Type 2 Diabetes Update For 2015

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Learning Objectives

At the conclusion of this presentation, the participant will be able to:

1. Review the role of 6 new drugs to treat Type 2 diabetes
2. Describe the mechanism of action the newest medications on the market for managing diabetes
3. List 4 indications, contraindications and precautions for 3 new classes of diabetes medications

Challenges in Type 2 Diabetes Why The Need For More Drugs?

• Large number of patients
  – Diabetes —25.8 million people
    • PREDIABETES—79 million people
  • Weight gain (2 to 10 lbs)
  • Progressive worsening of disease (ability to secrete insulin)
    (Need to add more drugs)
  • Controlling fasting and postprandial glucose
  • Glucose fluctuations (variability)


Diabetes: Here and Now
Presentation downloaded from: http://ce.unthsc.edu
A Few More Reasons

• Managing complications and co-morbidities (balloon theory)

• Durability—sustaining optimal long-term glycemic control

• Hypoglycemia  (Do we take it serious enough?)

Durability

• How long does a oral med work?

• How do we know when it stops working?

Variability: More Harm Than We Thought?

• Several studies to back up theory

• Needs more studies
Ideal Diabetes Drug

• No hypoglycemia
• No weight gain
• Well tolerated
• Good A1C lowering ability
• Given orally q d
• Helps with lipid profile and BP
• Low cost 😊

How Do We Choose A Drug

• What are the patient’s glycemic goals?
• How far are they from these goals?
• What is their current diabetes regimen and/or what have they taken in the past?
• How long have they had diabetes?
• What is the principal problem? Fasting or postprandial
• Is there unacceptable risk from hypoglycemia
• Non-glycemic effects: CV, weight, lipids, blood pressure
• Contraindications, special populations, comorbidities, etc.
• Cost

What Is FDA Looking For In Approving A New Diabetes Medication?

• Low Incidence of Hypoglycemia

• Low CV risks

• Possible CV improvement
Hypoglycemia and Mortality

“Self-report or admission to ED for severe hypoglycemia is associated with 3.4-fold increased risk of death.”

T2DM: The 3-Legged Stool

- Nutrition
- Physical Activity
- Medications

Blood Glucose Monitoring

New Sites Of Action

- Six different sites
  - Beta cells of pancreas
  - Alpha cells
  - Brain
  - Muscle and adipose tissue
  - Liver
  - GI tract
GLP-1 Agonists

• Glucose dependent
  — Decrease glucagon
  — Increase Insulin from beta cells
  — Delay absorption from stomach
  — Decrease insulin resistance

GLP-1 Agonists

• Exenatide Byetta

• Exenatide Extended Release—Bydureon
  — Thyroid C cell tumors
  — Acute Pancreatitis?
• Once a week dosing vs daily dosing?

• liraglutide Victoza
  — medullary thyroid carcinoma (MTC)
  — New Indication of weight loss

GLP-1 Agonists

— Dulaglutide Trulicity
  • Medullary thyroid carcinoma
  • Acute pancreatitis?
  • Injection pen
— Albiglutide Tanzeum
  • MTC
  • Pancreatitis
DPP-4 Inhibitors

• Raise the drawbridge or lower the water?

• Protect a natural enzyme DPP-4, from breaking down GLP-1

DPP-4 Inhibitors

• Sitagliptin Januvia
• Alogliptin Nesina
• Saxagliptin Onglyza
• Linagliptin Trajenta

What Once Was Bad In Some Cases Is OK

Yesterday

| Glucose in Urine |

Today

| Glucose in Urine | Yesterday |

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Kidney and Glucose

- Produces glucose
- Utilizes glucose
- Filters glucose
- Reabsorbs glucose

Normal Renal Handling of Glucose
Sodium-Glucose Co-transporters (SGLT2s)

- 180 g/day/1.73 m² (filtered glucose load)¹
- SGLT2 transports 90% of filtered glucose out ¹-⁴
- SGLT1 transports the remaining 10% ¹-⁴

SGLT = sodium-glucose co-transporter.

Normal Kidney: Glucose Reabsorption
(Plasma Glucose ≤180 mg/dL)

Adapted with permission from Rothenberg PL et al.
SGLT = sodium-glucose co-transporter.
SGLT2 Inhibitors Reduce Renal Glucose Reabsorption and Increase Urinary Glucose Excretion

Glomerulus → Tubule → Distal

Glucose → SGLT2 → SGLT2 inhibitor → SGLT1

Renal Threshold for Glucose Excretion ($RT_G$) in Healthy Adult Subjects

Healthy: 180 mg/dL

Renal Threshold for Glucose Excretion Is Increased in T2DM

T2DM: type 2 diabetes mellitus

Healthy: 180 mg/dL

T2DM: 240 mg/dL

Plasma glucose (mg/dL) vs. Urinary glucose excretion (g/day)

The “Flozin” Family

• Canagliflozin—Invokana®

• Dapagliflozin—Farxiga®

• Empagliflozin  Jardiance®

Limitations of SGLT2 Inhibitor Therapy

• Increased risk of genito-urinary infections
  – Increase in UTIs but treatable, with no recurrence
  – Increased mycotic genital infections, more so in women or with history of genital infections

• Risk of dehydration
  – Some dehydration in patients with very high glucose levels (osmotic diuresis)
  – Very few cases of dehydration reported

• Electrolyte disturbances—hyperkalemia
  Potassium-sparing diuretics

Group Considerations

Caution in

• Elderly patients at risk of dehydration

• Women with history of infections

• Compromised renal function
  – Stage 3 or 4 of chronic kidney disease
Combo Drugs

• Actoplus MET metformin/pioglitazone
• Avandamet rosiglitazone/metformin
• Duetact glimepiride/pioglitazone
• Glucovance Glyburide/metformin
• Metaglip metformin/glipizide
• Kazano metformin/alogliptin
• Oseni Alogliptin/pioglitazone
• Prandimet repaglinide/metformin

Other New Combos

• dapagliflozin/metformin Xigduo
• canagliflozin Invokamet/metformin

New Insulins

• Insulin Glargine Injection Toujeo-300
  • True 24 hour
  • Unit for unit for pens
  • Versus U-500?

• Inhaled Human Insulin Afrezza
  • Ultra rapid acting (peaks 15-20 min)
  • Duration 2-3 hours
  • Easy To Teach
Inhaled Human Insulin--Afrezza

Candidates : Who? When?

• Metformin not tolerated (approx. 15%)\(^1\)
• Metformin no longer works
• Add on to initial oral therapy (2\(^{nd}\) or 3\(^{rd}\))
• Added to basal + with or without metformin?
• Need of added benefits of weight loss (or weight neutral) and and slightly above goal for hypertension

Patient Case: Roy

Presentation:

– 47 yr old AA male Type 2 DM x 8 yr

Social/Lifestyle Hx:

– Truck Driver x 20 yrs. Limited PA and lots of fast food
– Wt loss of 5 lbs in last month due to “trying to eat smarter and just working harder at it”
– A trial on a sulfonylurea caused frequent hypoglycemia due to erratic eating habits and he refuses “any kind of shots.”

Diabetes Self-Management:

• "Checks 2-3 times a week at different times"
• FPG avg 134 mg/dL
• FPG avg 188 mg/dL

Hx, Physical Lab:

– HW/Ht: 6’0”, 210 lb, BMI 28.5
– BP 145/84 mm Hg
– SBP 7.5%
– Serum Creatinine 1.2 mg/dL
– Microalbumin < 30 mg/dL

Meds:

Enalapril 10mg q.d
Amlodipine 20mg q.d
Metformin 1000mg bid
ASA 81 mg d
Coming Down The Pipe?

• Newer Insulins?

• More orals???

• Artificial Pancreas?