COMPLEMENTARY THERAPIES TO IMPROVE GLUCOSE CONTROL IN TYPE 2 DIABETES:
ROLE OF GLP-1 RECEPTOR AGONISTS AND BASAL INSULIN

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Professor of Medicine
Director, Harold Schnitzer Diabetes Health Center
Oregon Health & Science University
Portland, Oregon

Robert J. Tanenberg
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Professor of Medicine, Division of Endocrinology
Brody School of Medicine East Carolina University
Medical Director, East Carolina University Diabetes and Obesity Institute
Medical Director, Inpatient Diabetes Program
Pitt County Memorial Hospital
Greenville, North Carolina

September 19
2013
1:00pm – 2:30pm
Boston Convention and Exhibition Center
415 Summer Street
Boston, MA 02210
Session 4: Complementary Therapies to Improve Glucose Control in Type 2 Diabetes: Role of GLP-1 Receptor Agonists and Basal Insulin

Learning Objectives
1. Apply strategies to individualized therapy in the treatment of patients with type 2 diabetes.
3. Describe the similarities and differences between individual GLP-1 receptor agonists.
4. Summarize the clinical rationale and evidence for combining GLP-1 receptor agonists with basal insulin so as to address various underlying pathophysiologic components of type 2 diabetes.

Faculty

Andrew Ahmann, MD, MS
Professor of Medicine
Director, Harold Schnitzer Diabetes Health Center
Oregon Health & Science University
Portland, Oregon

Dr Ahmann received board certification in internal medicine in 1983 and endocrinology and metabolism in 1986. Dr Ahmann received a masters degree in pharmacy from North Dakota State University in 1976 after completing a clinical pharmacy residency at the Palo Alto VA and Stanford University. He received his medical degree in 1980 from the University of Colorado School of Medicine in Denver, and completed his residency at the Fitzsimons Army Medical Center in Colorado. He completed his endocrinology and metabolism fellowship and research fellowship at Walter Reed Medical Center in Washington, DC. Dr Ahmann has been very involved in community and national diabetes efforts to improve the lives of those with diabetes. He has volunteered at Gales Creek Camp in the past and then has volunteered each summer at the Chris Dudley Basketball Camp for kids with diabetes since 1998. He chaired the task force to develop the Oregon Diabetes Coalition, served as the first chair of that organization, and now serves on the executive committee. He was the medical chair of the Oregon Diabetes Collaborative and serves as president of the American Diabetes Association (ADA) Portland Area Leadership Board. He remains highly involved in teaching medical students, residents, and fellows as well as physician assistant students and pharmacy students. He has been involved in national diabetes projects with the ADA, the American Association of Clinical Endocrinologists, and the Endocrine Society. He received the Portland Area Juvenile Diabetes Research Foundation Hope Award in 2008. He enjoys hiking, golfing, and spending time with his two sons, daughters-in-law, and grandson, who live in the Portland area.

Robert J. Tanenberg, MD, FACP
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Robert J. Tanenberg, MD, FACP, is professor of medicine, division of endocrinology, Brody School of Medicine, East Carolina University (ECU), in Greenville, North Carolina. He serves as medical director of the ECU Diabetes and Obesity Institute and director of the clinical diabetes fellowship. Dr Tanenberg is also the medical director of the inpatient diabetes program at Pitt County Memorial Hospital, an 860-bed teaching and tertiary referral medical center in Greenville, North Carolina. In addition, Dr Tanenberg directs the ECU-Diabetes Research Center for Clinical Trials, where he has been a principal investigator for over 60 diabetes research studies. Dr Tanenberg is board certified in internal medicine, and in endocrinology and metabolism. After earning his medical degree from the University of Illinois, Chicago, Dr Tanenberg completed a medicine residency at the Mayo Clinic, Rochester, Minnesota, and an endocrine fellowship at the University of Minnesota, Minneapolis. He was also fellowship-trained in diabetes at the Joslin Diabetes Center, Boston, Massachusetts. He was formerly on the faculty of Georgetown University School of Medicine and director of the Diabetes Treatment Center at Georgetown University Hospital. He was also a consultant to the National Institutes of Health for the landmark Diabetes Control and Complications Trial. With special interests including insulin therapy, Type 1 diabetes, and treatment of patients with diabetic neuropathy, severe insulin resistance, and metabolic syndrome, Dr Tanenberg has over 100 publications including articles, book chapters, and abstracts. He has been
published in scientific journals that include *Diabetes, Metabolism, Endocrine Practice, Diabetes Technology and Therapeutics, Mayo Clinic Proceedings*, and the *New England Journal of Medicine*. He has been endocrinology editor for *Hospital Physician* and is an editor of the lay journal *Diabetes Health*. He lectures throughout the country on the treatment of diabetes and the prevention and treatment of diabetic complications.

**Faculty Financial Disclosure Statements**

The presenting faculty reports the following:

Dr Ahmann has served as a consultant for Eli Lilly & Novo Nordisk, serves on the speakers bureau for Novo Nordisk, and has a research grant from Eli Lilly.

Dr Tanenberg serves on speakers bureaus for Boehringer Ingelheim, Eli Lilly, and sanofi-aventis, U.S., and has conducted clinical trials supported by Johnson & Johnson, Lilly, Novo-Nordisk, and sanofi-aventis, U.S.

**Education Partner Financial Disclosure Statement**

The content collaborators at Horizon CME have reported the following:

Brian Lee, PharmD, Elizabeth Wilkerson, CHES, Cara Williams, PharmD, and Arianna Sunford, BHA, have no financial relationships to disclose.

**Acronym List**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG</td>
<td>Blood glucose</td>
<td>GIP</td>
<td>Glucose-dependent</td>
</tr>
<tr>
<td>EP</td>
<td>Education Partner</td>
<td>OAD</td>
<td>insulinotropic polypeptide</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
<td>PPG</td>
<td>Oral antidiabetic drug</td>
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<tr>
<td></td>
<td></td>
<td>T2DM</td>
<td>Type 2 diabetes</td>
</tr>
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</table>

**Suggested Reading List**


Session 4


Session 4
SESSION 4
1–2:30pm

Complementary Therapies to Improve Glucose Control in Type 2 Diabetes: Role of GLP-1 Receptor Agonists & Basal Insulin

SPEAKER
Andrew Ahmann, MD, MS
Robert J. Tanenberg, MD, FACP

Presenter Disclosure Information

The following relationships exist related to this presentation:

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Learning Objectives

- Apply strategies to individualize therapy in the treatment of patients with type 2 diabetes
- Incorporate appropriate strategies for timely initiation, selection, titration, and self-management of basal insulin in patients with type 2 diabetes
- Describe the similarities and differences between GLP-1 receptor agonists
- Summarize the clinical rationale and evidence for combining GLP-1 receptor agonists with basal insulin to address the various underlying pathophysiologic components of type 2 diabetes

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.

Drugs

<table>
<thead>
<tr>
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<th>US Trade Name</th>
<th>Generic Drug Name</th>
<th>US Trade Name</th>
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<tbody>
<tr>
<td>alogliptin</td>
<td>Nesina</td>
<td>insulin lispro</td>
<td>Humalog</td>
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<tr>
<td>atenolol</td>
<td>Tenormin</td>
<td>linagliptin</td>
<td>Tradjenta</td>
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<tr>
<td>bromocriptine</td>
<td>Parlodel, Cycloset</td>
<td>iragludide</td>
<td>Victoza</td>
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<tr>
<td>canagliflozin</td>
<td>Invokana</td>
<td>isoleptin</td>
<td>Pinivil, Zestri</td>
</tr>
<tr>
<td>coloacetate</td>
<td>Welchol</td>
<td>metformin</td>
<td>Glucophage</td>
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<td>exenatide</td>
<td>Byetta</td>
<td>pioglitazone</td>
<td>Actos</td>
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<td>glimepiride</td>
<td>Amaryl</td>
<td>premilnide</td>
<td>Symrin</td>
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<tr>
<td>hydrochlorothiazide (HCTZ)</td>
<td>Mircast, Hidrolix</td>
<td>saxaglupin</td>
<td>Onglyza</td>
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<td>Novolog</td>
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<td>Lantus</td>
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</tr>
<tr>
<td>insulin glulisine</td>
<td>Apidra</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin human aspart (NPH)/insulin human regular</td>
<td>Humulin, Novolin</td>
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</tbody>
</table>

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Boston, MA – September 19, 2013
Type 2 Diabetes Epidemiology

The Diabetes Epidemic: 2012 Global Prevalence


World 371 Million
8.3% Prevalence

N. America & Caribbean
00
10.5% Prevalence

34 M

Middle East & N. Africa

10.9% Prevalence

55 M

Europe

6.7% Prevalence

26 M

South & Central America

9.2% Prevalence

70 M

SE Asia

8.7% Prevalence

15 M

Africa

4.3% Prevalence

132 M

Western Pacific

8.0% Prevalence

Type 2 Diabetes Pathophysiology

Pathophysiologic Progression of T2DM Vascular Complications

Pathophysiologic Defects of T2DM

The Incretin System: A Regulator of Post-Prandial Glucose Metabolism
A1C Goal Setting

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

- Glycemic targets
  - HbA1c < 7.0% (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)

- Individualization is key:
  - Tighter targets (6.0-6.5%) - younger, healthier
  - Looser targets (7.5-8.0%) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
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<tr>
<th>STUDY</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
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<td>UKPDS</td>
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<td>ACCORD</td>
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<td>ADVANCE</td>
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<tr>
<td>VADT</td>
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  5. ACCORD Study Group. NEJM. 2010;363:233–244.

Approach to Management of Hyperglycemia

<table>
<thead>
<tr>
<th>more stringent</th>
<th>less stringent</th>
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<tbody>
<tr>
<td>highly motivated, adherent, excellent self-care capacities</td>
<td>less motivated, non-adherent, poor self-care capacities</td>
</tr>
<tr>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>newly diagnosed</td>
<td>long-standing</td>
</tr>
<tr>
<td>short</td>
<td>long</td>
</tr>
<tr>
<td>absent</td>
<td>few/mild</td>
</tr>
<tr>
<td>severe</td>
<td>few/mild</td>
</tr>
<tr>
<td>absent</td>
<td>severe</td>
</tr>
<tr>
<td>readily available</td>
<td>limited</td>
</tr>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td></td>
</tr>
<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td></td>
</tr>
<tr>
<td>Important comorbidities</td>
<td></td>
</tr>
<tr>
<td>Established vascular complications</td>
<td></td>
</tr>
<tr>
<td>Resources, support system</td>
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Type 2 Diabetes Treatment Options

Primary Sites of Action of Therapeutic Options for T2DM

- Liver: Glucose Production
  - Metformin
  - TZDs
  - Insulin
  - DPP-4 inhibitors
  - GLP-1 Agonists

- Pancreas: Alpha Cell: Glucagon Secretion
  - GLP-1 Agonists
  - DPP-4 inhibitors
  - Pramlintide
  - Beta Cell: Insulin Secretion
  - Sulfonylureas
  - GLP-1 Agonists

- Intestine: Digestion & Absorption
  - GLP-1 Agonists
  - Alpha Glucosidase Inhibitors
  - Colesevelam (mechanism uncertain)

- Muscles & Adipose Tissue: Insulin Resistance
  - Metformin
  - TZDs
  - Insulin
  - GLP-1 Agonists

Primary Sites of Action of Therapeutic Options for T2DM Cont’d

Kidney: Glucosuria
Sodium glucose co-transporter-2 (SGLT-2) inhibitors
Canagliflozin

Brain: Appetite/Metabolic Regulation
GLP-1 Agonists
Exenatide
Liraglutide

Kidney: Glucose Reabsorption
Canagliflozin

Leveraging the Incretin Effect – The Therapeutic Potential of GLP-1 and GIP

Incretin-Based Therapy for Diabetes
GLP-1 Agonists and DPP-4 Inhibitors

GLP-1 Agonists
- A1c reduction ~0.8%-2.0%
- Significant and sustained weight loss
- Injected therapy
- Potential GI side effects
- Low rates of hypoglycemia
- Improved CV risk factors
- Limited data on CV risk factors
- Multiple mechanisms of action
  - Slows gastric emptying
  - Improves satiety
  - Increases insulin secretion, decreases glucagon release
  - Modest weight loss

DPP-4 Inhibitors
- A1c reduction 0.5%-1.1%
- Weight neutral
- Oral administration (generally QD)
- No significant GI side effects
- Low rates of hypoglycemia
- No significant CV side effects
- Limited data on CV risk factors
- Improves insulin sensitivity
- Increased food intake, slows gastric emptying

Incretin-based Therapies
Disadvantages/Risks

GLP-1 Agonists
- Gastrointestinal side effects (nausea, vomiting)
- Associated with pancreatitis
- C-cell hyperplasia/medullary thyroid tumors in rodents
- Associated with renal insufficiency
- Expensive
- Injectable

DPP-4 Inhibitors
- Modest A1c efficacy
- Urticaria/angioedema
- Associated with pancreatitis
- Expensive

DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>A1C Reduction</th>
<th>Metabolism</th>
<th>Elimination Half-life</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>0.5-0.8%</td>
<td>Liver</td>
<td>2.5-3.1 h</td>
<td>Dosage adjustment in moderate to severe renal dysfunction</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>0.5-0.8%</td>
<td>Liver (CYP3A4/5)</td>
<td>113-131 h</td>
<td>Drug interaction with strong CYP3A4 inhibitors</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>0.5-0.8%</td>
<td>Enterohepatic</td>
<td>16-7.25 h</td>
<td>Drug interaction with P-glycoprotein/CYP 3A4 inducers</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>0.5-0.8%</td>
<td>Liver (10-20%)</td>
<td>14-55 h</td>
<td>Dosage adjustment in moderate to severe renal dysfunction</td>
</tr>
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GLP-1 Actions on the Alpha and Beta Cells Are ‘Glucose-Dependent’ in Type 2 Diabetes

Data are mean ± SE. * P<0.05
GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>ΔA1C Reduction</th>
<th>Elimination Half-life</th>
<th>Duration of Action</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>1.0-1.5%</td>
<td>13 h</td>
<td>Long</td>
<td>Submit for FDA approval. Long biological half-life due to high affinity for GLP-1 receptor (6x greater than native GLP-1). Once daily injection.</td>
</tr>
<tr>
<td>Exenatide ER</td>
<td>1.0-1.5%</td>
<td>2.4 h</td>
<td>Long</td>
<td>Once weekly injection.</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>~1.0%</td>
<td>2-4 h</td>
<td>Short</td>
<td>Avoid use in severe renal dysfunction. Twice daily injection.</td>
</tr>
<tr>
<td>Exenatide</td>
<td>~1.0%</td>
<td></td>
<td></td>
<td>Do not use in patients with personal or family history of medullary thyroid cancer. Once daily injection.</td>
</tr>
</tbody>
</table>


Impact of Exenatide BID Therapy Over 3 Years: Effect on A1c and Body Weight

Change in A1c (%)  
Change in Body Weight (kg)

Type 2 Diabetes Antihyperglycemic Therapy: General Recommendations

Starting Insulin
UKPDS: at 6 years, more than 50% of patients need insulin to reach target (FPG ≤ 6.0 mmol/L).


Type 2 Diabetes and Need for Insulin


Effect of Basal Insulin on HbA₁c, Weight, and Hypoglycemia

Physiologic Insulin Secretion

Pharmacokinetic Profiles of Human Insulins and Analogs

Treat-to-Target Trial

Insulin glargine was associated with 41% risk reduction in hypoglycemia, p<0.00.
Strategies for Insulin Selection

- Convenience (once daily vs. twice or three times daily)
- Proven safety
  - Analogs - ORIGIN study showed low hypoglycemic risk, no adverse CV effects, and no cancer risk
  - NPH - a little more hypoglycemic risk than analogs
- Cost
  - NPH $?
  - Analogs $-$ $$
- Insurance coverage
  - Analogs - coverage varies and may require prior authorization

Patient Barriers to Insulin Initiation

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Addressing the Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sense of failure</td>
<td>+ Insulin is an inevitable step</td>
</tr>
<tr>
<td></td>
<td>+ Discuss with patients early in the disease about insulin</td>
</tr>
<tr>
<td></td>
<td>+ Do not use insulin as threat, but as solution</td>
</tr>
<tr>
<td>Insulin causes complications</td>
<td>+ Acknowledge the patient’s fear</td>
</tr>
<tr>
<td></td>
<td>+ Provide information about the provider’s experiences of the effectiveness of insulin</td>
</tr>
<tr>
<td>Loss of independence</td>
<td>+ Empower patient to take control of BG</td>
</tr>
<tr>
<td></td>
<td>+ Provide self-management education</td>
</tr>
<tr>
<td></td>
<td>+ Use insulin pens and insulin regimens that offer maximum flexibility</td>
</tr>
<tr>
<td>Insulin ineffectiveness</td>
<td>+ Give “limited” trial with appropriate insulin doses</td>
</tr>
<tr>
<td></td>
<td>+ Monitor for symptom improvement (nocturia, energy level, etc.)</td>
</tr>
</tbody>
</table>


When To Start Insulin in T2DM

- When combination oral/injectable agents become inadequate
- Unacceptable side effects of other agents
- Patient with advanced hepatic or renal disease
- Special circumstances (e.g., steroids, infection, pregnancy)
- Patient with hyperglycemia in the hospital
- “Severely” uncontrolled diabetes*

*Defined as fasting glucose > 250 mg/dl, random glucose > 300 mg/dl, A1C > 10%, ketonuria, or symptomatic (polyuria, polydipsia, and weight loss) by ADA 2009 Consensus Statement. After glucose controlled, oral agents can be added and insulin withdrawn if preferred.


Sequential Insulin Strategies in T2DM

- Number of injections and Regimen complexity:
  - Basal insulin only (usually with oral agents)
  - Basal insulin + 1 (meal-time) rapid-acting insulin injection
  - Basal insulin + 2 (meal-time) rapid-acting insulin injection

- Premixed insulin twice daily


Patient Barriers to Insulin Initiation

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Addressing the Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fear of injections</td>
<td>+ Insulin needles are small</td>
</tr>
<tr>
<td></td>
<td>+ Less painful than finger sticks for BG testing</td>
</tr>
<tr>
<td></td>
<td>+ Have patient give a low dose insulin injection in office</td>
</tr>
<tr>
<td></td>
<td>+ Insulin pen is less threatening</td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
<td>+ Incidence is low, especially with basal analogs</td>
</tr>
<tr>
<td></td>
<td>+ Teach patient to recognize and treat (Rule of 15)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>+ Meet with dietitian before initiation of insulin</td>
</tr>
<tr>
<td></td>
<td>+ More physiologic insulin delivery may minimize weight gain</td>
</tr>
<tr>
<td></td>
<td>+ Minimize with metformin and GLP-1 receptor agonists</td>
</tr>
<tr>
<td>Cost</td>
<td>+ Insulin is typically less expensive than using multiple oral medications</td>
</tr>
<tr>
<td></td>
<td>+ Use premix insulins or less expensive insulins</td>
</tr>
</tbody>
</table>


Summary of Comparative Insulin Trials

- Any insulin will lower glucose and A1C; the more injections and the higher the dose, the better the control.
- All insulin use results in weight gain and increases the risk of hypoglycemia.
- Generally, insulin analogs reduce the incidence of hypoglycemia over human insulins - but generally do not result in better overall glycemic control.
- Insulin strategies that include prandial dosing (e.g., basal-bolus; premixed) will generally reduce A1c to a greater extent than basal-only, but at the expense of more weight gain, hypoglycemia.

Advancing Basal Insulin

Bedtime or morning long-acting insulin
OR
Bedtime intermediate-acting insulin
Daily dose: 0.1-0.2 u/kg
Increase dose by 2 units every 3 days
until FPG is 70-130 mg/dL
If FPG is >180 mg/dL, increase dose
by 4 units every 3 days.
Check FBG daily
Continue regimen and check A1C every 3 months
In the event of hypoglycemia or FPG level <70 mg/dL:
Reduce bedtime insulin dose by 4 units, or by 10% if >40 units.

A Recommendation for Starting and Adjusting Basal Insulin

FBG=fasting blood glucose
FPG=fasting plasma glucose

Patient vs. Physician Adjusted Basal Insulin

HbA1c Change

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24 Weeks</th>
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<tbody>
<tr>
<td>Patient Adjusted</td>
<td>8.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Physician Adjusted</td>
<td>8.9</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Severe</th>
<th>Symptomatic</th>
<th>Nocturnal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Adjusted</td>
<td>1.1</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Physician Adjusted</td>
<td>29.7</td>
<td>29.3</td>
<td></td>
</tr>
</tbody>
</table>

Patients can be safely instructed to adjust their insulin dose

When Basal Alone is Not Enough

When is Basal Alone Not Enough?

When A1C values are still not at target AND...

- Basal insulin dose titrated to 0.4-0.6 units/kg/day
- Fasting BG levels at or approaching target
- Post-prandial BG values remain above target

Mimicking Physiologic Insulin Secretion: “Basal-Bolus” Insulin Therapy

BG=blood glucose

Premixed (Biphasic) Insulin Analogs

- **Premixed insulins**
  - Humalog 75/25, 50/50 – Intermediate + rapid-acting
  - Novolog 70/30 – Intermediate + rapid-acting
  - Humulin 70/30 – Intermediate + short-acting
  - Novolin 70/30 – Intermediate + short-acting
- Premixed insulin may be appropriate
  - When basal/bolus cannot be used
  - For those with regular lifestyles, who eat similar amounts at similar times each day (similar total calories and similar content for carbohydrate/fat/protein)
  - Those who wish only 2 injections/day

How to Intensify Using the Basal Plus Approach

- Choose the “target” meal to initiate prandial coverage
  - Breakfast or the largest meal of the day
- Start 4-6 units of a rapid-acting insulin analog 10-15 minutes before the meal
- Adjust prandial insulin dose based on
  - 2-h PPG -> target < 180 mg/dl
  - Next pre-prandial or HS BG -> target < 130 mg/dl
- If A1C remains above target add 2nd prandial dose
  - Usually need about 8-12 units of prandial insulin to cover meal(s)

Summary

- Identify appropriate candidates for intensive diabetes management
- Address barriers to treatment intensification
- Make use of multidisciplinary approach to diabetes management
- Start and optimize basal insulin
  - Involve patient in insulin dose adjustments
- Intensify by adding prandial coverage in a simplified manner

What Do We Know About the Relative Benefits of GLP-1 Agonists vs. Basal Insulin?

Glucose Effect of Short-acting GLP-1 Receptor Agonist Compared to Basal Insulin
Long-acting GLP-1 RA vs. Basal Insulin

**LEAD-5 Study**

A1c Reduction  Body Weight Reduction

- **Liraglutide 1.8mg**
- **Placebo**
- **Insulin Glargine**

**Change in A1c (%)**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Baseline</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.3%</td>
<td>8.3%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

- **p < 0.0001**
- **p = 0.0015**

**Change in body weight (kg)**

- **Liraglutide**
- **Placebo**
- **Glargine**

- *Significant vs. Glargine (p<0.0001) and placebo (p=0.0001); Mean±2SE*


**What Do We Know About Combining GLP-1 Receptor Agonists and Basal Insulin?**

**Potential Benefits of Combining GLP-1-based Therapies with Insulin**

**GLP-1-based therapies**
- **Insulin secretion (glucose-dependent)**
- **Beta-cell preservation**
- **Glucagon secretion (glucose-dependent)**
- **Risk of hypoglycemia**
- **Body weight**
- **PPG levels**
- **Satiety**
- **GI tract motility**

**Basal insulin therapy**
- **Insulin levels (insulin supplementation)**
- **Beta-cell rest**
- **Corrects glucotoxicity**

- Relies on endogenous prandial insulin response
- Moderate risk of hypoglycemia

- Weight gain
- **PPG levels**

**Exenatide BID Added to Basal Insulin Effect on HbA1c and PPG**

Adults with T2DM and HbA1c = 7.1% to 10.5% receiving glargine ± metformin ± pioglitazone were randomized to exenatide (10 mcg twice a day) or placebo for 30 weeks.

**Efficacy**

<table>
<thead>
<tr>
<th>Glargine + PBO (n = 123)</th>
<th>Glargine + EXN (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight Change</strong></td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Discontinuation due to Adverse Events (% of pts)</strong></td>
<td>1.0</td>
</tr>
</tbody>
</table>

- *P<.001; †P=.02; BID=twice daily; PBO=placebo; EXN=exenatide; PPG=postprandial glucose; SMBG=self-monitored blood glucose.*

**Exenatide BID Added to Basal Insulin Effect on Insulin Dose and Weight**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PB D</th>
<th>EXN BID</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Change</td>
<td>1.0</td>
<td>-1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia*</td>
<td>1.2</td>
<td>1.4</td>
<td>0.49</td>
</tr>
<tr>
<td>Discontinuation due to Adverse Events (% of pts)</td>
<td>1</td>
<td>9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- *1 reported event of major hypoglycemia (PBO group)*

**Baseline insulin doses = 45.5 and 47 U/day in EXN BID and PBO groups, respectively.**

**Respective changes = 13 and 20 IU/day.**

EXN = exenatide; PBO = placebo.

**Key Points**

- Combining basal insulin and GLP-1 receptor agonists offers an effective alternative to managing both post-prandial and fasting glucose
- Majority of clinical experience thus far is with short-acting exenatide
- Less weight gain observed with combination
- Lower insulin requirements
- Significant A1c reduction with minimal increase in hypoglycemia

**Conclusions**

- Type 2 diabetes is marked by progressive beta cell dysfunction and need for progressive therapy
- Clinicians should initiate basal insulin early in the course of type 2 diabetes when significant hyperglycemia persists or if patient fails to reach the target A1c on other therapies
- GLP-1 agonists offer opportunities for intervention at multiple points in the progression of therapy
- GLP-1 agonists may have potential advantages over basal insulin as the first injectable added to oral agents
- More experience in combining GLP-1 agonists and basal insulin is needed to fully characterize benefits

**Patient Cases**

**Case 1**

- A 54 y.o. woman presents for routine yearly follow-up without specific complaints. She was diagnosed with type 2 DM 9 years ago on a routine annual visit. Her initial A1c was 7.5 %
- She was initially treated with metformin in addition to receiving diabetes education, starting regular exercise and adjusting her diet. HbA1c dropped to 6.6%
- However, 5 years later her A1c rose to 7.7% and glimepiride was added
Case 1 Continued

- **Medical Problems:**
  - Type 2 Diabetes
  - Hypertension
  - Hyperlipidemia
  - Postmenopausal

- **Medications:**
  - Metformin 1000 mg bid
  - Glimepiride 4 mg qd
  - Lisinopril 10 mg qd
  - Simvastatin 20 mg qd

Case 1 Continued

- **Social:** Bank officer, married, mother of 3
- **Habits:** non-smoker, exercises 30+ minutes 3-4 days weekly. She is committed to losing weight and has been working with the dietitian recently.

- **PE:**
  - BP = 136/82   Wt = 189 lbs  (BMI = 31.4)
  - Normal exam including fundi and neurological

- **Labs:**
  - Creatinine = 0.95 mg/dl  Electrolytes normal
  - Liver enzymes normal  LDL = 79
  - HbA1c = 8.0 %

Case 2

- **A 66 y.o. man was diagnosed with type 2 DM 12 years ago**

- **Medical Problems:**
  - Hypertension
  - CAD (previous CABG)

- **Medications:**
  - Metformin 1000 mg bid
  - Glimepiride 4 mg qd
  - Lisinopril 10 mg qd
  - Simvastatin 20 mg qd

Case 2 Continued

- **Social:** Married, retired
- **Habits:** nonsmoking; Tries to walk at least 30 minutes 5 times weekly.

- **PE:**
  - BP = 131/82   Wt = 224 lbs  (BMI = 32.4)
  - Decreased vibratory sensation and monofilament

- **Labs:**
  - LDL = 98 mg/dl  HDL = 35  Creatinine = 1.33 mg/dl
  - HbA1c = 8.1 %

THANK YOU!