A Clinical Update in Diabetes Management

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A Clinical Update in Diabetes Management

Accreditation: Sanofi Aventis

Program Overview:
• Approximately 24 million Americans have diabetes, and an additional 50 million or more people have “pre-diabetes.” Due to the high prevalence of diabetes mellitus, it is not surprising that therapeutic advances in the management of diabetes face health care priority in the United States. Participants in this presentation will learn about new drugs approved for the management of diabetes (e.g., saxagliptin, sitagliptin, and news about medications currently available to treat diabetes, e.g., new developments with exenatide, insulin, and the risk of adverse effects with insulin therapy). This presentation also includes news about medications currently available to treat diabetes, e.g., new developments with exenatide, labeling changes with insulin, and news about medications currently available to treat diabetes, e.g., new developments with exenatide, insulin, and the risk of adverse effects with insulin therapy.)

• Recent research has influenced this important part of practice. Last, participants will review updated medical management guidelines for type 2 diabetes mellitus from the American Diabetes Association and other groups.

Objectives:
• Describe current thinking on blood glucose control, including guideline recommendations published by the ADA/AACE/ACE for the management of diabetes mellitus.
• Describe new therapeutic options available for the management of diabetes mellitus, their role in therapy, and medications in the pipeline.
• Identify the controversial evidence concerning metabolic goal-setting for patients with diabetes and the use of specific medications (e.g., TZDs and cardiovascular risk, insulin and cancer risk.)

Target Audience:
• Pharmacists, Technicians

CE Credits:
• Pharmacists: 0798
• Nurses: N-043-L01-P
• Pharmacy Technicians: 0798

Legal Disclaimer: The material presented here does not necessarily reflect the views of Pharmaceutical Education Consultants or the companies that support educational programming. A qualified healthcare professional should always be consulted before using any therapeutic product discussed. Participants should verify all information and data before treating patients or employing any therapies described in this educational activity.

Speaker Disclosure: Dr. McPherson has no actual or potential conflicts of interest in relation to this program.

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Speaker: Dr. Mary Lynn McPherson is a Professor in the Department of Pharmacy Practice and Science at the University of Maryland School of Pharmacy. She serves as a consultant pharmacist for both local and national hospice and palliative care programs, and has designed a critical thinking process for appropriate drug use in end of life patients. She serves on the Board of the Hospice Network of Maryland, chairing the Education and Outreach Committee. She also serves on the Board of the Maryland Pain Initiative and the Advisory Board of the American Society of Pain Educators.

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Saxagliptin (Onglyza)

- Second DPP-4 inhibitor approved by FDA
  - First was sitagliptin (Januvia)
- MOA – reduce plasma glucose levels by blocking the enzymatic degradation of incretin hormones, thus prolonging the incretin effect

- Minimal adverse effects (headache, URI, UTI)
- Low risk of hypoglycemia
  - May potentiate hypoglycemic agents
- Concerns re: sitagliptin-induced pancreatitis
- Metabolized by CYP3A4
  - Start at 2.5 mg with use of 3A4/5 inhibitors
  - 2.5 mg for patients with CrCL < 50 ml/min
- Role in therapy
Liraglutide (Victoza)

- An incretin mimetic (a synthetic analog of GLP-1) similar to exenatide.
- Mechanism of action
  - Stimulates post-meal insulin secretion
  - Decreases post-meal glucagon secretion
  - Suppresses appetite in T2DM patients.

Exenatide Issues

- FDA approved exenatide injection (Byetta) allowing for its use as monotherapy along with diet and exercise to improve glycemic control in T2DM.
  - Previously approved for use only in patients who were taking other diabetes medications and had not achieved glycemic control
- FDA hedges approval of long-acting Byetta
  - Once a week formulation (Bydureon)
  - Delivers measured doses over the 168-hour span
- FDA has requested more information of the manufacturer regarding manufacture, labeling and risk management plan.
Exenatide Issues

- Long-acting Byetta may be tied to increased cancer risk.
- Data on intravenous dosing and a once-weekly formulation of exenatide “seem to give a similar signal” as cancers seen in rodent studies of liraglutide.
- Will likely at least earn a black box warning to dissuade general practitioners from using this product.

Which of the following is CORRECT?

- a. Saxagliptin inhibits DPP-4, and is usually well tolerated by patients
- b. Saxagliptin reduces the A1c by 0.5-1%
- c. Post-meal, liraglutide stimulates post-meal insulin secretion and reduces glucagon secretion
- d. Exenatide therapy reduces the A1c to a greater degree than liraglutide

Increased Risk of Cancer with Insulin Analogs?

- Insulin glargine (Lantus) – one of the most prescribe insulins worldwide.
- Concern has arisen due to reports of a possible increase in cancer risk with insulin glargine use.
  - Insulin has been shown to promote the growth of both healthy and malignant cells in culture systems.

Thiazolidinedione Controversy

- Rosiglitazone (Avandia); Pioglitazone (Actos)
- Reduce glucose levels by enhancing insulin sensitivity
- Adverse effects include fluid retention, edema, doubled heart failure risk
  - Rosi + metformin + SU vs. metformin + SU
  - After 5.5 years, no significant increase in CV hospitalization or death in Rosiglitazone group
  - Rosi increased HF, limb fractures in women
TZD Controversy

• Rosiglitazone vs. pioglitazone and CV risk?
• Study compared two agents, and evaluated risk of MI, HF and death in older adults with T2DM treated with TZDs for median of 9.6 months
  – Pioglitazone – lower risk of death, MI, HF hospitalization vs. rosiglitazone
• Another study showed at 15% increase in mortality with rosiglitazone vs. pioglitazone

TZD Controversy

• Thiazolidinedione Drugs and Cardiovascular Drugs. A Science Advisory From the AHA/ACCF. Feb 23, 2010.
  – TZDs should not be used with an expectation of benefit with respect to IHD events. Use with the understanding that they may increase the risk of HF
  – Meta-analysis have raised important concerns re: rosiglitazone, which has not been raised on the available data with pioglitazone
  – However, there remains an inadequate foundation of randomized clinical trials to properly judge the safety or efficacy of either agent with respect to IHD.

TZD Controversy

  – Claims manufacturer knew rosiglitazone caused as many as 83,000 heart attacks between 1999 and 2007.
  – Claims manufacturer knew about this data.
  – Claims 500 heart attacks and 300 instances of heart failure could be averted each month if patients switched to pioglitazone
  – “Some” FDA staff recommend removing rosi from market
What would YOU do?

a. Take rosiglitazone off the market
b. Leave rosiglitazone on the market, but strengthen warnings on prescribing information
c. Leave rosiglitazone on the market with no changes to prescribing information

FDA Advisory Committee Recommendations – 7-14-10

- 33 panel members considered the fate of Avandia:
  - 12 voted to withdraw the drug from market
  - 10 voted that sales should be restricted and label warnings should be enhanced
  - 7 voted only to support enhanced warnings on drug’s label
  - 3 voted to make no changes
  - 1 member abstained

www.nytimes.com/2010/07/15/

New Drugs on the Horizon for DM

- Bromocriptine (Cycloset) for type 2 diabetes
- Dopamine agonist
  - Used to treat Parkinson’s disease or decrease prolactin levels
- Can reduce insulin resistance, probably through a central mechanism
- Reduces A1c by 0.5%
- 0.8 mg once daily, increase up to 4.8 mg qd
- Give in AM, within 2 hours of arising, with food
- Causes hypotension, syncope, nausea

New Insulin Products on the Horizon

- Alternatives to subcutaneous insulin injection
- Technosphere (AFRESA)
  - Insulin powder for inhalation pre-metered into single use cartridges for administration with a hand-held inhaler
  - Inhaled insulin with a fast onset and short duration of action that mimics early, meal-related insulin release
  - Meal-time insulin that dissolves rapidly upon inhalation and is absorbed quickly, reaching peak insulin levels in 12-14 minutes
New Insulin Products on the Horizon

- Technosphere (AFRESA)
  - Safety data indicates this product is well tolerated
  - No product-related changes in pulmonary function after 4 years of continuous treatment
  - When used as meal-time insulin, patients maintain BG control
  - Study in COPD patients shows rate and extent of absorption is not decreased by the disease
  - Exubera was listed to decline in pulmonary function and variable absorption in COPD

- Oral-Lyn
  - Buccal spray formulation of human insulin
  - Bypasses potential GI degradation and first pass metabolism by delivery liquid insulin to the buccal mucosa through a "RapidMist" device
  - FDA approved under an IND, approved for T1 or T2DM where there is no alternate treatment

Guidelines and Goal Setting

- Diabetes Screening Tool to Promote Early Detection
  - Over 60 million Americans have diagnosed diabetes, undiagnosed diabetes, or prediabetes
  - Tool builds on risk factors:
    - Age
    - Gender
    - Family history of diabetes
    - HTN or treated for HTN
    - Overweight/obese
    - Level of physical activity

Mrs. G. is a 58 year old Hispanic woman, 5’2”, 224 pounds, presenting for her annual physical. She has hypertension and dyslipidemia. Her mother and sister have type 2 diabetes. Her physician draws routine blood work and includes an A1c, which is 6.8%. Concerned she calls her back for a fasting glucose a week later, which is 134 mg/dl. What are her risk factors for diabetes? How do we classify Mrs. G?

A. Prediabetes
B. Diabetes
C. Unable to determine from data given in case

### ADA Uses A1c to Diagnose DM

<table>
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<tr>
<th>Category</th>
<th>A1c</th>
<th>FPG</th>
<th>2 hour OGTT</th>
<th>Random plus symptoms</th>
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<tbody>
<tr>
<td>Diabetes</td>
<td>&gt; 6.5%</td>
<td>≥ 126 mg/dl</td>
<td>≥ 200 mg/dl</td>
<td>≥ 200 mg/dl</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>5.7-6.4%</td>
<td>100-125 mg/dl</td>
<td>140-199 mg/dl</td>
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</tr>
</tbody>
</table>

American Diabetes Association, January 2010

### Therapeutic Goals

- **ACCORD** – Action to Control Cardiovascular Risk in Diabetes
  - Large clinical trial of adults with established T2DM who are at especially high risk of CV disease
    - History of DM on average for 10 years
    - Over one third had existing cardiovascular disease
    - Rest had > 2 CV risk factors
  - Three clinical trials, evaluating best way to decrease the high rate of major CVD events (MI, CVA, death)

### ACCORD

- Three treatment approaches:
  - Intensive lowering of blood glucose levels compared to more standard blood glucose goals
  - Intensive vs. standard blood pressure lowering
  - Treatment of dyslipidemia with two drugs (fibrate plus statin) vs. one drug alone (statin)
- Primary outcome for all three questions:
  - First occurrence after randomization of a major CVD event, specifically nonfatal MI, nonfatal CVA, or CVA death.
ACCORD

- Secondary outcomes included total mortality (death), microvascular outcomes, health-related quality of life and cost-effectiveness.
- Blood glucose control study
  - Standard – A1c 7 – 7.9%
  - Intensive – A1c < 6%
- Study stopped February 2008

ACCORD BP Clinical Trial

- Intensive BP (SBP < 120 mmHg)
- Standard BP (SBP ~ 134 mmHg)
- No significant difference in the primary study outcomes between the two groups
  - Significant reduction in the rate of CVAs
- Overall, trial showed standard treatment for hypertension was just as good as intensive lowering treatment for CV outcomes.

ACCORD Lipid Clinical Trial

- Simvastatin (Zocor)
- Simvastatin plus fenofibrate (Tricor or Trilipix)
- There was a significant difference between the levels of HDL cholesterol and TG between two groups
- Two groups did not differ in the rates of the combined outcome of heart attacks, strokes, or CV death

Medical Management Guidelines T2DM
Tier 1: Well-validated core therapies

- Lifestyle + Metformin
- Lifestyle + Metformin + Basal Insulin
- Lifestyle + Metformin + Insulin Secretagogues
- Lifestyle + Metformin + GLP-1 Agonist

Tier 2: Less well validated therapies

- Lifestyle + Metformin + Pioglitazone
- Lifestyle + Metformin + GLP-1 Agonist

Aspirin for Primary Prevention of Cardiovascular Events in PWD

- Low-dose ASA (75-162 mg QD) “is reasonable” for patients with 10 year CV disease risk > 10% and no risk factors for bleeding.
- ASA “should not be recommended” for diabetic men younger than 50 and women younger than 60 with no other risk factors.
- ASA “might be considered” for those at intermediate risk.
- www.diabetes.org/phd