Combining a Glucagon-like Peptide-1 Receptor Agonist with Basal Insulin: The Why and How

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CME Information

- This Live activity, Combining a Glucagon-like Peptide-1 Receptor Agonist with Basal Insulin: The Why and How, from 04/15/2016 - 04/15/2017, has been reviewed and is acceptable for up to 1.00 Prescribed credit(s) by the American Academy of Family Physicians. Physicians should claim only the credit commensurate with the extent of their participation in the activity.
At the completion of this activity, the participant will be able to:

• Describe the benefits of reducing postprandial glucose
• Identify the benefits and limitations of classes of medications for lowering postprandial glucose
• Identify the benefits and limitations of available short- and long-acting glucagon-like peptide-1 receptor agonists.
• Select a glucagon-like peptide-1 receptor agonist based on patient clinical and personal needs.
Case Study- Mary

• 61 yo female diagnosed with T2DM 8y ago

• Management
  • Initially- lifestyle + metformin
  • Subsequent additions
    • Sulfonylurea → symptomatic hypoglycemia
    • Pioglitazone → fluid retention
    • Basal insulin added 1½ y ago
      • Now 52 units/d (0.62 units/kg)
      • Has experienced 3 episodes of mild hypoglycemia
Case Study - Mary (cont)

- HbA1c has never been <7.0% (now 7.9%)
- Over past month
  - FPG 103-136 mg/dL
  - PPG 164-213 mg/dL
- Has gained 2.6 kg since starting basal insulin (BMI now 31 kg/m²)
- BP 134/82 mmHg
- Occasional tingling in feet
- Grade 1 retinopathy
- Current medications
  - Metformin 1000 mg BID
  - Basal insulin 52 units/d (0.62 units/kg)
  - HCTZ 25 mg QD
Case Study - Mary (cont)

Why is her HbA1c 7.9% despite her FPG being reasonably well controlled?

Why is she experiencing postprandial hyperglycemia?
Fasting vs Postprandial Glucose Contribution to HbA$_{1c}$

![Graph showing the contribution of fasting and postprandial plasma glucose to HbA$_{1c}$ across different ranges.]

- **<7.3**: 70% Postprandial, 30% Fasting
- **7.3-8.4**: 50% Postprandial, 50% Fasting
- **8.5-9.2**: 45% Postprandial, 55% Fasting
- **9.3-10.2**: 40% Postprandial, 60% Fasting
- **>10.2**: 30% Postprandial, 70% Fasting

Increasing 2-hour PPG is associated with an increasing risk of all-cause mortality, particularly for PPG ≥200 mg/dL.

2-h Lunch PPG and HbA1c as Risk Factors

Blood glucose parameters were categorized independently according to achievement of ADA targets.

## Glycemic Effects of Glucose-Lowering Medications

<table>
<thead>
<tr>
<th>Glycemic Effects</th>
<th>Fasting Plasma Glucose Lowering</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutral</td>
</tr>
<tr>
<td>Postprandial Glucose Lowering</td>
<td>Neutral</td>
</tr>
<tr>
<td>Mild</td>
<td>•Bromocriptine</td>
</tr>
<tr>
<td>Moderate</td>
<td>•AGi</td>
</tr>
<tr>
<td>Moderate/Marked</td>
<td>•Rapid-/Short-acting Insulin</td>
</tr>
</tbody>
</table>
Optimization of Basal Insulin Therapy

Approximately 60% of patients with T2DM can achieve $\text{HbA}_{1c} \leq 7.0\%$ with basal insulin (+ oral agents) if taken CONSISTENTLY.

What is Meant by Optimized Basal Insulin?

**Efficacy**
- HbA\(_{1c}\) at goal
  - ≤7% for this patient
- FPG 80-130 mg/dL

**Safety/Tolerability**
- Minimize hypoglycemia
  - Severe
  - Nocturnal
- Minimize weight gain

**Patient Factors**
- Needs, interests, capabilities
- Schedule/Lifestyle
- SMBG

Is More Basal Insulin Better?

Increasing doses of basal insulin may lead to diminishing returns
—Reduction in FPG and HbA1c plateau
—Incidence of hypoglycemia rises over time

N=367 In combination with 1 or 2 oral agents

When Basal Insulin May Not Be Enough to Achieve Glycemic Control

- HbA$_{1c}$ >7.0%, despite FPG 80-130 mg/dL
- And...
  - Total basal insulin dose exceeds 0.5-1 unit/kg/day$^1$
  - Severe, nocturnal, or frequent symptomatic hypoglycemia
  - Difference between bedtime and AM (BeAM) blood glucose >55 mg/dL$^2$
    - Less likely to achieve HbA$_{1c}$ ≤7.0%
    - Increased risk of nocturnal hypoglycemia
  - Weight gain

Avoiding Overbasalization

- If the basal insulin dose is correct, the bedtime blood glucose should be about the same as the next morning’s FPG (assuming no prandial insulin at nighttime).
- If the blood glucose decreases significantly overnight (i.e., BeAM > 55 mg/dL), the basal dose is too high.
- If the blood glucose increases significantly overnight, the basal dose is too low.

BeAM, bedtime to pre-breakfast
Intensifying Once-Daily Basal Insulin

Options:

- Basal Insulin BID
- Basal-Plus Bolus before largest meal
- Basal-Bolus BID-TID
- Premixed BID
- GLP-1 Receptor Agonist

# Pharmacokinetics of GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Exendin-4Analogs</th>
<th>Short-Acting</th>
<th>Long-acting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Exenatide BID</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Exenatide QW</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>( t_{\frac{1}{2}} ) 2.4 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Lixisenatide</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( t_{\frac{1}{2}} ) 3 hours</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human GLP-1Analogs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Albiglutide</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( t_{\frac{1}{2}} ) 5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Dulaglutide</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( t_{\frac{1}{2}} ) 5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Liraglutide</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( t_{\frac{1}{2}} ) 13 hours</td>
</tr>
</tbody>
</table>

*Approved in Europe; NDA filed in US.

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GLP-1 is secreted from L-cells of the jejunum and ileum. That in turn...

- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Improves insulin sensitivity
- Leads to a reduction of food intake

After food ingestion...

# Pharmacodynamics of GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Effects</th>
<th>Short-Acting</th>
<th>Long-Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood glucose</td>
<td>Modest reduction</td>
<td>Strong reduction</td>
</tr>
<tr>
<td>Postprandial blood glucose</td>
<td>Strong reduction</td>
<td>Modest reduction</td>
</tr>
<tr>
<td>Fasting insulin secretion</td>
<td>Modest stimulation</td>
<td>Strong stimulation</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Modest</td>
<td>Modest</td>
</tr>
<tr>
<td>Gastric emptying rate</td>
<td>Deceleration</td>
<td>Transient effect</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Modest reduction</td>
<td>Modest reduction</td>
</tr>
<tr>
<td>Body weight</td>
<td>1-5 kg Reduction</td>
<td>1-5 kg Reduction</td>
</tr>
<tr>
<td>Induction of nausea</td>
<td>20% to 50%; attenuates over weeks to many months</td>
<td>20% to 40%; attenuates over 4 to 8 weeks</td>
</tr>
</tbody>
</table>

Glycemic Efficacy of GLP-1 RAs in Head-to-Head Trials

Change in HbA1c (%)

-1.5 -1 -0.5 0

Added to Met ± SU
Added to Met ± SU ± TZD
Added to Met ± SU ± TZD
Added to Met ± SU ± TZD
Added to Met ± TZD
Added to Met
Added to Met

Exenatide 10 mcg BID
Liraglutide 1.8 mg QD
Exenatide 2 mg QW
Albiglutide 50 mg QW
Dulaglutide 1.5 mg QW
Lixisenatide 20 mcg QD (Investigational)

*P <0.05 between groups
†Noninferiority vs liraglutide not met.
‡Dulaglutide noninferior to liraglutide, P < .0001
§Noninferior vs exenatide BID

Changes in Non-Glycemic Endpoints With GLP-1 RAs

Meta-analysis of 25 randomized clinical trials
Patients with or without type 2 diabetes mellitus who received exenatide 10-20 mcg/day, exenatide 2 mg/week, or liraglutide 1.2-1.8 mg/day for ≥20 weeks

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Change</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>-2.90 kg</td>
<td>-3.59 to -2.22</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-3.57 mmHg</td>
<td>-5.49 to -1.66</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-1.38 mmHg</td>
<td>-2.02 to -0.73</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-3.9 mg/dL</td>
<td>-6.19 to -1.55</td>
</tr>
</tbody>
</table>

Tolerability of GLP-1 RAs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Regimen</th>
<th>Percent of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>10 mcg BID</td>
<td>25%</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>1.8 mg QD</td>
<td>NR</td>
</tr>
<tr>
<td>Exenatide</td>
<td>2 mg QW</td>
<td>NR</td>
</tr>
<tr>
<td>Albglutide</td>
<td>50 mg QW</td>
<td>NR</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>1.5 mg QW</td>
<td>NR</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>20 mcg QD*</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Investigational; NR, not reported

Prandial Insulin vs GLP-1RA in Combination with Optimized Basal Insulin + Metformin

- Adults with T2DM
- HbA$_1c$ 7.0-10.0%
- Receiving insulin glargine plus metformin

Glargine optimization over 12 wks to achieve FPG $\leq$100 mg/dL

Those who didn’t achieve HbA$_1c$ $\leq$7.0%...

Exenatide 10-20 mcg BID (↓Basal Insulin $\geq$10%)

315

1:1

312

Lispro TID (↓Basal Insulin 33-50%)

Prandial Insulin vs GLP-1RA in Combination with Optimized Basal Insulin + Metformin (cont.)

![Graph showing the effect of Exenatide BID and Lispro TID on HbA1c (%)](image)

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Prandial Insulin vs GLP-1RA in Combination with Optimized Basal Insulin + Metformin (cont.)

**ΔFasting Glucose** (mg/dL)

- Exenatide BID
- Lispro TID

*P=0.002 for all time points except 0

**Blood Glucose** (mg/dL)

- Dotted line: At randomization
- Solid line: Study end

*P<.001

- FPG
- Post-Breakfast
- Pre-Lunch
- Post-Lunch
- Pre-Dinner
- Post-Dinner
- 0300 h

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Albiglutide vs Prandial Insulin as Add-on to Insulin Glargine + Oral Agents

Albiglutide 30 or 50 mg QW; Prandial insulin TID

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Lixisenatide* vs Liraglutide as Add-on to Insulin Glargine ± Metformin: Similar Reductions in the 24-h Plasma Glucose Profile

*P<0.05 for lixisenatide 20 mcg vs. liraglutide 1.2 mg; †P<0.05 for lixisenatide 20 mcg vs. liraglutide 1.8 mg; ‡P<0.05 for liraglutide 1.2 mg and 1.8 mg vs. lixisenatide 20 mcg; §P<0.05 for liraglutide 1.8 mg vs. lixisenatide 20 mcg.

*Approved in Europe; NDA filed in US.
Lixisenatide* vs Liraglutide as Add-on to Optimized Insulin Glargine ± Metformin

Responses at end of 28 weeks of therapy

<table>
<thead>
<tr>
<th>Measure</th>
<th>Lixisenatide 20 mcg</th>
<th>Liraglutide 1.8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>-0.6</td>
<td>-0.7</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>-1.6</td>
<td>-2.4</td>
</tr>
<tr>
<td>Daily Insulin Dose (units)</td>
<td>-4.7</td>
<td>-4</td>
</tr>
</tbody>
</table>

N=80


*Approved in Europe; NDA filed in US.
Insulin Detemir as Add-on Therapy to Metformin + Liraglutide¹

• Adults with T2DM
• Treated with metformin (HbA₁c 7.0-10.0%) or metformin + SU (HbA₁c 7.0-8.5%)

12-wk run-in:
--SU DC’d
--Liraglutide initiated and titrated to 1.8 mg/d

If HbA₁c ≥7.0%
Randomize

If HbA₁c <7.0%
Continue metformin + liraglutide

Continue metformin + liraglutide (observational group)

Add insulin detemir 10 units evening/bedtime; titrate to 74-108 mg/dL FPG

26 weeks of treatment

Insulin Detemir as Add-on Therapy to Metformin + Liraglutide\(^1\) (cont.)

![Graph showing change in HbA1c (%) over time for Liraglutide + Detemir, Liraglutide, and Liraglutide (obs). Randomization point at Week 0.]

\(^1\)Weeks 0-26

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Insulin Detemir as Add-on Therapy to Metformin + Liraglutide$^1$ (cont.)

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Efficacy Results from Observational Studies of Basal Insulin in Combination with a GLP-1RA

**HbA$_{1c}$ (%)**

**Body Weight (kg)**

**Insulin Dose (units/d)**

**Conclusion:** Combination therapy improved glycemic control without weight gain or an increased risk of hypoglycemia.

Recommendations for GLP-1 RA Use in Combination With Basal Insulin

- GLP-1 RA may be used in combination with basal insulin in patients who do not reach their glycemic target with 2-3 glucose-lowering medications\textsuperscript{1-4}
  - If taking a SU, consider discontinuing or reducing the dose of SU
  - If adding GLP-1RA to basal insulin, consider reducing basal insulin dose 10-20% if HbA1c ≤7.5%
    - Thereafter, adjust basal insulin dose based on SMBG
- Monitor for hypoglycemia

### Study Results: Summary

<table>
<thead>
<tr>
<th>Metric</th>
<th>Exenatide</th>
<th>Lispro</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_{1c}$ reduction</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>FPG reduction</td>
<td>&gt;</td>
<td></td>
</tr>
<tr>
<td>PPG reduction</td>
<td>≈</td>
<td></td>
</tr>
<tr>
<td>Minor hypoglycemia</td>
<td>&lt;</td>
<td></td>
</tr>
<tr>
<td>Nocturnal hypoglycemia</td>
<td>&lt;</td>
<td></td>
</tr>
<tr>
<td>Weight change</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Glargine dose</td>
<td>&gt;</td>
<td></td>
</tr>
<tr>
<td>Treatment satisfaction</td>
<td>&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Combination Products: IDegLira*

26-week double-blind, randomized trial
N=413 adults with type 2 diabetes treated with basal insulin + metformin ± SU/glinide
†P<0.0001

*Investigational combination of insulin degludec and liraglutide

Combination Products: LixiLan*

- **LixiLan-O** (30-wk)
  - Patients treated with metformin ± oral agent (N=1170); metformin continued
  - LixiLan superior HbA1c reduction compared with
    - Lixisenatide
    - Glargine U100
  - Similar safety profile

- **LixiLan-L** (30-wk)
  - Patients treated with glargine U100 ± oral agents (N=736); metformin continued if taking
  - LixiLan superior HbA1c reduction compared with glargine U100 +/- oral agents
  - Similar safety profile

*Investigational combination of insulin glargine 100 units/mL and lixisenatide

GLP-1 RAs in Combination with Insulin

<table>
<thead>
<tr>
<th>Glucagon-like Peptide-1 Receptor Agonist</th>
<th>Approved for Use in Combination with</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal Insulin</td>
</tr>
<tr>
<td>Albiglutide QW</td>
<td>✓</td>
</tr>
<tr>
<td>Dulaglutide QW</td>
<td></td>
</tr>
<tr>
<td>Exenatide BID</td>
<td>✓</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td></td>
</tr>
<tr>
<td>Liraglutide QD</td>
<td></td>
</tr>
</tbody>
</table>

Case Study - Mary (cont)

**Recall**

- HbA1c 7.9%
- Over past month
  - FPG 103-136 mg/dL
  - PPG 164-213 mg/dL
- Has gained 2.6 kg since starting basal insulin (BMI now 31 kg/m²)
- BP 134/82 mmHg
- Occasional tingling in feet
- Grade 1 retinopathy
- Current medications
  - Metformin 1000 mg BID
  - Basal insulin 52 units/d (0.62 units/kg)
  - HCTZ 25 mg QD
Case Study- Mary (cont)

• What changes would you make to her diabetes treatment plan?
  • Do her previous hypoglycemia episodes while on basal insulin affect your decision?

• If you were to add a GLP-1RA, which would you choose?
  • What if she had fasting hyperglycemia as well?
  • Do her weight and blood pressure affect your choice?
  • How would medication adherence affect your choice?

• What education would you provide to her about medication side effects?
Questions and Answers
Combining a Glucagon-like Peptide-1 Receptor Agonist with Basal Insulin: The Why and How

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