to 1.5 mg sc Qwk if needed
- Supplied as single-dose prefilled pen
Safety: Medullary Thyroid Cancer Risk

• All GLP-1 RAs are contraindicated in patients with a personal or family history of MTC or MEN2 because of the occurrence of C-cell tumors in rodents.

• The C-cell tumor risk humans is unknown, because human relevance could not be determined in clinical trials.

• The value of routine calcitonin and/or ultrasound monitoring is uncertain.

2010;362:774-777.
Safety: Renal Impairment

- Exenatide BID or ER is not recommended in those with severe renal impairment or end-stage renal disease (CrCl<30 mL/min) and all GLP-1 RAs should be used with caution in patients with renal transplantation or moderate renal impairment.

Safety: Pancreatitis

• Pancreatitis has been reported with all incretin-based therapies, although no causal relationship has been established.
• Patients should know signs and symptoms of pancreatitis and stop taking incretin-based therapies if signs and symptoms occur.
• If pancreatitis is confirmed, therapy should not be restarted.

CV OUTCOME TRIALS with GLP-1RAs

ELIXA – Lixisenatide (not yet approved in the USA)
No CV risk or benefit – Neutral effect
No increase in CHF

Trials ongoing with the other drugs in the class
## Synthetic Human Amylin Analog

### Pramlintide

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Amylin mimetic: ↓PPG, suppresses glucagon secretion, slows gastric emptying, promotes satiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>Modest ( ↓ A1C 0.5%)</td>
</tr>
<tr>
<td>Advantages</td>
<td>No dosage adjustment required in renal impairment</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Nausea, headaches, anorexia, vomiting, abdominal pain, fatigue, dizziness, risk of severe hypoglycemia with insulin Only approved in combination with prandial insulin but cannot be combined in the same syringe</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Confirmed diagnosis of gastroparesis, hypoglycemia unawareness</td>
</tr>
</tbody>
</table>
When To Start Insulin in T2DM

- When combination oral/injectable agents become inadequate
- Unacceptable side effects of oral/injectable agents
- Patient wants more flexibility
- Special circumstances (i.e. steroid use, infection, pregnancy)
- Patients with hepatic or renal disease,
- Patients with CAD, ↑TG

CAD=coronary artery disease; T2DM=type 2 diabetes mellitus; TG=triglycerides.

Key Points: Insulin Initiation

- Diabetes is a progressive disease and many individuals with T2DM eventually need insulin to control their blood glucose.

- There are cultural taboos and misconceptions regarding insulin therapy; it is important to understand and acknowledge patients' specific concerns and design individualized treatment plans that fit their needs.

- Start with a simple regimen, such as a once-daily basal insulin analog, and up-titrate the dose based on FPG; if A1C remains high when FPG is in the target range, add a DPP-4 inhibitor, a GLP-1 RA, or mealtime insulin.

T2DM=type 2 diabetes mellitus; FPG=fasting plasma glucose; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; RA=receptor agonist; A1C=glycated hemoglobin.

Key Points: Insulin Initiation

• Allow patients to give the first injection during the office visit (because the first injection is often the biggest hurdle)

• Alternately, to help diminish fear, give patient a mock shot as soon as insulin is discussed (this can be done before insulin is initiated)

• Insulin pens facilitate the initiation and acceptance of insulin

• PCP and/or nurse educator should provide ongoing, enthusiastic support, advice, and trouble-shooting

PCP=primary care provider.
Insulin Pens

• More convenient than traditional vial and syringe
• More accurate, repeated doses
• Easier to use for those with visual or fine motor skill impairment
• Less injection pain
  – Polished and coated needles are not dulled by insertion into a vial of insulin before a second insertion into the skin

Insulin Therapy in Type 2 Diabetes

Current Strategies

- **Basal insulin therapy**
  - Long-acting insulin analog once daily
  - Intermediate-acting NPH at bedtime

- **Human or analog insulin (prandial or premixed w/ intermediate)**
  - Once daily at largest meal
  - Twice daily (breakfast and dinner)
  - Three times daily (with each meal)

- **Intensive insulin therapy**
  - Basal +
    - rapid-acting analog insulin
      - Once daily at largest meal
      - Twice daily at meals
      - Three times daily (with each meal)

- **Insulin pump therapy**

NPH=Neutral Protamine Hagedorn.

Insulin Analogs More Closely Match the Physiologic Insulin Profile Than Human Insulin

- **Bolus (meal-related) insulin analogs**
  - Rapid absorption
  - Peak action coincides with peak carbohydrate absorption

- **Basal insulin analogs**
  - Slow and steady rate of absorption
  - Protracted action

Algorithm for Adding/Intensifying Insulin

**Start Basal (Long-Acting Insulin)**

- **A1C < 8%**
  - TDD: 0.1–0.2 U/kg
- **A1C > 8%**
  - TDD: 0.2–0.3 U/kg

**Insulin titration every 2–3 days to reach glycemic goal:**

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
  - If hypoglycemia, reduce TDD by:
    - BG < 70 mg/dL: 10% – 20%
    - BG < 40 mg/dL: 20% – 40%

*Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)*

**Intensify (Prandial Control)**

- **Add GLP-1 RA**
  - Or SGLT-2i
  - Or DPP-4i

- **Add Prandial Insulin**
  - Basal Plus 1, Plus 2, Plus 3
    - Begin prandial insulin before largest meal
    - If not at goal, progress to injections before 2 or 3 meals
    - Start: 10% of basal dose or 5 units
  - Basal Bolus
    - Begin prandial insulin before each meal
    - 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
    - Start: 50% of TDD in three doses before meals

**Glycemic Control Not at Goal**

- Insulin titration every 2–3 days to reach glycemic goal:
  - Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
  - If hypoglycemia, reduce TDD basal and/or prandial insulin by:
    - BG consistently < 70 mg/dL: 10% - 20%
    - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

*Glycemic Goal:

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk
Long-Acting Insulin Analogs vs NPH In Type 2 Diabetes
A Meta-Analysis

• Long-acting analogs provide comparable glycemic control to NPH

• Reduced risks of nocturnal and symptomatic hypoglycemia

• May be associated with less weight gain than NPH

NPH=Neutral Protamine Hagedorn.

Pitfalls and Caveats In the Use of Basal Insulin (BI)

<table>
<thead>
<tr>
<th>The Challenge</th>
<th>The Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptitrating dose based on elevated pre-supper blood glucose → nocturnal hypoglycemia</td>
<td>• Post-lunch hyperglycemia is the culprit; only titrate BI based upon fasting blood glucose</td>
</tr>
<tr>
<td>Over-reliance on BI to control PP hyperglycemia when added to non-prandial agents (eg, metformin, thiazolidinediones)</td>
<td>• As both fasting and PP hyperglycemia are present, consider use of a prandial agent before/at time of BI addition</td>
</tr>
</tbody>
</table>
| Delay in down-titration of BI with improved glycemia → hypoglycemia and pre-emptive eating | • Discuss this scenario with patient as glycemic control is re-established: “Less insulin is needed to maintain control than establish control”  
• Reduction of OHAs, such as SUs or gliptines, may also be required |

PP=postprandial; BI=basal insulin; OHA=oral hypoglycemic agents; SU=sulfonylurea.
At Some Point, Raising Basal Dose Alone Will Be Inadequate, Failing to Address PPG

Mealtime insulin response is missing; high postprandial readings every meal

This may lead to hypoglycemia if food changes or meals are missed

PPG = post prandial glucose; μU=micro units; mL=milliliter.

Incretin-Based Therapy in Combination With Basal Insulin
A Promising Tactic for the Treatment of Patients With T2DM

- Consider non-insulin options with synergistic mechanisms of action and low hypoglycemia risk when intensifying regimens beyond basal insulin
  - DPP-4 inhibitors when A1C reductions of <1.0% are needed
  - GLP-1 receptor agonists when A1C reductions ≥1.0% are needed (and patients may benefit from possible weight loss)
  - Insulin doses may be able to be - or may need to be - lowered
  - Targets insulin deficiency and glucagon excess

DPP-4=dipeptidyl peptidase-4 ;GLP-1=glucagon-like peptide-1; A1C=glycated hemoglobin; T2DM=type 2 diabetes mellitus.

Adding a GLP-1 RA to Basal Insulin Therapy with or Without OADs in T2DM Improves Glycemic Control

GLAR + EXE ± MET ± PIO vs GLAR + PBO ± MET ± PIO (30 weeks)

N = 259

<table>
<thead>
<tr>
<th>ΔTDD (U/day)</th>
<th>ΔA1C (%)</th>
<th>ΔWt (kg)</th>
<th>ΔHypo (EPY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7</td>
<td>-4.75</td>
<td>-2.5</td>
<td>0.2</td>
</tr>
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<td>-2.5</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

Mean between-group difference from baseline (units as shown)

-7 -4.75 -2.5 -0.25 2

ΔTDD (U/day) ΔA1C (%) ΔWt (kg) ΔHypo (EPY)

- Hypo, BG < 54 mg/dL; major hypo, loss of consciousness or seizure or assistance required.
- P < .05; c P < .001.
- Mean duration of diabetes: 12 years.

 Patients receiving EXE had 8%-33% more GI adverse events and headaches than patients receiving PBO
- 1 patient in the PBO group had 2 major a hypoglycemic episodes

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; EXE=exenatide; PIO=pioglitazone; GLAR=glargine; PBO=placebo; MET=metformin; EPY=Events per-participant/per-year; Hypo=hypoglycemia; TDD=total daily dose; U=unit; kg=kilogram; INS=insulin; A1C=glycated hemoglobin; Wt=weight; T2DM=type 2 diabetes mellitus; BG=blood glucose; mg=milligrams; dL=deciliters.

Options When Not at Goal with 1 Injection of Basal Insulin

• Basal Plus
   Add prandial insulin at main meal

   or

• Switch to Premixed Insulin (if regular meal schedule)

   or

• Switch to Basal/Bolus

   or

• Add an incretin-based therapy (DPP-4 inhibitor or GLP-1 RA, if patient is not already on incretin therapy)

DPP-4=dipeptidyl peptidase-4;
GLP-1=glucagon-like peptide-1;
RA=receptor agonist

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Meal-Time Insulin
Rapid-Acting Analogs (Aspart, Glulisine, Lispro) vs Regular

The Basal-Bolus Insulin Concept

- **Basal insulin**
  - Controls glucose production between meals and overnight
  - Nearly constant levels
  - 50% of daily needs
- **Bolus insulin (mealtime or prandial)**
  - Limits hyperglycemia after meals
  - Immediate rise and sharp peak at 1-hour postmeal
  - 10% to 20% of total daily insulin requirement at each meal
- **For ideal insulin replacement therapy,** each component should come from a different insulin with a specific profile

Basal-Bolus Insulin Treatment with Insulin Analogs

Lispro, glulisine, or aspart

Glargine, Detemir or Degludec

Normal pattern

µU=milli units; mL=milliliters; B=breakfast; L=lunch; D=dinner.

Effect of Adding 1, 2, or 3 Pre-meal Rapid-acting Insulin Injections To a Background of Basal Insulin Analog Therapy in Patients Requiring Therapy Intensification

A1C=glycated hemoglobin.

Inhaled Human Insulin

- Approved July 2014
- Dry powder, human regular insulin
- Adsorbed onto Technosphere microparticles
- Dissolves immediately when inhaled
- Ultra-rapid acting: peak concentration at 12-15 minutes, back to baseline at 180 minutes
- Bioavailability: 21-30% of subcut. dose
- Mealtime glycemic control
- Need to use with basal insulin in type 1 DM
**Inhaled Human Insulin**

- **Adverse Effects/Contraindications**
  - Hypoglycemia: similar or lower than sc insulin
  - Decreased FEV1: small, occurs w/i first 3 months, potentially reversible with discontinuation
  - Lung cancer: 2 cases in clinical trials—both heavy smokers
  - Not recommended in smokers or recent stoppers
  - Contraindicated in COPD, asthma
  - REMS: baseline, 6 mo. and annual spirometry
    - 5 year monitoring to assess risk of lung cancer, change in PFTs
## Concentrated Insulins

<table>
<thead>
<tr>
<th></th>
<th>Approved</th>
<th>Conc</th>
<th>Volume</th>
<th>Supplied</th>
<th>#units</th>
<th>Admin.</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine U-300</td>
<td>February 2015</td>
<td>3X</td>
<td>1/3</td>
<td>Prefilled Pen</td>
<td>450</td>
<td>QD</td>
<td>More compact sc depot with smaller surface area; “Flatter” insulin</td>
</tr>
<tr>
<td>Lispro U-200</td>
<td>May 2015</td>
<td>2X</td>
<td>1/2</td>
<td>Prefilled Pen</td>
<td>600</td>
<td>AC TID</td>
<td>Bioequiv. to Lispro U-100; Similar time to max. conc.</td>
</tr>
<tr>
<td>Regular U-500</td>
<td>1952 (Beef)</td>
<td>5X</td>
<td>1/5</td>
<td>Vial (20 mL)</td>
<td>10,000</td>
<td>AC BID-TID</td>
<td>Prefilled pen approved Jan2016</td>
</tr>
</tbody>
</table>
Hypoglycemia: Clinical Consequences

Acute
• Symptoms (sweating, irritability, confusion)
• Accidents
• Falls

Long-term
• Recurrent hypoglycemia and hypoglycemia unawareness
• Refractory diabetes
• Dementia (elderly)
• Cardiovascular events
  – Cardiac autonomic neuropathy
  – Cardiac ischemia
  – Fatal arrhythmia
  – Angina

Real-World Choices Depend On the Patient

- Injection frequency preference
  - Some patients may prefer premix
- Frequency of self-monitoring of blood glucose
- Variability of lifestyle, including meal timing and carbohydrate content of meals
- Presence of postprandial hyperglycemia
- Patient’s ability to follow the prescribed regimen
- Educational and emotional support available to patient
- Cost of analogue insulin options may be nearly double that of NPH or regular insulin
Summary

• Many patients on basal insulin therapy will ultimately require treatment intensification

• Current options include:
  – Addition of mealtime control via addition of prandial insulin, leading to multiple daily insulin therapy
  – Switch to premix insulin
  – Add a SGLT-2 inhibitor, DPP-4 inhibitor or a GLP-1 agonist

DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.

Thank you!