The ABC’s of GLP’s: Practical Use of GLP-1 Receptor Agonists in Type 2DM Therapy

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Learning Objectives
Pharmacists
- Describe the “egregious eleven” targets for Type 2 DM therapy and identify which targets are impacted by GLP-1 receptor agonists
- Compare and contrast the safety and efficacy of available GLP-1 RAs
- Given a patient case, develop a therapeutic regimen that appropriately incorporates a GLP-1 RA

Technicians
- Describe the complexity of targets for Type 2 DM therapy
- List the medications and devices available for GLP-1 RA therapy
- Identify patients that would benefit from discussing diabetes treatment with a pharmacist

Type 2 DM Epidemic

- 29.1 million Americans
- 86 million with prediabetes
- Annual cost of Diabetes: $245 billion!

By the time a person is diagnosed with T2DM, approximately how much pancreatic β-cell function has been lost?

A. < 10%
B. B. 10 – 30%
C. C. 30 – 50%
D. D. 50 – 80%

Progressive Nature of Type 2 Diabetes

GLP-1 receptor agonists (GLP-1 RAs) directly impact all of the following targets for Type 2 DM except:

A. Glucose dependent insulin secretion of pancreatic beta cells
B. Postprandial glucagon secretion of pancreatic alpha cells
C. Insulin sensitivity of muscle and adipose tissue
D. Satiety and gastric emptying
The Incretin Effect is Reduced in Type 2 Diabetes

American Diabetes Association (ADA)
Clinical Recommendations 2017
- Lifestyle: 3 minutes of activity every 30 minutes
- Hypoglycemia < 54mg/dL
- Therapy for Type 2 DM
  - At time of diagnosis
    - Metformin (unless CI) + Lifestyle (Medical Nutrition Therapy and exercise)
    - Newly diagnosed with symptoms and marked elevated BG or A1c
      - Insulin therapy +/- additional agents
  - If non-insulin monotherapy at max dose does not achieve A1c target over 3 months, add:
    - Second oral agent
    - GLP-1 agonist
    - Insulin
    - Consider empagliflozin and liraglutide in established CVD

Postprandial GLP-1 Concentrations Are Lower in Subjects With Type 2 Diabetes

Postprandial Glucose Contribution to A1C


Available GLP-1 Agonists

- Exenatide (Byetta)
- Exenatide ER (Bydureon)
- Liraglutide (Victoza)
- Albiglutide (Tanzeum)
- Dulaglutide (Trulicity)
- Lixisenatide (Adlyxin)

Side Effects: GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Gastrointestinal (nausea/vomiting/diarrhea)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>&gt; 85% patients lose weight</td>
</tr>
<tr>
<td>Black Box Warnings</td>
<td>Pancreatitis, medullary thyroid carcinoma (MTC)</td>
</tr>
<tr>
<td>Effect on Other cardiac risk factors</td>
<td>↓ Tryglycerides, ↑ HDL, ↑ blood pressure</td>
</tr>
</tbody>
</table>

GLP-1 Agonists Warnings

- Decrease dose of secretagogue to prevent hypoglycemia
- 50% or stop
- FDA Med guide
  - Pancreatitis
    - Conflicting data, more cases with exenatide (1 per 1000 pt-years)
    - Caution with alcohol abuse disorder or hx of gallstones
    - Counseling on symptoms: abdominal pain, radiate to back
  - Family hx of medullary thyroid carcinoma (MTC)
    - 2% of human MTC express GLP-1 receptors
    - Rodent model has 20-40 x more receptors
    - Liraglutide and once-weekly exenatide
    - Don’t use if personal history of MTC
- Gastroparesis
### A1c Lowering vs Exenatide bid

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration/ N</th>
<th>Pt Demographics (mean)</th>
<th>A1c lowering</th>
<th>A1c Difference/Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>DURATION-1 Byetta/Bydureon</td>
<td>30 wk N=295</td>
<td>A1c 8.3% Duration DM: 6.7 yr</td>
<td>Exenatide bid: -1.5 Exenatide QW: -1.9</td>
<td>0.4% (p=0.0025)</td>
</tr>
<tr>
<td>DURATION-5 Byetta/Bydureon</td>
<td>24 wk N=252</td>
<td>A1c 8.4% Duration DM: 7 yr</td>
<td>Exenatide bid: -1.6 Exenatide QW: -0.9</td>
<td>0.7% (p=0.001)</td>
</tr>
<tr>
<td>GetGoal-X Byetta/Adylixin</td>
<td>24 wk N=834</td>
<td>A1c 8.0% Duration DM: 6.8 yr</td>
<td>Exenatide bid: -0.79 Lixisenatide: -0.96</td>
<td>-0.17% (p value not reported)</td>
</tr>
<tr>
<td>AWARDS-1 Trulicity/Byetta</td>
<td>26 wk N=978</td>
<td>A1c 8.1% Duration DM: 9 yr</td>
<td>Dulaglutide 1.5mg: -1.51 Dulaglutide 0.75mg: -1.3</td>
<td>0.52% (1.5mg) (p=0.001 for both doses)</td>
</tr>
</tbody>
</table>

### A1c Lowering vs Liraglutide

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration/ N</th>
<th>Pt Demographics (mean)</th>
<th>A1c lowering</th>
<th>A1c Difference/Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAD-6 Byetta/Victoza</td>
<td>26 wk N=164</td>
<td>A1c 8.1% Duration DM: 8.2 yr</td>
<td>Exenatide bid: -0.79 Liraglutide: -1.2</td>
<td>-0.33% (p=0.0001)</td>
</tr>
<tr>
<td>DURATION-6 Bydureon/Victoza</td>
<td>26 wk N=911</td>
<td>A1c 8.5% Duration DM: 8.5 yr</td>
<td>Exenatide QW: -1.28 Liraglutide: -1.48</td>
<td>-0.21% (p=0.02)</td>
</tr>
<tr>
<td>HARMONY-7 Tanzeum/Victoza</td>
<td>22 wk N=841</td>
<td>A1c 8.2% Duration DM: 8.4 yr</td>
<td>Albiglutide: -0.78 Liraglutide: -0.99</td>
<td>-0.21% (p=0.08, Non-Inferiority)</td>
</tr>
<tr>
<td>AWARDS-6 Trulicity/Victoza</td>
<td>26 wk N=759</td>
<td>A1c 8.1% Duration DM: 7.2 yr</td>
<td>Dulaglutide: -1.42 Liraglutide: -1.37</td>
<td>-0.06% (p=0.001, Non-Inferiority)</td>
</tr>
</tbody>
</table>

### Safety/ Tolerability

<table>
<thead>
<tr>
<th>Trial</th>
<th>Significant Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>DURATION-1 Byetta/Bydureon</td>
<td>N/V: Byetta vs Bydureon Injection site reactions: Bydureon &gt; Byetta</td>
</tr>
<tr>
<td>LEAD-6 Byetta/Victoza</td>
<td>GI effects similar, nausea with liraglutide at 26 wk (3% vs 9%)</td>
</tr>
<tr>
<td>DURATION-5 Byetta/Bydureon</td>
<td>N/V: Byetta vs Bydureon, although rates low Injection site reactions: Bydureon &gt; Byetta (1% vs 10%)</td>
</tr>
<tr>
<td>DURATION-6 Bydureon/Victoza</td>
<td>N/V: Dulaglutide &gt; Bydureon (decreased over time) Injection site reactions: Bydureon &gt; Dulaglutide (module formation)</td>
</tr>
<tr>
<td>GetGoal-X Byetta/Adylixin</td>
<td>Nausea: Byetta &gt; Lixisenatide (25.1% vs 24.5%) Hypoglycemia: Byetta &gt; Lixisenatide (7.9% vs 2.5%) no pts on sulfonylureas</td>
</tr>
<tr>
<td>HARMONY-7 Tanzeum/Victoza</td>
<td>GI effects similar effects at 7% initially Injection site reactions: albiglutide &gt; liraglutide (12.2% vs 5.4%)</td>
</tr>
<tr>
<td>AWARDS-1 Trulicity/Byetta</td>
<td>GI effects similar (worse in first 2 weeks)</td>
</tr>
<tr>
<td>AWARDS-6 Trulicity/Victoza</td>
<td>No difference in GI effects (peaked at 1 week)</td>
</tr>
</tbody>
</table>

### GLP-1 Agonists Head to Head Trials Summary

- A1c lowering (most to least)
  - Liraglutide Bydureon Byetta
- Efficacy of Post Prandial and Fasting Glucose Lowering
  - PPG > FPG: Exenatide bid
  - FPG: PPG: Longer acting
- Weight
  - Similar, maybe Liraglutide Bydureon
- GI side effects
  - Bydureon has less than liraglutide or Byetta
- Injection site reactions
  - Liraglutide has less than Bydureon

### Cardiovascular Data for GLP-1RAs

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary Outcome</th>
<th>Results</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEUK</td>
<td>Measure</td>
<td>NT or hospitalization for unstable angina in past 180 days followed by 2 yrs</td>
<td>flexible: 6.3 events (95% CI: 6.2 to 6.4)</td>
</tr>
<tr>
<td>LEADER</td>
<td>Measure</td>
<td>NT or hospitalization for unstable angina in past 180 days followed by 2 yrs</td>
<td>flexible: 6.3 events (95% CI: 6.2 to 6.4)</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>Measure</td>
<td>≤50 yrs known CVD, HF, or on antiplatelet or anticoagulation therapy with risk factors for CVD</td>
<td>composite event rate: 4.6% (95% CI: 3.6 to 5.5)</td>
</tr>
<tr>
<td>SUSTAIN-7</td>
<td>Measure</td>
<td>≥60 yrs known CVD, HF, or on antiplatelet or anticoagulation therapy with risk factors for CVD</td>
<td>composite event rate: 4.6% (95% CI: 3.6 to 5.5)</td>
</tr>
</tbody>
</table>

* p-value statistically significant
**Ongoing CV Trials with GLP-1 RAs**

<table>
<thead>
<tr>
<th>Trial/Medication</th>
<th>Primary Outcome</th>
<th>Anticipated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCEL Exenatide QW/Bydureon</td>
<td>The primary safety: time to first occurrence of major cardiovascular events (MACE; cardiovascular death, myocardial infarction, or stroke) up to 7.5 years</td>
<td>April 2018</td>
</tr>
<tr>
<td>REWIND Dulaglutide/Trulicity</td>
<td>Time to first occurrence of composite of MACE, up to 6.5 years</td>
<td>July 2018</td>
</tr>
<tr>
<td>HARMONY Outcomes Albiglutide/Tanzeum</td>
<td>Time to first occurrence of major cardiovascular MACE(Non-inferiority), follow up of 3-5 years</td>
<td>May 2019</td>
</tr>
</tbody>
</table>

**GLP-1RA Combination Therapy with Basal Insulin**

<table>
<thead>
<tr>
<th>Trial/Medication</th>
<th>Patient included</th>
<th>A1c Lowering</th>
<th>Hypoglycemia</th>
<th>WT change</th>
</tr>
</thead>
<tbody>
<tr>
<td>iGlarLixi 100/33</td>
<td>iGlar vs iLixi (iGlar vs iLixi)</td>
<td>Mean change vs iGlar vs iLixi</td>
<td>-1.4% vs -1.7%</td>
<td>-1.2 kg</td>
</tr>
</tbody>
</table>

More of side effects with GLP-1 groups, but wt loss, some evidence of less hypoglycemia with equal A1c lowering, decreased insulin requirements

**Other Notable Differences**

- **Albiglutide (Tanzeum)**
  - Once weekly pen, no mixing
  - Autoinjector
    - No needle, no attaching needed
- **Lixisenatide (Adlyxin) and Exenatide (Byetta)**
  - Don’t use if eGFR < 30ml/min/1.73m²
- **QW and QD had ↑pt satisfaction vs BID**
- **PPG vs FPG**

**Other Lixilan-O Trial iGlarLixi (Soliqua) Results**

<table>
<thead>
<tr>
<th>iGlarLixi</th>
<th>lipid</th>
<th>FPG</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>iGlar</td>
<td>1.3</td>
<td>6.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Lixi</td>
<td>1.4</td>
<td>6.9</td>
<td>5.9</td>
</tr>
</tbody>
</table>

**Lixilan-O Trial iGlarLixi (Soliqua)**

- 1170 patients with Type 2 DM uncontrolled with oral therapy including metformin
  - Mean age 58
  - Duration of DM 8.8 years
  - 90% Caucasian
  - Baseline A1c 8.1%

- **iGlarLixi vs Glar or Lixi**
  - Doses titrated weekly
  - 6-week run-in
  - Primary outcome: change in A1c
    - 7-point SMBG and weight
    - Symptomatic hypoglycemia

- **Insulin degludec/liraglutide (Kulitoofy)**
  - iDegLira 100/3.6
  - Max 50 u iDeg, 1.8mg Lira

16 units starting dose
(16 u idegudec, 5.15mg liraglutide)
Threaten 2-4 units every 2-4 days based on pt response
Down-titration available to 10 units min dose

Diabetes Care 2016;39(11)2026-35

View Larger Image: For visual clarity, please see alternative information available on diabetes care.
DUAL II, DUAL III Trials IDegLira (Xultophy)

<table>
<thead>
<tr>
<th>Trial/comparators</th>
<th>A1c reduction [%]</th>
<th>Hypoglycemia/Pr year</th>
<th>Weight change</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUAL II IDegLira IDeg</td>
<td>IDegLira: -1.9 IDeg: -0.9</td>
<td>1.5 2.5</td>
<td>IDegLira: -1.8kg IDeg: 0.0kg</td>
</tr>
<tr>
<td>DUAL III IDegLira GLP-1 RA</td>
<td>IDegLira: -1.3 GLP-1: -0.3</td>
<td>2.8 0.1</td>
<td>IDegLira: +2.0kg GLP-1: -0.8kg</td>
</tr>
</tbody>
</table>


DUAL V Trial IDegLira (Xultophy)

- N=557 patients with A1c levels 7% -10% uncontrolled on insulin glargine (20u-50u), on 1500mg metformin
  - IDegLira daily (n=278) or
  - Continued insulin glargine up-titration, no maximum (n=279)
- Baseline characteristics:
  - Mean age of 58.8 years, BMI 31.7
  - Duration of diabetes 11.5 years
  - A1c was 8.4% in the IDegLira group and 8.2% in the insulin glargine
  - Pre-trial iglargine dose 32 units

Lingvay et al. JAMA.2016;315(9):898-907

DUAL V Results

- Primary endpoint: A1c reduction
  - IDegLira: 1.81% vs glargine: -1.13 [p<0.001]
  - Adjusted treatment difference = 0.59%
- Wt loss
  - IDegLira: -1.4kg vs insulin glargine + 1.8kg
  - Insulin sparing effects
    - After 10 weeks, the IDegLira dose was stable at 41 U of insulin degludec vs 66 U in the insulin glargine group
  - Less hypoglycemia in the IDegLira (79 vs 137)
  - Less nocturnal hypoglycemia IDegLira (17 vs 68)
  - A1c levels of less than 7%
  - More IDegLira patients achieved 71.6% vs 47.0% [p<.001]

Lingvay et al. JAMA.2016;315(9):898-907

Pros and Cons for Fixed Combinations

- Pros
  - Trials included:
    - Patients had long diabetes duration (about 12 years)
    - Poorly controlled
    - Treatment arms in combination
  - Insulin sparing effects
  - Wt neutral or loss
  - Less hypoglycemia
  - Less GI side effects
  - Patient adherence
- Cons
  - Trials
    - A1c > 10% excluded
    - Max of 50-60 unit dosing
    - Limited patient numbers
    - Limited ethnicities
    - Limited duration trials
    - Not all oral drugs continued
  - No head to head trials yet
  - Titration issues?
  - Labeling states must fail either basal or GLP-1 first

GLP-1 RA Use in Type 1 DM?

- ADJUNCT ONE and ADJUNCT TWO trials
  - Effects of liraglutide plus multiple daily insulin or pump in Type 1DM with A1c 7-10%
  - A1c reduction
    - ADJUNCT ONE: liraglutide 1.2mg: -0.54% liraglutide 1.8mg: -0.49%
    - ADJUNCT TWO: liraglutide 1.2mg: -0.35% liraglutide 1.8mg: -0.23%
  - Wt loss (2 to 4.7kg with 1.2mg, 4 to 5.1kg with 1.8mg)
  - Hypoglycemia
    - Higher rates with liraglutide
  - Higher rate of hyperglycemia with ketosis in both trials

Diabetes Care 2016;39:1693-1701,1702-36

A 60 year-old obese white man presents to your clinic with an A1c of 8.3% currently taking metformin 1000mg BID, Lisinopril 20mg QD, amlodipine 10mg QD, and atorvastatin 40mg QD. His GFR is 64ml/min/1.73m².

Which of the following is the best treatment for his Type 2 DM at this time?

A. Add insulin glargine and insulin aspart
B. Add empagliflozin
C. Discontinue metformin and add iglarixi
D. Add liraglutide
GLP-1RAs Affect Several Targets for Type 2DM

- GLP-1: Secreted upon the ingestion of food
  - Promotes satiety and reduces appetite

Liver:
- Glucagon reduces hepatic glucose output
- Decreased insulin requirements

Beta cells:
- Enhances glucose-dependent insulin secretion

Beta cells:
- Glucose-dependent postprandial glucagon secretion
- Decreased insulin requirements

Alpha cells:
- Decrease glucagon secretion

Stomach:
- Helps regulate gastric emptying

Colon/Biome Dysregulation/Inflammation

GLP-1 Agonists Counseling Tips

- Time to effect
- Adverse Effects
  - N/V “fullness”
  - Lowered weight over time (2-5 weeks)
  - Smaller meals, less fat
  - Hypoglycemia
  - Decreased insulin requirements
  - Reduce rate/extent of orally admin drugs

- Monitoring
  - FPG, PPG
  - A1c
  - Renal function (at least annually)
  - LIRA-RENAL trial
  - 2x GI side effects in Stage 3B than those with Sdage 3A
  - Symptoms of pancreatitis

Conclusions

- Differences exist in A1c lowering, FPG and PPG effects, wt loss, side effects and CV data of GLP-1 Ras
  - Consider patient characteristics and preferences

- Combinations of GLP-1 RAs/basal insulin
  - A1c reduction, ↓hypoglycemia, wt effects, ↓ GI effects

- Patient counseling regarding administration and expectations is necessary to increase adherence
  - Adverse event and treatment expectations and education
  - Significant differences in administration in agents

In the Pipeline

- Semaglutide once weekly phase III
  - New drug application filed December 2016

- Oral GLP-1 RAs
  - Semaglutide oral tablet in phase IIa clinical trials
  - PIONEER trials

- Oral capsule basal insulin?
  - ORM-0801 Phase IIa results September 2017