IMPROVING OUTCOMES IN TYPE 2 DIABETES

Integrating GLP-1 Receptor Agonists Into Multimodal Treatment Regimens

OCTOBER 15, 2014
Donald E. Stephens Convention Center
Rosemont, IL

Educational partner

INTEGRITAS COMMUNICATIONS
LEARNING OBJECTIVES

Upon completion of these educational activities, participants will be better prepared to:

1. Discuss the pathologic mechanisms of T2DM that support the need for prompt diagnosis and aggressive treatment.

2. Identify patient-centered treatment goals for patients with T2DM that encompass good overall glycemic control and improvements in other clinical parameters.

3. Evaluate the clinical profiles of GLP-1 receptor agonists for the treatment of T2DM.

4. Individualize therapeutic regimens for T2DM to maximize efficacy and minimize hypoglycemia, weight gain, and other potential treatment-related risks.

5. Communicate with patients with T2DM about lifestyle modifications, antihyperglycemic options, and the need for treatment adherence.
SESSION 4
12:45pm – 2:00pm

Improving Outcomes in Type 2 Diabetes: Integrating GLP-1 Receptor Agonists Into Multimodal Treatment Regimens

SPEAKERS
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Lawrence Blonde, MD, FACP, FACE
Jeff Unger, MD

Presenter Disclosure Information
► Vivian Fonseca, MD, receives grant research support via Tulane University from Abbott Laboratories; Eli Lilly and Company; GI Dynamics, Inc.; Novo Nordisk A/S; Pan American Laboratories; Reata Pharmaceuticals Inc.; and sanofi-aventis US LLC. He receives honoraria for consulting and lectures from Abbott Laboratories; AstraZeneca; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Daiichi Sankyo Company, Limited; Eli Lilly and Company; GlaxoSmithKline; Janssen Pharmaceuticals, Inc.; Novo Nordisk A/S; PamLab, Inc.; sanofi-aventis US LLC.; and Takeda Pharmaceuticals USA, Inc.

► Jeffrey Unger, MD, receives honoraria from Abbott Laboratories; Janssen Pharmaceuticals, Inc., Novo Nordisk A/S; and Valeritas, Inc.

Off-Label/Investigational Discussion
► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Medications Discussed in Program
• Medication classes
  ▶ GLP-1 receptor agonists
  ▶ DPP-4 inhibitors
  ▶ Statins
  ▶ ACE inhibitors
  ▶ Insulins
  ▶ Amylin mimetics
  ▶ Thiazolidinediones
  ▶ Meglitinides
  ▶ SGLT-2 inhibitors
  ▶ α-glucosidase inhibitors
  ▶ Sulfonylureas

• Specific medications
  ▶ Lisinopril
  ▶ Atenolol
  ▶ Atorvastatin
  ▶ Metformin
  ▶ Insulin glargine
  ▶ Insulin detemir
  ▶ Colesevelam
  ▶ Bromocriptine
  ▶ Sitagliptin
  ▶ Saxagliptin
  ▶ Linagliptin
  ▶ Exenatide BID
  ▶ Exenatide QW
  ▶ Liraglutide
  ▶ Albiglutide
  ▶ Dulaglutide
  ▶ Semaglutide
  ▶ Lixisenatide

Educational Objectives
• Discuss the pathologic mechanisms of T2DM that support the need for prompt diagnosis and aggressive treatment
• Identify patient-centered treatment goals for patients with T2DM that encompass good overall glycemic control and improvements in other clinical parameters
• Evaluate the clinical profiles of GLP-1 receptor agonists for the treatment of T2DM
• Individualize therapeutic regimens for T2DM to maximize efficacy and minimize hypoglycemia, weight gain, and other potential treatment-related risks
• Communicate with patients with T2DM about lifestyle modifications, antihyperglycemic options, and the need for treatment adherence

GLP-1: glucagon-like peptide-1; T2DM: type 2 diabetes mellitus.
Scientific Insights Into INCRETIN SIGNALING and TYPE 2 DIABETES

Vivian Fonseca, MD, FRCP
Professor of Medicine and Pharmacology
Tulane University Health Sciences Center
New Orleans, Louisiana

Reducing T2DM Complications
Multidimensional Treatment Goals

Walter PCP Visit

• Family history
  – Mother had T2DM
• Medical history
  – Hypertension diagnosis 5 years ago
    – Lisinopril 40 mg daily
    – Atenolol 50 mg daily
    – Episodes of unstable angina
    – Daily low-dose aspirin
    – Forgets medications 1-2 times weekly

Despite no overt symptoms of hyperglycemia, should Walter be screened for T2DM?

Achieving Treatment Goals
Room for Improvement in T2DM

Screening Asymptomatic Persons for Diabetes

A1c <7.0%, BP <130/80 mm Hg, LDL <100 mg/dL

Key Points

• Incretin effect: more insulin is secreted in response to orally delivered glucose compared with intravenously administered glucose
• The gastrointestinal hormones GLP-1 and GIP stimulate insulin release in response to food intake
• GLP-1 also reduces glucagon release following food intake, slows gastric emptying, and increases satiety
• Reduced incretin effect is an early sign of T2DM development

GLP-1 and GIP are rapidly degraded by DPP-4

Clinical research has focused on degradation-resistant GLP-1 RAs and inhibitors of DPP-4

DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus.

Walter
Workup and Diagnosis

- A1c, 8.8%
- FPG, 199 mg/dL
  - Second test 197 mg/dL
- eGFR, 80 mL/min/1.73 m²
- ACR, 2.4 mg/mmol
- Normal sensory exam

Lipids
- LDL-C, 103 mg/dL
- HDL-C, 40 mg/dL
- TG, 155 mg/dL
- TC, 205 mg/dL

ACR, albumin/creatinine ratio; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; TC, total cholesterol.

Walter receives a diagnosis of T2DM.

Walter
Setting Glycemic Targets

- Age, 62 years
- BMI, 30.1 kg/m²
- A1C, 8.8%
- Family history of T2DM
- History of unstable angina
- Normal renal function
- Not adherent to other drug therapies


What would you set as an A1c target for Walter?

- Target A1c <7.0%
- Walter and PCP discuss lifestyle modifications
- PCP suggests a certified diabetes educator
  - Patient education
  - Detailed dietary and exercise recommendations

Diabetes Education and Lifestyle Modifications

- Skills-based diabetes education to support informed self-management
- Disease process and treatment options
- Nutritional management and physical activity
- Blood glucose monitoring
- Safe use of medications (e.g., risks of hypoglycemia)
- Strategies to address psychosocial issues and promote behavior change
- Physical activity
  - At least 150 min/week of moderate activity
  - AERObic, resistance, flexibility
  - Individualize dietary recommendations
  - Discuss macronutrient content and eating patterns
  - Monitor carbohydrate intake
  - Reduce calories to achieve weight loss
  - Moderate calorie restriction (500-1000 kcal/day) recommended initially

What are the potential benefits of these approaches?

- P <0.001; b P =0.01 vs support and education alone.
- N=2570 for lifestyle intervention and 2575 for support and education.

**LOOK AHEAD Study**

Intensive Lifestyle Intervention and Risk Reduction

- Diet modification, exercise, behavioral training
- Group support with in-person and telephone follow-ups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intensive Lifestyle Intervention</th>
<th>Support and Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss, %</td>
<td>-6.5a, b</td>
<td>-0.88</td>
</tr>
<tr>
<td>Treadmill fitness, % METs</td>
<td>12.74a, b</td>
<td>1.96</td>
</tr>
<tr>
<td>A1c, %</td>
<td>-0.36a, b</td>
<td>-0.09</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>-3.33a, b</td>
<td>-2.97</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>-2.92a, b</td>
<td>-2.48</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>3.67a, b</td>
<td>1.97</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>-25.56a, b</td>
<td>-19.75</td>
</tr>
</tbody>
</table>

*P<0.01. **P<0.001 vs support and education alone.

**Rates of Severe Hypoglycemia**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>UKPDS1</th>
<th>ADVANCE2</th>
<th>ACCORD3</th>
<th>VADT4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON GLY INS</td>
<td>1.4</td>
<td>2.4</td>
<td>4.6</td>
<td>3.8</td>
</tr>
<tr>
<td>STD INT</td>
<td>7.3%</td>
<td>7.1%</td>
<td>7.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>STD INT*</td>
<td>7.5%</td>
<td>6.5%</td>
<td>8.5%</td>
<td>6.5%</td>
</tr>
<tr>
<td>STD INT*</td>
<td>7.5%</td>
<td>6.5%</td>
<td>8.5%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

*Hypoglycemia requiring assistance. Intensive glycemic control was defined differently in these trials.

**ADVANCE**

Severe Hypoglycemia vs Adverse End Points

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0.70</td>
</tr>
<tr>
<td>1.25</td>
<td>0.49</td>
</tr>
<tr>
<td>1.5</td>
<td>0.25</td>
</tr>
<tr>
<td>1.75</td>
<td>0.15</td>
</tr>
<tr>
<td>2.0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**ADA/EASD Recommendations**

Managing Hyperglycemia in T2DM

- **Initial Drug Monotherapy**
  - Efficacy (A1c)
    - High
    - Moderate
    - Low
  - Site Effects
    - Cost
    - Metformin
      - High
      - Moderate
      - Low
    - GLP-1 RA
      - High
      - Moderate
      - Low
  - Major Side Effect(s)
    - Costs
    - Edema, HF, Fx's
    - Rare
    - GI/Hypoglycemia
      - Low
      - High
      - Variable

**AACE/ACE Algorithm for Glycemic Control**

<table>
<thead>
<tr>
<th>Lifestyle Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry A1c &lt;7.5%</td>
</tr>
<tr>
<td>Monotherapy</td>
</tr>
<tr>
<td>Glucagon-like peptides (GLP-1 RA)</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
</tr>
<tr>
<td>SGLT-2 inhibitor*</td>
</tr>
<tr>
<td>T2D</td>
</tr>
<tr>
<td>Entry A1c &gt;9.5%</td>
</tr>
<tr>
<td>Dual Therapy</td>
</tr>
<tr>
<td>GLP-1 RA + Insulin</td>
</tr>
<tr>
<td>Insulin + Other Agents</td>
</tr>
</tbody>
</table>

**Walter**

Treatment Initiation and Follow-up

- Prescribed metformin 500 mg twice daily
  - Titrated up to 1000 mg twice daily over next month
- 3-month follow-up appointment
  - A1c, 8.0%
    - Previous value, 8.8%
    - Target value, <7.0%
  - FPG, 140 mg/dL
    - Previous value, 189 mg/dL
    - PPG, 210 mg/dL (2-h post-meal)
  - No significant changes in any other clinical parameters

PCP suggests adding an incretin-based agent to Walter’s regimen.
**Select Antidiabetic Therapies and Hypoglycemia**

<table>
<thead>
<tr>
<th>Drug</th>
<th>ΔA1c Reduction, %</th>
<th>Hypoglycemia Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide twice daily</td>
<td>0.5-1</td>
<td>4-5</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>0.8-1.14</td>
<td>8-12</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>0.7-0.9</td>
<td>0.10-10</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>0.6-1</td>
<td>2.6-12-12</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>0.4-0.9</td>
<td>3.5-10</td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td>0.6-1.0</td>
<td>0.6-10</td>
</tr>
<tr>
<td>Sulfonlureas</td>
<td>1.2</td>
<td>18-30</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>0.6-1.4</td>
<td>0.3-10</td>
</tr>
<tr>
<td>Basal insulin†</td>
<td>1.5-3.5</td>
<td>29.9-61.2</td>
</tr>
</tbody>
</table>

GLP-1 RAs and Blood Pressure
Meta-Analysis of Data From Obese and Overweight Individuals

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change vs Control</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>-3.57 mm Hg</td>
<td>-5.49 to -1.66</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>-1.38 mm Hg</td>
<td>-2.02 to -0.73</td>
</tr>
</tbody>
</table>

*Includes 11 or 12 trials examining overweight and obese individuals with or without T2DM treatments included randomize 1:3:3:1 ratio in glucose.
Comparing GLP-1 RAs
Shorter- vs Longer-Acting Formulations

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Shorter Acting</th>
<th>Longer Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID, liraglutide</td>
<td>2-5 hours</td>
<td>12 hours to several days</td>
</tr>
</tbody>
</table>

**Effects**
- FPG reduction: Modest, Strong
- Postprandial hyperglycemia reduction: Modest, Strong
- Fasting insulin secretion stimulation: Reduction
- Glucagon secretion: Reduction
- Weight reduction, kg: Yes, Yes
- Potential for nausea: Yes, Yes

- Nausea may be limited by using an incremental dosing approach
- Recommend eating smaller meals and not overeating
- Patients with irregular meal habits may benefit from longer-acting formulations

Not approved by the FDA for use in the United States.

Combining GLP-1 RA and Basal Insulin Analogs

**Basal Insulin Analogs**
- Simple to initiate
- Control nocturnal hyperglycemia
- FPG

**GLP-1 RAs**
- Lower hyperglycemia risk than NPH
- Modest weight increase (1 to 3 kg)
- Achieve A1c targets in ~50%-60%

**Additive Effects**
- Simple to initiate
- Can control FPG and PPG
- Do not impair a-cell response to hypoglycemia (reduce severe hypoglycemia)
- Weight-lowering
- Achieve A1c targets in ~40%-60%

Potential for better overall A1c control

Walter

**Key Points**
- Individualize goals and treatment intensity for T2DM
  - Consider comorbidities
  - Address psychosocial factors
  - Take steps to reduce risk of hypoglycemia
- Ensure lifestyle modifications are the foundation of any treatment regimen for T2DM
- Monitor multiple metabolic targets for comprehensive management and reduction of cardiovascular risk
  - A1c, lipids, BP
- Consider appropriate roles of GLP-1 RAs
  - Clinically relevant reductions in A1c
  - Relatively low risks of hypoglycemia
  - Potential for weight loss and other cardiovascular benefits

Build-a-Case

**Oliver: Background**
- 53-year-old fifth-grade teacher
  - Lives with wife of 25 years and 2 daughters
  - Visits PCP for check-up after missing last 2 appointments
- Reports feeling rundown over last 4 months
  - Gets up ≥2 times nightly to urinate
- 1-2 glasses of wine with dinner each night
- Does not smoke
- Trying to eat healthily but has found it difficult
  - Drinks caffeinated soda each day
  - No exercise other than walking to and from school

Build-a-Case

**Oliver: Background**
- Medical history
  - Dyslipidemia diagnosis 9 years ago
  - Atorvastatin 20 mg once daily
- Family history
  - Mother was obese
  - Died of MI at age 63
  - Father treated for dyslipidemia
  - BMI, 32.1 kg/m²
  - BP, 125/79 mm Hg

- Dark discolored skin around neck and underarms
- A1c, 8.9%
- FPG, 185 mg/dL
- TC, 190 mg/dL
- TG, 145 mg/dL
- HDL-C, 50 mg/dL
- LDL-C, 90 mg/dL
**How does Oliver’s erectile dysfunction affect your approach to patient assessment?**

**Additional Considerations in T2DM
Erectile Dysfunction**

- Erectile dysfunction and T2DM commonly co-occur.
  - In patients with diabetes, erectile dysfunction is as predictive for future cardiovascular events as traditional risk factors.
- Erectile dysfunction may also reflect low testosterone.
  - More common in men with diabetes independent of age or BMI.
  - Testing testosterone levels in all male patients with diabetes?
  - Testosterone replacement therapy has not consistently improved erectile dysfunction or cardiometabolic health in clinical trials.


**How do Oliver’s reports of falling asleep at work and excessive snoring at night affect your approach to patient assessment?**

**Additional Considerations in T2DM
Excessive Sleepiness and Snoring**

- Excessive sleepiness during day and snoring suggest OSA.
- OSA is common in patients with T2DM, especially obese individuals.
- Risk factors for OSA:
  - Large neck circumference
  - Excessive use of alcohol or sedatives before bedtime
  - Mallampati score, class III or IV
- Polysomnography testing required to confirm the diagnosis.
- CPAP may improve glycemic control in patients with diabetes, although published data are not consistent.


**How do Oliver’s feelings of depression affect your approach to patient assessment?**

**Additional Considerations in T2DM
Depression**

- Emotional well-being should be assessed routinely and not only when a deterioration in psychological status is evident.
- Key opportunities for depression screening include:
  - Time of diagnosis
  - During follow-up or emergency visits
  - Any time the patient’s overall medical status changes
- Consider simple questions to identify individuals who should undergo more extended evaluations:
  - eg, “How are you sleeping?” or “How are your energy levels?”
- Ongoing relationships with patients provide an important opportunity for uncovering depression:
  - May increase likelihood that mental health referrals will be accepted.

**Build-a-Case**

**Oliver: Diagnosis**

- Oliver receives diagnosis of T2DM
- Advised to lose weight via exercise and reduced caloric intake
  - Referred to a dietician who specializes in diabetes counseling
- Family committed to helping Oliver with his diabetes

**Build-a-Case**

**Oliver: Initial Treatment and Follow-up**

- Prescribed metformin 500 mg twice daily
- Saxagliptin 5 mg once daily added 2 months later
- 4-month follow-up appointment
  - Participating in water aerobics twice weekly
  - Complying with recommendations from the dietician
  - Lost 5 lbs (BMI, 31.4 kg/m²)
  - A1c, 8.1%
  - FPG, 152 mg/dL
  - No retinopathy
  - Adherence problems addressed with pill box, education for his wife, and switch to saxagliptin/metformin ER 5 mg/1000 mg combination taken once daily
- Begin conversation about other options if Oliver is unable to reach his glycemic goal

**Additional Considerations in T2DM**

**Chronic Kidney Disease**

- Updated system for classifying kidney disease severity
  - Maintained the thresholds for estimated GFR and albuminuria
  - Added 3 albuminuria stages to consider with previous GFR stages
  - Emphasizes the need for an overall clinical diagnosis
- Use of many antihyperglycemic agents may be limited by impaired renal function (eg, special precautions or dose adjustments)
  - Metformin
  - GLP-1 RAs
  - DPP-4 inhibitors
  - SGLT-2 inhibitors
  - Sulfonylureas
  - Insulin
- For example, impaired insulin excretion requires slow titration of doses to reduce risks of hypoglycemia

**Alcoholism**

- Patients with T2DM and alcoholism history should be educated on increased hypoglycemia risks with continued heavy alcohol use
  - Especially with insulin or insulin secretagogues
- Sulfonylureas and other secretagogues should be avoided in patients with advanced liver disease
- Doses of DPP-4 inhibitors available in the United States do not need to be adjusted for mild or moderate hepatic impairment
- GLP-1 RAs safe patients with moderate liver dysfunction
  - May even improve liver enzyme profiles, although overall results mixed
- Appropriately dosed insulin preferred over other diabetes agents in patients with advanced liver disease

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How does Oliver’s history of coronary artery disease affect treatment recommendations?

### Additional Considerations in T2DM Coronary Artery Disease

- Oliver is at very high cardiovascular risk<sup>1</sup>
  - Exercise should start with short periods at low intensity, with slow increases in intensity and duration
  - Should exercise recommendations be made in consultation with Oliver’s cardiologist?<n
- Should Oliver’s statin therapy be adjusted?<sup>2</sup>
  - TC, 190 mg/dL
  - TG, 145 mg/dL
  - HDL-C, 50 mg/dL
  - LDL-C, 90 mg/dL
- Significant efforts needed to help Oliver lose weight<sup>2</sup>
  - Tailoring of his antihyperglycemic regimen should minimize the chances of weight gain
  - How much weight loss is required to see benefits?


### Build-a-Case

**Oliver: Treatment Tailoring**

- At follow-up appointment 6 weeks later, Oliver reports better adherence
- A1c, 7.8%
- FPG, 140 mg/dL
- 2-hour PPG, 185 mg/dL
- All other clinical parameters are unchanged
- You discuss further adjustments to his treatment regimen

### Conclusions

- Comprehensive T2DM management requires diligent monitoring of blood sugars, lipid profile, blood pressure, and body weight
  - Treatment is founded on lifestyle and behavioral modifications
- Significant hypoglycemic episodes are associated with serious adverse outcomes
- GLP-1 RAs augment signaling in the pleiotropic incretin hormone system
  - Efficacy in reducing hyperglycemia, with relatively low risks of hypoglycemia and potential for weight loss
  - Potential cardiovascular benefits remain an area of active research