Intensification of Outpatient Diabetes Management: A Case-Based Approach

Matthew P. Gilbert, DO, MPH
The University of Vermont College of Medicine
Division of Endocrinology and Diabetes
Burlington, VT
Disclosures

• No financial disclosures
Introduction

• 2009 data:
  – 11.7% males, 10.2% females >20 years of age
• 2034 estimates:
  – 44.1 million affected at a cost of $336 billion
• CDC Publication October 2010:
  – Diabetes prevalence will increase from 14% (2010) to 21% (2050) if incidence increases are low and mortality remains high
  – If continued rises in incidence and lowering of mortality, prevalence will be 33% in 2050
As Wild and his partners watched the outlaw riding at full speed along the top of the cliff they suddenly saw his horse slip and slide over the brink. A yell of fear came from the villain as he pitched from the saddle.
Case Presentation
Joe

- 48-year-old male
- Type 2 diabetes, hypertension and dyslipidemia
- Laid off 1 year ago
- Depressed, eating and drinking more; gained 10 lb
- BP and lipids well controlled
- Normal renal and hepatic function

**Meds**
- Metformin 1000 mg BID
- Glimepiride 4 mg BID
- Lisinopril 20 mg Daily
- Atorvastatin 40 mg Daily
- HCTZ 25 mg Daily

**Recent HbA1c History**
- Current: 8.6%
- 4 months ago: 8.1%
- 8 months ago: 7.8%
- 12 months ago: 7.1%
- FBG several days weekly: ≥200 mg/dL for last 6 months
## Relative A1c Lowering and Risks of Hypoglycemia and Weight Gain

<table>
<thead>
<tr>
<th>Agent</th>
<th>Efficacy (ΔA1C)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>0.85%</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>0.42%</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>0.61%</td>
<td>↓</td>
<td>←→</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.5%-0.8%</td>
<td>↓</td>
<td>←→</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>0.52-0.94%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>1.0%-1.5%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Insulin</td>
<td>Unlimited</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>vs.</th>
<th>Basal Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Exenatide (Byetta®)</td>
<td></td>
<td>• Glargine (Lantus®)</td>
</tr>
<tr>
<td>• Liraglutide (Victoza®)</td>
<td></td>
<td>• Detemir (Levemir®)</td>
</tr>
<tr>
<td>• Albiglutide (Tanzeum®)</td>
<td></td>
<td>• NPH</td>
</tr>
<tr>
<td>• Exenatide extended-release (Bydureon®)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Brief Review of GLP-1RA
**Biology of Incretin Hormones**

- **“Incretin effect”**
- May account for 50-70% of total insulin secreted after a meal
- Incretins are hormones that enhance glucose-stimulated insulin secretion

---

Reduced Incretin Effect

Control Subjects

Patients with T2DM

Glucagon-like Peptide-1 (GLP-1)

• Secreted from intestinal endocrine L-cells
• L-cells have direct contact with intestinal lumen
• Meal ingestion is the primary physiologic stimulus for GLP-1 secretion
• Half-life is less than 2 minutes
• Inactivated by DPP-4
GLP-1 Receptor Agonists

- Resistant to enzymatic degradation by DPP-4
- Extends half-life to hours from minutes
- Mimics the physiologic actions of native GLP-1
- Administered twice daily with morning and evening meals (exenatide)
- Daily (liraglutide) and once weekly preparations (exenatide extended release and albiglutide) are now available
Structure of GLP-1 and Analogs

Native human GLP-1

Liraglutide

97% amino acid homology to human GLP-1

Exenatide

53% amino acid homology to human GLP-1
GLP-1 RA: Safety

- Low risk of hypoglycemia
- Contraindicated in patients with gastroparesis
- Pancreatitis?
- Not associated with an increase in cardiovascular risk
- Nausea is the most common adverse event
- Long-acting GLP-1 RA are associated with lower rates of gastrointestinal adverse events
Choosing the Right GLP-1RA
FDA Approved GLP-1 RA

- Exenatide (Byetta®)
- Liraglutide (Victoza®)
- Albiglutide (Tanzeum®)
- Exenatide extended-release (Bydureon®)
Liraglutide vs. Exenatide

- Inadequately controlled T2DM on metformin, sulfonylurea or both
- Multinational, 26-week, open-label, parallel group, (n=464)
- Primary outcome was change in A1c
Liraglutide vs. Exenatide

<table>
<thead>
<tr>
<th></th>
<th>Δ HbA1c (%)</th>
<th>HbA1c &lt; 7.0 (%)</th>
<th>Δ Fasting Glucose (mg/dl)</th>
<th>Δ Weight (kg)</th>
<th>Hypoglycemia (events per patient year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 1.8 mg Daily</td>
<td>-1.12</td>
<td>54</td>
<td>29</td>
<td>-3.24</td>
<td>1.93</td>
</tr>
<tr>
<td>Exenatide 10 mcg BID</td>
<td>-0.79</td>
<td>43</td>
<td>11</td>
<td>-2.87</td>
<td>2.60</td>
</tr>
</tbody>
</table>

Liraglutide once a day provided significantly greater improvements in glycemic control than did exenatide BID, and was generally better tolerated.

Albiglutide vs. Liraglutide

- 32-week, open label, phase 3 trial
- 162 sites, 8 countries
- 841 adults; T2DM
- Liraglutide had greater reduction in A1c (0.21%)
- Albiglutide had less GI adverse events

## Albiglutide vs. Liraglutide

<table>
<thead>
<tr>
<th>Event</th>
<th>Albiglutide (n=404)</th>
<th>Liraglutide (n=408)</th>
<th>% difference (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>305 (75.5%)</td>
<td>317 (77.7%)</td>
<td>-2.2% (-8.0% to 3.6%)</td>
<td>0.4587</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>60 (14.9%)</td>
<td>55 (13.5%)</td>
<td>1.4% (-3.4% to 6.2%)</td>
<td>0.5752</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>42 (10.4%)</td>
<td>45 (11.0%)</td>
<td>-0.6% (-4.9% to 3.6%)</td>
<td>0.7705</td>
</tr>
<tr>
<td>Nausea</td>
<td>40 (9.9%)</td>
<td>119 (29.2%)</td>
<td>-19.3% (-24.6% to -14.0%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Injection-site reaction†</td>
<td>28 (6.9%)</td>
<td>5 (1.2%)</td>
<td>5.7% (3.0% to 8.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>25 (6.2%)</td>
<td>23 (5.6%)</td>
<td>0.6% (-2.7% to 3.8%)</td>
<td>0.7393</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>24 (5.9%)</td>
<td>28 (6.9%)</td>
<td>-0.9% (-4.3% to 2.4%)</td>
<td>0.5914</td>
</tr>
<tr>
<td>Increased lipase concentration</td>
<td>22 (5.4%)</td>
<td>28 (6.9%)</td>
<td>-1.4% (-4.7% to 1.9%)</td>
<td>0.4007</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (5.4%)</td>
<td>22 (5.4%)</td>
<td>0.1% (-3.1% to 3.2%)</td>
<td>0.9732</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (5.0%)</td>
<td>38 (9.3%)</td>
<td>-4.4% (-7.9% to -0.8%)</td>
<td>0.0154</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise indicated. *p values are for the percentage difference. †This analysis includes only events for which injection-site reaction was the preferred term. Additional analyses were done to assess injection-site reactions and other related preferred terms.

*Table 3: Adverse events that occurred in 5% or more of patients in the treatment groups combined.*

Exenatide once weekly vs. Liraglutide

- DURATION-6 trial
- 26 week, open-label, randomized, parallel-group
- 912 adults with T2DM on oral agents
- Primary end point was change in A1c from baseline

Exenatide once weekly vs. Liraglutide

Exenatide once weekly vs. Liraglutide

Conclusions: GLP-1RA

- Liraglutide has been shown to have slightly better efficacy (A1c) than exenatide, albiglutide and exenatide extended release
- Longer acting GLP-1RA have less GI adverse events
- Balance convenience and adherence factors with adverse event profiles
Choosing the Right Basal Insulin
Head to Head Comparison Glargine vs. Detemir in Type 2 Diabetes

52-weeks - Baseline A1c 8.6% $n = 582$

- Average daily doses:
  - Glargine once daily 0.44 U/kg.
  - Detemir once daily 0.78 U/kg.
  - Detemir twice daily 1.0 U/kg.

$P = NS$

Less Hypoglycemia With Insulin Analogs Versus NPH: Meta-analysis in T2DM

<table>
<thead>
<tr>
<th></th>
<th>Severe</th>
<th>Symptoms and PG &lt;36 mg/dL</th>
<th>Symptoms and PG &lt;70 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>1.01</td>
<td>[0.49; 2.07]</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>0.64</td>
<td>[0.39; 1.04]</td>
<td>0.073</td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>0.52</td>
<td>[0.27; 1.00]</td>
<td>0.0498</td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>0.44</td>
<td>[0.25; 0.76]</td>
<td>0.003</td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>0.74</td>
<td>[0.25; 2.23]</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>0.51</td>
<td>[0.35; 0.76]</td>
<td>0.000</td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>0.64</td>
<td>[0.46; 0.88]</td>
<td>0.018</td>
</tr>
<tr>
<td>CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions: Basal Insulin

- Analogs have similar efficacy, but with less hypoglycemia when compared to NPH
- Detemir often has to be dosed twice a day and at a higher dose when compared to glargine
- Formulary considerations
- Cost considerations
Basal insulin vs. GLP-1RA
Exenatide vs Once-Daily Insulin Glargine: Self-Monitoring Blood Glucose Profiles (n=549)

Both medications lowered A1C from 8.2% to 7.1% from baseline

Weight change: exenatide −2.3 kg, glargine +1.8 kg
Nausea: exenatide 57.1%, glargine 8.6%

Liraglutide vs. Insulin Glargine
26-weeks. Baseline A1c 8.2%. \( N = 549 \)

<table>
<thead>
<tr>
<th></th>
<th>LIRA</th>
<th>GLAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change (kg)</td>
<td>-1.8</td>
<td>+1.6</td>
</tr>
<tr>
<td>Major hypoglycemia</td>
<td>0.06</td>
<td>0.0</td>
</tr>
<tr>
<td>(events/patient-year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor hypoglycemia</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>(events/patient-year)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\( P < 0.05 \)

Once Weekly Dulaglutide vs. Glargine and Metformin and Glimepiride

- Open label 78 week study compared once weekly 1.5 mg or 0.75 mg Dulaglutide vs. Glargine – on maximal doses metformin and glimepiride (n=807).
- Baseline – A1c 8.1%

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>DU 1.5 mg</th>
<th>DU 0.75 mg</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c change (%)</td>
<td>-0.90±0.07%</td>
<td>-0.62±0.07%</td>
<td>-0.59±0.07%</td>
</tr>
<tr>
<td>% pts A1c &lt;7%</td>
<td>49%</td>
<td>34%</td>
<td>31%</td>
</tr>
<tr>
<td>Wt. change (kg)</td>
<td>-2.0±0.3</td>
<td>-1.5±0.3</td>
<td>+1.3±0.3</td>
</tr>
</tbody>
</table>

Tips and My Own Views

• By 2 oral agents, if A1c > 8% likely need an injectable
• In clinical trials, basal insulin vs. GLP-1 RA therapy have similar lowering when A1c up to 9.0-9.5%
• Different clinical profiles
• Insulin:
  + dose flexibility
  - weight gain, hypoglycemia
• GLP-1 RA:
  + weight control, minimize hypoglycemia (not with SU)
  - GI side effects, cost, ? unknown side effects
Joe (cont)

- Decides to add insulin “sounds safest to me, plus I have friends who take insulin.”
- Wt 100 kg, normal renal and hepatic function.
- “What now?”

**Meds**
- Metformin 1000 mg BID
- Glimepiride 4 mg BID
- Lisinopril 20 mg Daily
- Atorvastatin 40 mg Daily
- HCTZ 25 mg Daily

**Recent HbA1c History**
Current: 8.6%
4 months ago: 8.1%
8 months ago: 7.8%
12 months ago: 7.1%
FBG several days weekly: ≥200 mg/dL for last 6 months
Starting Basal insulin
Bedtime or morning long-acting insulin OR
Bedtime intermediate-acting insulin
Daily dose: 10 units or 0.2 U/kg

Check FBG daily

Increase dose by 2 units every 3 days until FBG is 90–130 mg/dL.
If FBG is >180 mg/L, increase dose by 4 units every 3 days.

Continue regimen and check HbA₁c every 3 months

In the event of hypoglycemia or FBG level <70 mg/dL.
Reduce bedtime insulin dose by 4 units, or by 10% if >60 units.

Tips and My Own Views

- Choose basal insulin - analog if affordable:
  - Detemir typically less potent than glargine
- Starting dose – 0.2 to 0.3 units/kg
- Home titration schema – proven effective
  - 1 unit increase daily to fasting BG 90-130 mg/dL.
- Maximal dose:
  - Meta-analyses say average person takes 0.45 u/kg
- BG testing – minimally twice daily
  - Daily fasting, and alternating pre-meal
Joes returns 3 months later
Watching diet and exercising
Feeling really good.
Faithfully taking Glargine.
No weight gain or hypoglycemia.
But concerned – “my morning BG is really good, usually very low 100s, but I’m 200 or more by bedtime.”

Meds
- Metformin 1000 mg BID
- Glimepiride 4 mg AM
- Glargine 52 units HS
- 20 mg lisinopril/12.5 mg HCTZ AM
- Atorvastatin 40 mg HS

Current HbA1c 7.7%
Failing Basal Insulin and OA

- Lifestyle modification
- Add bolus insulin to largest meal only (Basal Plus)
- Add bolus insulin to all meals (Basal-Bolus)
Stepwise Treatment of Type 2 Diabetes

- Lifestyle changes + Metformin
- Additional Oral agents
- Basal
  - Add basal insulin and titrate
- Basal Plus
  - Add prandial insulin at main meal
- Basal Bolus
- Further intensification

Progressive deterioration of β-cell function
All-to-Target: Stepwise Intensification With Glargine and Glulisine vs Aspart Premix

- 60-week study of 3 treatment strategies in 572 patients on orals with average A1c 9.4%.
- 49% reached A1c <7% with basal plus versus 39% with premix (p<0.05)
- 40-60% reduction in hypoglycemia with basal plus versus premix (P<0.01)

Mealtime Insulin

• Use rapid-acting analogs, not regular insulin
  – Easier timing, less postprandial hypoglycemia
  – Can be taken up to 20 minutes after start eating
  – Available in vials or pens
• Start with 1 shot, at largest meal or with all 3:
  – By weight – 0.05 to 0.1 units/kg
• Titrate to:
  – <160 mg/dL 2 hours post-prandial
• With basal plus, continue oral medications until full basal-bolus regimen

Leahy JL. *Endocrinol Metab Clin North Am* 2012;41:119-144
Final Thoughts

• Individualize treatment of T2DM
• Consider use of basal insulin or GLP-1RA earlier in the course of the disease
• Balance between clinical efficacy, adherence and adverse events
Questions & Comments

Kingfisher Tower, Otsego Lake, Cooperstown, NY