PHARMACOLOGIC MANAGEMENT OF TYPE 2 DIABETES

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OBJECTIVES

- Manage a diabetes patient using ADA Standards of Medical Care
- Identify oral therapies for type 2 diabetes and select appropriate agents
- Identify basic insulin regimens for type 2 diabetes and select and adjust appropriate agents
DIABETES IN THE US

1994

2005

Age-Standardized Prevalence of Diabetes Diagnoses per 100 Adult Population by State (www.cdc.gov/diabetes/statistics/prev/state)
IMPACT OF DIABETES MELLITUS

- 6th leading cause of death
- Leading cause of new cases of blindness in ages 20-74
- Leading cause of end-stage renal disease
- Most frequent cause of non-traumatic limb amputations
- 2-4 times more likely to have heart disease or suffer a stroke
  - Heart disease is leading cause of diabetes-related deaths
- Total economic cost
  - 1997 $98 billion
  - 2002 $132 billion
  - 2007 $174 billion

www.diabetes.org
DIABETES IN KENTUCKY

Percent of population with diabetes
- 5.4% - 7.9%
- 8.0% - 9.1%
- 9.2% - 10.1%
- 10.2% - 12.5%
DIABETES IN KENTUCKY

- 7th in nation for adults with diabetes (8.9%)
- 40% of adult Kentuckians have pre-diabetes or are at risk for developing diabetes
- 6th leading cause of death
- Highest prevalence in Eastern Ky
- #4 in nation for sedentary lifestyle
- #6 in nation for obesity
RISK FACTORS FOR TYPE 2 DM

- Family history
- Overweight (BMI \( \geq 25 \text{ kg/m}^2 \))
- Habitual physical inactivity
- Race/ethnicity (e.g., African-Americans, Hispanic-Americans, Native Americans, Asian-Americans, and Pacific Islanders)
- Previously identified IFG or IGT
- Hypertension (\( \geq 140/90 \text{ mmHg in adults} \))
- HDL cholesterol \( \leq 35 \text{ mg/dl} \) and/or a triglyceride level \( \geq 250 \text{ mg/dl} \)
- History of GDM or delivery of a baby weighing \( >9 \text{ lbs} \)
- Polycystic ovary syndrome
**TYPE 1 VS. TYPE 2**

- **Type 1**
  - About 5-10% of all diagnosed
  - Formerly, Juvenile Diabetes
  - Most common in children or young adults, but can occur after the age of 30
  - Must use insulin to survive

- **Type 2**
  - About 90-95% of all diagnosed
  - Formerly, Adult Onset Diabetes
  - Most commonly diagnosed in adults, but increasing number of children with type 2
IMPORTANCE OF TIGHT GLYCEMIC CONTROL

- Diabetes Control and Complications Trial (DCCT)
  - Type 1
    - 1983-1993
  - 1441 patients randomized with either intensive or conventional (1-2 shots/day) of insulin
  - Intensive therapy = maintaining glucose concentrations near normal range
  - Results: >60% risk reduction for retinopathy, nephropathy, and neuropathy for intensive group, i.e., delay in onset and slow progression of these 3 major complications

- What about cardiovascular risk?
IMPORTANCE OF TIGHT GLYCEMIC CONTROL

- DCCT 17-year follow-up to assess incidence of **cardiovascular** disease (nonfatal MI, stroke, death from CV, confirmed angina, or need for coronary-artery revascularization)
  - Through February 2005
- Type 1 patients who are intensively managed for diabetes have reduced risk of cardiovascular disease (significantly linked to those patients who have a decrease in A1c)
  - December 22, 2005
- What about type 2?
IMPORTANCE OF TIGHT GLYCEMIC CONTROL

- United Kingdom Prospective Diabetes Study (UKPDS)
  - Over 5000 patients
  - Type 2
  - To study benefits of intensive pharmacological therapy
  - Results: retinopathy, nephropathy, and possibly neuropathy benefit with intensive therapy
  - Every % point decrease in A1c = 35% reduction in risk of microvascular complications
IMPORTANCE OF TIGHT GLYCEMIC CONTROL

- **UKPDS 10 year follow-up**
  - Patients asked to attend annual UKPDS clinics post-trial x 5 years
  - Years 6-10, questionnaires were used to assess
  - Between-group differences in A1c were lost after first year
  - Despite loss of glycemic differences, a continued reduction in microvascular risk and new risk reductions for MI and death from any cause were observed
IMPORTANCE OF TIGHT GLYCEMIC CONTROL?

ACCORD

- Randomized control trial
  - In type 2 diabetes patients who have established CV disease or additional CV risk factors, does intensive glycemic control targeting A1c <6% decrease CV risk compared to A1c target of 7-7.9%
  - 10,251 patients; Mean A1c 8.3%
  - Primary outcome = nonfatal MI or stroke or death from CV cause
  - Intensive glucose-lowering arm halted 18 months early due to increased risk for CV death & more all cause deaths
IMPORTANCE OF TIGHT GLYCEMIC CONTROL?

**ADVANCE**

- Is intensive glucose control (6.5% or lower) with a gliclazide regimen better than standard control with non-gliclazide regimen in high risk T2DM?
  - High risk = h/o major macrovascular or microvascular disease or at least one other risk factor for vascular disease
- 11,140 patients; Mean A1c 7.5%
- Primary endpoints = composites of major macrovascular (CV death, nonfatal MI, stroke) and major microvascular events (nephropathy or retinopathy)
- Intensive group had significant reduction in major microvascular events; no benefit on macrovascular outcomes
IMPORTANCE OF TIGHT GLYCEMIC CONTROL?

- VADT
  - 1800 subjects with type 2 diabetes assigned to standard vs. intensive glucose-lowering groups
    - 40% had previous CV event
  - Primary outcome = reduction in CV events (stroke, MI, severe HF, CABG, amputation, and CV death)
  - Followed for 6.25 years; no difference in CV events between intensive and standard groups
SUMMARY OF TIGHT GLYCEMIC CONTROL

- Lowering A1c reduces microvascular complications
- Lowering A1c early in the course of therapy reduces macrovascular risks (DCCT; UKPDS)
  - “Banks” benefit for years to come
- Intensively lowered A1c with target of 6.5% or less doesn’t reduce CV events in older type 2 diabetes patients with high risk for CV disease
  - Less aggressive goals might be better for older patients with heart disease
ADA STANDARDS OF CARE

- American Diabetes Association: Clinical Practice Recommendations 2009
  - www.diabetes.org
  - *Diabetes Care* 2009, Volume 32, Supplement 1
STANDARDS OF CARE-SUMMARY

- A1c goal < 7%; test every 3-6 months (point of care acceptable)
  - May target even lower A1c goals for some individuals without significant hypoglycemia
    - Short duration of diabetes, long life expectancy, no significant CVD

- Blood pressure goal <130/80; test at every visit
  - Preferred agents ACEI or ARBs
STANDARDS OF CARE-SUMMARY

- **Cholesterol-test annually**
  - Total cholesterol <200 mg/dL
  - LDL <100 mg/dL, <70 option for overt CVD
  - TG < 150 mg/dL
  - HDL > 40 men; >50 women; preferably >60
    - Statin use regardless of lipid levels
      - Overt CVD
      - Without CVD, over 40, one or more CVD risk factor

- **Microalbuminuria-test annually**

- **Serum creatinine-test annually (to estimate GFR)**
STANDARDS OF CARE-SUMMARY

- Dilated eye exam-test annually
- Foot exam
  - Visual exam every visit
  - Sensory exam annually
- Influenza vaccine annually; pneumococcal once before age 65, once after 65 (5 years apart)
- Individualized MNT by dietitian
- DSME when diagnosed and prn thereafter
- Aspirin 75-162 mg/day as primary prevention for increased CV risk
  - >40 yo OR
  - Additional risk factors (family history of CVD, HTN, smoking, dyslipidemia, albuminuria)
<table>
<thead>
<tr>
<th>Metric</th>
<th>Normal</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial plasma glucose</td>
<td>&lt;100 mg/dL</td>
<td>70-130 mg/dL</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>&lt;140 mg/dL</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>4-6%</td>
<td>&lt;7%*</td>
</tr>
</tbody>
</table>

Note: Normal = nondiabetic; goals = diabetic

*General goal for all persons; may be more aggressive in some individuals
NEW UPDATES 2009

- Standards of Care 2009
  - Revisions to SMBG
    - May be useful in non-insulin type 2 patient
  - Major revisions to Glycemic Control Section
    - READ: C. Glycemic Control section pages S17-S23 in Diabetes Care, Volume 32, Supplement 1, January 2009
    - Goal A1c <7%

- Medication Algorithm Update for Type 2
    - Rosiglitazone not recommended
    - Discontinue SFUs with insulin initiation
DIAGNOSIS

- FPG > 126 mg/dL (no caloric intake for at least 8 hours)-Preferred test
- Presence of symptoms (polyuria, polydypsia, and unexplained weight loss) plus a casual glucose concentration ≥ 200 mg/dL (casual – any time of day regardless of last meal)
- 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test (OGTT-75g load)
- All must be confirmed on a subsequent day

THERAPY OPTIONS

1) Lifestyle Intervention
   • Diet
     ○ Medical nutrition therapy (MNT) by a registered dietitian knowledgeable and skilled in diabetes management
   • Physical Activity
     ○ Regular physical activity programs for all patients with diabetes who are capable
     ○ 150 min/week mod-intensity aerobic activity
     ○ Resistance training 3x/week
     ○ Medical evaluation prior to physical activity
     ○ Benefits: improved blood glucose control, reduced CV risk factors, weight loss, improved well-being
   • Ultimate goal: weight loss
     ○ The most cost-effective means of controlling diabetes
     ○ Not often achieved or maintained long term

2) Medication Management

ADA Standards of Care, January 2008; Consensus Algorithm, Diabetes Care, August 2006
MEDICATION MANAGEMENT OF TYPE 2 DM

Classes

1. Sulfonylureas
2. Biguanides
3. Thiazolidinediones (glitazones)
4. Alpha-glucosidase inhibitors
5. Meglitinides
6. DPP-IV inhibitors
7. Combinations
8. Non-insulin injectables (amylin & incretin mimetics)
9. Insulins
## SULFONYLUREA AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Dose</th>
<th>Max Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second Generation</strong></td>
<td><strong>Glipizide (Glucotrol)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg QD in elderly; 5 mg qd others</td>
<td>40 mg/qd or bid</td>
<td>&gt;15 mg qd should be divided; 30 min ac</td>
</tr>
<tr>
<td><strong>Glyburide (Diabeta, Micronase)</strong></td>
<td>1.25 mg qd in elderly; 2.5 mg qd others</td>
<td>20 mg qd/ or bid</td>
<td>&gt;10 mg qd should be divided; caution in elderly predisposed to hypoglycemia</td>
</tr>
</tbody>
</table>
## SULFONYLUREA AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Dose</th>
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<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second Generation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>1-2 mg qd initially; 1-4 mg qd maint</td>
<td>8 mg qd</td>
<td>Lower hypoglycemia risk</td>
</tr>
<tr>
<td>Glipizide extended release (Glucotrol XL)</td>
<td>5 mg qd</td>
<td>20 mg qd</td>
<td></td>
</tr>
<tr>
<td>Micronized glyburide (Glynase)</td>
<td>1.5 mg qd</td>
<td>12 mg qd</td>
<td>&gt;6 mg qd should be divided</td>
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</tbody>
</table>
SULFONYLUREA PEARLS

- MOA: stimulate insulin secretion from the pancreas
- Hypoglycemia-most common ADR
- Elderly are most susceptible to hypoglycemia
- Weight gain due to insulin release
BIGUANIDES

- **MOA**
  - Primary: decreases gluconeogenesis (reduces hepatic glucose production)
  - Improve peripheral sensitivity to insulin
  - Does NOT stimulate release of insulin

- **Drug:**
  - Metformin (Glucophage)
  - Metformin extended-release (Glucophage XR, Fortamet)
METFORMIN DOSING

- Administered with meals
- **Metformin**
  - Initial: 500 mg qd or bid
  - Max: 2.5 g divided bid or tid
- **Metformin extended release**
  - Typical: 500-1000 mg qd with evening meal
  - Max: 1500-2000 mg qd
- **Supplied as:**
  - 500 mg; 850 mg; 1000 mg
  - 500 mg, 1000 mg XR
METFORMIN ADVERSE EFFECTS

- GI
  - Diarrhea, nausea, abdominal pain, metallic taste, anorexia
    - Resolution: slow titration, take with food, should resolve over time

- Lactic Acidosis
  - Symptoms: weakness, malaise, heavy labored breathing
  - High risk: renal, liver, or cardiorespiratory contraindications
METFORMIN CONTRAINDICATIONS AND PRECAUTIONS

- Renal impairment, hepatic disease, congestive heart failure requiring pharmacologic treatment, or h/o lactic acidosis are contraindicated
- GFR < 60 ml/min; SCr ≥ 1.4 for females or 1.5 for males
- Iodinated parenteral contrast dye-hold 48 hrs before and 48 hrs after procedure
METFORMIN PEARLS

- Not associated with weight gain (may be associated with weight loss)
- B12 deficiency?
- Obtain SCr and hepatic function tests at baseline
- Caution in elderly until renal function verified
THIAZOLIDINEDIONES (GLITAZONES)

- **MOA**
  - “Insulin sensitizer”
    - Decrease insulin resistance in muscle and liver, which enhances glucose utilization and decreases hepatic glucose output
TZD AGENTS

- Rosiglitazone (Avandia)
  - Initial dose: 4 mg qd
  - Max: 8 mg daily in single or divided doses
  - Wait 12 weeks before increasing dose
- Pioglitazone (Actos)
  - Initial: 15-30 mg qd
  - Max 45 mg qd
  - May increase dose in 3-4 weeks
TZD ADVERSE EFFECTS

- Hepatotoxicity
  - Very rare with these two agents
  - Led to Rezulin withdrawal from market in 2000
  - Monitoring recommended as precaution
- Weight gain-mild to mod
- Increased fracture risk (distal upper or lower limb)
- See next slide for CV risks

*Circulation. 2003;108:2941-2948*
TZD AND CARDIOVASCULAR RISK

- AHA/ADA Joint Statement: Precaution to use in patients at risk for CHF
  - Circulation 2003;108:2941-2948
  - Avoid in advanced heart disease or severe CHF
  - Patients should report weight gain of over 3 kg/6.6 pounds, sudden onset of pedal edema, fatigue, or dyspnea

- FDA Black box Warnings for TZDs and Heart Failure 8/14/07
  - Observe for sx/sx of heart failure (weight gain, SOB, edema)
  - Do not use in those with serious or severe heart failure
TZD AND CARDIOVASCULAR RISK

- Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes
  - N Eng J Med 2007;356
  - Meta-analysis using rosiglitazone and outcome data for MI and death from CV causes, 42 trials included
  - Increased the risk of MI; increase (not significant) risk of death from CV causes
- FDA Black box Warnings for Avandia and myocardial ischemia 11/2007
  - Available data on risk of myocardial ischemia (stroke, MI) are inconclusive
AVANDIA LABELING UPDATE

- November 2007
- Co-administration of Avandia and insulin as well as concomitant use of nitrates is not recommended
TZD DRUG INTERACTIONS

- Pioglitazone + oral contraceptives
  - Potential reduction of oral contraceptive efficacy
- Pioglitazone + ketoconazole
  - Ketoconazole inhibits metabolism of pioglitazone = higher pioglitazone concentrations
- Rosiglitazone-no major interactions
TZD PEARLS

- Product Information: "liver enzymes should be checked prior to initiation of therapy and periodically thereafter per the clinical judgment of the healthcare professional"
  - D/C if ALT>3 times normal
- BID rosiglitazone may produce better results than qd dosing
- Pioglitazone more favorable effects on lipids than rosiglitazone
- Monitor for sx/sx of CHF

Actos & Avandia PI Dec 2003 & Aug 2004, respectively
ALPHA-GLUCOSIDASE INHIBITORS

MOA

- Inhibition of enzymes (glucosidases) present in brush-border cells of the mucosa of the small intestine responsible for breakdown of complex polysaccharides and sucrose into absorbable monosaccharides
- Delay CHO absorption
- Results in a reduction of postprandial hyperglycemia
ALPHA-GLUCOSIDASE INHIBITOR AGENTS

- Acarbose (Precose)
  - Dose: 25-100 mg with first bite of each meal
  - Begin with 25 mg and increase by 25 mg/meal q 4-8 weeks
  - Max: 100 mg tid (if >60kg)

- Miglitol (Glyset)
  - Dose: same as acarbose
  - Max: 100 mg tid
ALPHA-GLUCOSIDASE INHIBITOR ADVERSE EFFECTS

- GI
  - Flatulence, diarrhea, and abdominal pain
  - Due to fermentation of unabsorbed carbohydrate in small intestine
  - Minimize with slow titration; effects seem to lessen over time
ALPHA-GLUCOSIDASE INHIBITOR PEARLS

- If hypoglycemia occurs in patients on these drugs, administer oral glucose vs. sucrose since absorption of sucrose will be blunted by these drugs
  - Buy glucose tablets vs. hard candies
- Many patients will find side effects intolerable
MEGLITINIDES/GLINIDIES

- **MOA**
  - Similar to sulfonylureas in action
  - Stimulate the release of insulin
  - Rapid onset and short duration of action require dosing with meals to enhance postprandial glucose utilization
  - Structurally unrelated to sulfonylureas
MEGLITINIDE AGENTS

- Repaglinide (Prandin)
  - Initially, 0.5 mg with each meal if A1c < 8%; Others begin with 1-2 mg/meal
  - Max: 5 mg with each meal-tid or qid

- Netaglinide (Starlix)
  - Initially, 120 mg tid; 60 mg tid for patients with near-normal A1c
  - Max: 120 mg tid
MEGLITINIDE PEARLS

- Can cause hypoglycemia
- Skip dose if meal is skipped—offers some flexibility
- More expensive than sulfonylureas
- Best for postprandial hyperglycemia
COMBINATION MEDS

- Glyburide/metformin HCL (Glucovance)
  - 1.25 mg/250 mg; 2.5 mg/500 mg; 5 mg/500 mg
- Rosiglitazone maleate and metformin HCl (Avandamet)
  - 1 mg/500 mg; 2 mg/500 mg; 4 mg/500 mg
- Glipizide/metformin HCl (Metaglip)
  - 2.5 mg/250 mg; 2.5 mg/500 mg; 5 mg/500 mg
- Pioglitazone/metformin (ACTOplus met)
  - 15 mg/500 mg; 15 mg/850 mg
- Rosiglitazone/glimepiride (Avandaryl)
  - 4 mg/1 mg; 4 mg/2 mg; 4 mg/4 mg
- Pioglitazone/glimepiride (Duetact)
  - 30 mg/2 mg; 30 mg/4 mg
- Sitagliptin/metformin (Janumet)
  - 50 mg/500 mg; 50 mg/1000 mg
- Prandimet
  - 1 mg/500 mg; 2 mg/500 mg
PRAMLIINTIDE ACETATE (SYMLIN)

- Pancreas co-secretes amylin and insulin from beta cells
- Amylin is absolutely or relatively deficient in patients with diabetes
- Amylin slows gastric emptying, reduces postprandial glucagon secretion, increases satiety
  - Therefore deficiency of amylin results in more fluctuations with blood glucose levels
PRAMINTIDE ACETATE (SYMLIN)

- Synthetic analog of human amylin
- Indication: Type 1 or 2 diabetes
  - Adjunct treatment in patients using mealtime insulin who have failed to achieve desired glucose control despite optimal insulin therapy
  - Decreases A1c by ~0.5-0.7%
- Contraindications
  - Known hypersensitivity to SYMLIN or components
  - Confirmed diagnosis of gastroparesis
  - Recurrent severe hypoglycemia in past 6 months
  - Hypoglycemia unawareness
  - A1c >9%
  - Pediatric patients
PRAMlintide Acetate (Symlin)

- Adverse effects: N/V, hypoglycemia
- Dose:
  - Type 1 diabetes
    - Starting dose: 15 mcg prior to meals
    - Titration: ↑ by 15 mcg if no nausea present for 3 days to max of 60 mcg (generally 30 or 60 mcg maintenance)
  - Type 2 diabetes
    - Starting dose: 60 mcg prior to meals
    - Reduce insulin by 50%
    - Titration: ↑ to 120 mcg when no nausea present for 3-7 days
SYMLIN PEARLS
- Do not mix with insulin
- Supplied as
  - 60 pen injector
    - Doses 15 mcg, 30 mcg, 45 mcg, 60 mcg
  - 120 pen injector
    - Doses 60 mcg, 120 mcg
  - Vials for use with insulin syringe (next slide)
- Store in refrigerator unopened, then in refrigerator or room temperature for up to 30 days after opened
- Mealtime insulin should be reduced by 50% when initiating Symlin
- If skip meal, skip Symlin
- Do not adjust the dose for physical activity
- Do not use with drugs that delay gastric emptying
### Symlin Pearls

<table>
<thead>
<tr>
<th>Dosage Prescribed (mcg)</th>
<th>Increment Using a U-100 Syringe (Units)</th>
<th>Volume (cc or mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>2½</td>
<td>0.025</td>
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<tr>
<td>30</td>
<td>5</td>
<td>0.05</td>
</tr>
<tr>
<td>45</td>
<td>7½</td>
<td>0.075</td>
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<tr>
<td>60</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>120</td>
<td>20</td>
<td>0.2</td>
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</tbody>
</table>
INCRETIN-BASED THERAPIES

- GLP-1 Receptor Agonist
- DPP-IV Inhibitors
INCRETINS OVERVIEW

- Intestinal hormones released after meal ingestion
  - Glucagon-like peptide 1 (GLP-1)
  - Glucose-dependent insulino tropic polypeptide (GIP)

- Released from the intestine in response to food ingestion
  - Produced by the L-cells of the small intestine and binds to the GLP-1 receptor on the pancreatic B-cells
  - GLP-1 and GIP cause release of insulin in response to glucose levels
  - GLP-1 also suppresses glucagon secretion from alpha cells in response to glucose levels, slows gastric emptying, reduces food intake

INCRETINS OVERVIEW

- GLP-1 and GIP are rapidly degraded by DPP-IV (dipeptidyl-peptidase 4) enzyme
  - Enzyme present on many cells & tissues
  - Half-life of GLP-1 < 2 minutes
  - Therapeutic use of human GLP-1 limited

- The incretin effect is diminished in type 2 diabetes
EXENATIDE (BYETTA)

- Similar to glucagon like peptide (GLP-1)
  - Enhances glucose dependent insulin secretion (increases synthesis & secretion), delays gastric emptying, and suppresses glucagon, reduces food intake
  - Derived from gila monster saliva (resistant to DPP-IV enzyme)
- Indications: As adjunctive therapy for patients with type 2 diabetes who have not achieved glycemic control while taking:
  - Metformin
  - A sulfonylurea
  - TZDs
EXENATIDE (BYETTA)

- Adverse effects: N/V, hypoglycemia; acute pancreatitis (postmarketing)
  - 8/18/08-FDA issued an update for 6 cases of hemorrhagic or necrotizing pancreatitis associated with 2 deaths

- Dose:
  - Begin at 5 mcg BID
    - Administer up to 60 minutes before morning and evening meals
    - Do not administer after meals
  - May increase to 10 mcg BID after 1 month
    - Dose should be adjusted based on clinical response and tolerability

- Dosage Forms:
  - 1.2 ml prefilled pen, 60 doses, 5 mcg/dose
  - 2.4 ml prefilled pen, 60 doses, 10 mcg/dose
BYETTA PEARLS

- Fixed doses for all patients
- Store in refrigerator then at room temperature for up to 30 days
- If suspected pancreatitis, discontinue
- Decreases A1c by ~ 0.5-1%
- Administer SQ in thigh, abdomen, or upper arm
- Induces feelings of satiety and causes weight loss
  - 5 lb weight loss at 30 weeks
  - 11 lb weight loss at 2.5 years
- Only works in the presence of hyperglycemia
- Byetta LAR (long acting release)-once weekly on horizon
DPP-IV INHIBITORS

- MOA: Lengthens the activity time of GLP-1 and GIP
- Sitagliptin (Januvia)-25 mg, 50 mg, 100 mg
  - 100 mg once daily
  - 50 mg, CrCl >30-<50 ml/min; 25 mg CrCl <30 ml/min
  - Monotherapy or combo with TZD, SFU or metformin
  - Flat dosing-no titration

SITAGLIPTIN (JANUVIA)

- Weight neutral
- Post-marketing information
  - Potential increased risk of angioedema with ACE inhibitors
  - Allergic/hypersensitivity reaction including Stevens-Johnson syndrome
INSULIN AGENTS-OVERVIEW

- Rapid-acting
  - Lispro (Humalog)
  - Aspart (NovoLog)
  - Glulisine (Apidra)

- Short-acting
  - Regular (Humulin R, Novolin R)
INSULIN AGENTS

- **Intermediate-acting**
  - NPH (Humulin N, Novolin N)
  - Lente (Humulin L, Novolin L)
    - Novolin L discontinued 2003
    - Humulin L discontinued 2005

- **Long-acting**
  - Ultralente-insulin Zn suspension, extended (Humulin U Ultralente)
    - Humulin U discontinued 2005
  - Insulin glargine (Lantus)
  - Insulin detemir (Levemir)
INSULIN AGENTS

- NPH/Regular mixture (70%/30%)
  - Humulin 70/30; Novolin 70/30
- NPH/Regular mixture (50%/50%)
  - Humulin 50/50
- Protamine susp/Lispro (75%/25%)
  - Humalog Mix 75/25
- Protamine susp/Aspart (70%/30%)
  - Novolog Mix 70/30
## INSULIN ACTIONS

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset (hr)</th>
<th>Peak (hr)</th>
<th>Duration (hr)</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro, aspart, glulisine</td>
<td>5-15 min</td>
<td>1-2</td>
<td>3-4</td>
<td>Clear</td>
</tr>
<tr>
<td>Regular</td>
<td>0.5-1</td>
<td>2-4</td>
<td>5-7</td>
<td>Clear</td>
</tr>
<tr>
<td>NPH</td>
<td>2-4</td>
<td>4-10</td>
<td>12-18</td>
<td>Cloudy</td>
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<tr>
<td>Glargine</td>
<td>1-2</td>
<td>2-20*</td>
<td>24</td>
<td>Clear</td>
</tr>
<tr>
<td>Detemir</td>
<td>0.8-2</td>
<td>3-9 *</td>
<td>Up to 24</td>
<td>Clear</td>
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</tbody>
</table>

*Peak not pronounced

BARRIERS TO INSULIN THERAPY
“PSYCHOLOGICAL INSULIN RESISTANCE”

- Need to mix and inject insulins
- Fear of needles & frequent monitoring
- Feelings of guilt and failure
  - HCP use as scare tactic
  - Fear of increased disease severity
- Complexity of starting insulin therapy
  - Inadequate time and personnel to teach insulin therapy

BARRIERS TO INSULIN THERAPY
“PSYCHOLOGICAL INSULIN RESISTANCE”

- Limitations of various insulin preparations
  - Inconvenient and embarrassing (timing)
- Physician and patient concerns about hypoglycemia
  - Extra burden on physician during initiation of therapy
  - Lack of proper education to patient regarding hypoglycemia
- Physician and patient concerns about weight gain
INSULIN ISSUES FOR TYPE 2 DIABETES

- Weight Gain
  - As glycemic control improves, glucose is captured by the body instead of being lost in the urine and promotes growth of adipose tissue
  - Single bedtime injections are not associated with significant weight gain
  - Metformin + bedtime insulin best minimizes weight gain
PATIENT EDUCATION

- Learn the patient’s barriers
- Provide education on weight gain
  - Dietitian involvement is important
- Consider stress and infection effects on glucose
- Provide education on hypoglycemia
  - Signs/symptoms
  - How to treat
  - Don’t overcorrect!
- Focus on short-term benefits
  - More energy, feel better
SO NOW WHAT?
MANAGEMENT OF HYPERGLYCEMIA IN TYPE 2 DM

Consensus Algorithm

- Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy
- A consensus statement from the ADA and the European Association for the Study of Diabetes
- Diabetes Care, Volume 29, Number 8, August 2006 (Original)
- Diabetes Care, Volume 31, Number 1, January 2008 (TZD update)
- Diabetes Care, Volume 31, Number 12, December 2008 (Revision)
## REVIEW OF MEDICATION OPTIONS

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Site of Action</th>
<th>Expected A1c ↓</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Pancreatic Beta cell</td>
<td>1-2%</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Glinides</td>
<td>Pancreatic Beta cell</td>
<td>1-1.5% (Repaglinide is more effective)</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Biguanides</td>
<td>Liver, muscle</td>
<td>1-2%</td>
<td>GI distress, lactic acidosis</td>
</tr>
<tr>
<td>α-glucosidase inhibitor</td>
<td>Intestine</td>
<td>0.5-0.8%</td>
<td>GI distress</td>
</tr>
<tr>
<td>TZD</td>
<td>Liver, muscle, fat</td>
<td>0.5-1.4%</td>
<td>Weight gain, edema</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Pancreatic Beta cell</td>
<td>0.5-1%</td>
<td>GI distress</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>Liver, gut</td>
<td>0.5-1%</td>
<td>GI distress</td>
</tr>
<tr>
<td>Insulin</td>
<td>Muscle, tissue</td>
<td>1.5-3.5%</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Gut hormones (alpha &amp; beta cells)</td>
<td>0.5-0.8%</td>
<td>Expensive</td>
</tr>
</tbody>
</table>
## STANDARDS OF MEDICAL CARE

### GLYCEM IC GOALS OF THERAPY

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Goal (ADA)</th>
<th>Goal (AACE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial plasma glucose</td>
<td>&lt;100 mg/dL</td>
<td>70-130 mg/dL</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td>Postprandial plasma glucose</td>
<td>&lt;140 mg/dL</td>
<td>&lt;180 mg/dL</td>
<td>&lt;140 mg/dL</td>
</tr>
<tr>
<td>A1c (%)</td>
<td>4-6%</td>
<td>&lt;7%*</td>
<td>&lt;6.5%</td>
</tr>
</tbody>
</table>

Note: Normal vs. Goals!
*Near normal for individual patients without hypoglycemia (<6%)

TYPE 2 DIABETES MANAGEMENT

- Goals & Emphasis of Algorithm
  - Achieve & maintain normal glycemic goals
  - Change interventions at as rapid a pace as titration of medication allows, if glycemic goals are not achieved or sustained
  - Add insulin early in patients who do not meet target goals
TYPE 2 MANAGEMENT: STEP 1

- Lifestyle intervention & metformin
- Titrate metformin to maximum dose over 1-2 months
  - 500 mg once/twice daily; increase to 850-1000 mg twice daily in 5-7 days
- Lifestyle interventions should remain a focus throughout diabetes management

Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. Diabetes Care, V31, Number 12, December 2008, 1-11
TYPE 2 MANAGEMENT: STEP 2

- Additional Medications
  - Add within 2-3 months of initial therapy or any time A1c goal is not achieved
  - Tier 1: Choose basal insulin or a sulfonylurea
    - Determined by A1c level
    - Consider costs and adverse effects
    - If A1c > 8.5%, initiate insulin
  - Other medications may be considered in Step 2 based on individual patient needs
    - Tier 2: pioglitazone or GLP-1 agonist (consider hypoglycemia risk to choose Tier 2)
    - Rosiglitazone is not recommended
TYPE 2 MANAGEMENT: STEP 3

- Further adjustments
  - Start or intensify insulin
    - May require additional injections including short or rapid acting insulin before meals
  - If A1c close to goal (<8%), consider 3rd oral agent
  - Discontinue insulin secretagogues (sulfonylurea or glinides) when insulin is started, since they are not considered to be synergistic
  - Tier 2
    - Lifestyle + met+pioglitazone+SFU
ROLE OF INSULIN IN TYPE 2

- **UKPDS**
  - Approximately 6 years after diagnosis, ~50% of patients with type 2 required long-term insulin to sustain glycemic control

- Insulin therapy may also improve peripheral insulin sensitivity
  - Even short-term insulin therapy seems to result in long-term control improvement if given in early diabetes stages
  - Has lead to many experts advocating “early insulinization” to preserve β cell function and improve long-term control
BASAL INSULIN INITIATION & ADJUSTMENTS

- Start with bedtime intermediate-acting or bedtime/morning long-acting insulin (NPH or detemir/glargine)
  - Initiate 10 units or 0.2 units per kg
- Check fasting glucose daily
  - OPTION 1: Increase by 2 units every 3 days until fasting in target range; can increase by larger increments (e.g., 4 units) every 3 days if fasting >180
  - OPTION 2: Treat to Target Trial adjusted weekly based on FPG from preceding 2 days (glargine or detemir)
    - >180 mg/dL, add 8 units
    - 140-180 mg/dL, add 6 units
    - 120-140 mg/dL, add 4 units
    - 100-120 mg/dL add 2 units

BASAL INSULIN ADJUSTMENTS

- Management options for hypoglycemia
  - Identify the causes
  - OPTION 1: Reduce dose by 4 units or 10% whichever is greater
  - OPTION 2: Treat-to-Target. Do not increase dose that week. Reduce 2-4 units, if desired.
- If fasting is in target range (70-130) and A1c is above goal, check pre-prandial glucose levels for consideration of prandial insulin.

ONCE/TWICE DAILY PREMIXED INITIATION AND ADJUSTMENTS

- 6 Units BID if FPG > 180 mg/dL or 5 Units BID if FPG < 180 mg/dL
- Weekly titration based on last 3 days based on preprandial glucose readings
- Adjust pre-breakfast dose based on pre-supper value
- Adjust pre-supper dose based on pre-breakfast value

<table>
<thead>
<tr>
<th>Most values (last 3 days)</th>
<th>Dosage Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80</td>
<td>-2 units</td>
</tr>
<tr>
<td>80-110</td>
<td>No change</td>
</tr>
<tr>
<td>111-140</td>
<td>+2 units</td>
</tr>
<tr>
<td>141-180</td>
<td>+4 units</td>
</tr>
<tr>
<td>&gt;180</td>
<td>+6 units</td>
</tr>
</tbody>
</table>

DAWN VS SOMOGYI

- If AM hyperglycemia, check 3 AM BG
  - If BG elevated
    - Increase evening NPH (Dawn)
    - Move NPH to HS (TID regimen)
  - If BG low
    - Decrease evening NPH (Somogyi)

- Would mainly apply to patients who are already on insulin vs. initiation of insulin
BASAL-BOLUS INSULIN INITIATION AND ADJUSTMENTS

- Most patients with type 2 DM do not start out on basal-bolus regimen
- Most common situations
  1. Adding mealtime insulin to background regimen
  2. Moving from premixed insulin to basal-bolus (more complex insulin regimen)
BASAL-BOLUS INSULIN ADDING MEALTIME BOLUS TO BASAL

- If fasting in range, check pre lunch, dinner, and bedtime
- Add 2\textsuperscript{nd} injection if needed depending on results
- Add 4 units of rapid or regular before meal
  - Increase by 2 units every 3 days until in range
  - Pre-lunch out of range, add rapid at breakfast
  - Pre-dinner out of range, add rapid at lunch or NPH at breakfast
  - Pre-bed out of range, add rapid at dinner
INSULIN THERAPY-PEARLS

- Take patient factors into consideration
- No standards to initiate and adjust insulin
  - Goal is get <7% as fast as possible!
- Choosing rapid vs. regular
- Cost issues
  - Rapid vs. regular; NPH vs. glargine; lancets & test strips
MINI-CASE #1

- 57 year old male
- A1c 8.2%
- Newly diagnosed with type 2 diabetes
- Medications at this visit?
MINI-CASE #2

- 48 year old female, type 2 diabetes
- A1c 7.7%
- Currently on metformin XR 2 grams daily at bedtime
- Next step?
- What if she tells you she is a bus driver and will lose her job if she has low blood sugar?
THE CASE OF AMY FERRY-PART 1

- See Handout for Assessment & Workup (Homework)
- Assess your patient
  - A1c = 6.4%
  - Lipids above ADA goals of therapy
  - Blood pressure does not meet ADA goals of therapy
THE CASE OF AMY FERRY-PART 1

- Drug therapy problems
  - Needs Additional Drug Therapy
    - Lipid management-statins
    - ASA
    - ACE inhibitor
  - Dose too low
    - Fish oil (3-5 grams DHA+EPA/day)
    - Most capsules contain 300-500 mg/capsule
    - Will need 10-12 capsules/day to meet requirements for triglyceride reduction
- No microalbuminuria screen or foot exam
THE CASE OF AMY FERRY-PART 1

- **Plan**
  - Simvastatin 20 mg daily
    - Reassess lipid panel in 6 weeks
  - Increase fish oil dose for triglyceride reduction
    - 2-4 grams EPA+DHA/day
  - Lisinopril 10 mg daily
    - Reassess blood pressure in one week
  - ASA 81 mg daily
  - Perform sensory foot exam
  - Download blood glucose meter
  - Provide pneumonia vaccination

- **Follow-up**
  - 2 months for resolution of drug therapy problems
THE CASE OF AMY FERRY-PART 2

• 18 months from initial date
• Assess your patient
  • A1c = 7.9%
  • Meds same as last visit except Simvastatin 80 mg daily, lisinopril/HCTZ 20/12.5 mg daily, & ASA 81 mg daily
  • Blood pressure & lipids meet goals of therapy
  • Needs a flu shot
  • Had annual microalbuminuria screen, serum creatinine, & foot exam all WNL
THE CASE OF AMY FERRY-PART 2

- **Assessment, continued**
  - Drug therapy problems
    - Needs additional drug for glucose control

- **Plan**
  - 3rd oral agent or insulin?
    - Assess patient factors such as cost, willingness to inject insulin, risks/benefits of orals available, current A1c
    - Options: sitagliptin?, TZDs?, glinides?, alpha glucosidase inhibitor?, basal insulin?

- **Follow-up**
  - When? What are your goals of therapy?
THE CASE OF AMY FERRY-PART 3

- 5 years from initial visit
- Assess your patient
  - A1c = 8.7%
  - Meds same as 18 month visit except now on 3rd oral agent, pioglitazone 45 mg daily
  - Blood pressure & lipids meet goals of therapy
  - Up to date on vaccines
  - Had all other annual labs/preventive care tests
THE CASE OF AMY FERRY-PART 3

Assessment, continued
- Drug therapy problems
  - Needs additional drug for glucose control

Plan
- Initiate basal insulin therapy
  - Which one? Detemir, glargine, or NPH?
  - 10 units qhs
  - Monitoring parameters-fasting glucose
  - Discontinue orals?
  - Education (hypoglycemia, insulin teaching, reinforce monitoring)

Follow-up
- When? What are your goals of therapy?
THE CASE OF AMY FERRY-PART 4

- 1 week from last visit
- Assess your patient
  - Review glucose log
  - Fasting levels x 7 days
    - 177, 169, 188, 159, 166, 174, 183
    - Average = 174 mg/dL
  - No signs/symptoms of hypoglycemia, none recorded
- Assess injection site

- Plan
  - Increase dose by 2 units
  - Patient to call/email in 3 days with fasting results or have patient adjust 2 units every 3 days
  - Reinforced sx/sx hypoglycemia and appropriate treatment
THE CASE OF AMY FERRY-PART 5

- 6 months from Part 4
- Assess your patient
  - A1c = 7.4%
  - Fasting levels average 107 mg/dL
  - No sx/sx hypoglycemia
  - Current insulin dose 48 units qhs glargine
  - Patient’s largest meal is supper
- Plan
  - Add 4 units rapid or regular before supper
  - Check pre-bed readings x 3 days
  - Call/email in 3 days with results
  - Reinforce sx/sx hypoglycemia and appropriate treatment
THE CASE OF AMY FERRY-PART 6

- 3 days from last visit
- Assess your patient
  - Patient emails pre-bedtime results x 3 days
  - Average = 220
  - No hypoglycemia
- Plan
  - Increase rapid/regular by 2 units
  - Continue to monitor and report results every 3 days
THE CASE OF MARK SMITH-PART 1

- Patient referred from primary physician requesting initiation of 70/30 insulin (NPH/regular)
- See Handout for Assessment & Workup
- Drug Therapy Problems
  - Needs additional drug for glucose management
  - Dose too low for blood pressure control
- Plan
  - Increase losartan to 100 mg daily
  - Discontinue glyburide when initiating insulin
  - Initiate insulin
THE CASE OF MARK SMITH - PART 1

- Plan, continued
  - Begin with 6 units before breakfast; 6 units before supper
  - 70/30 NPH/regular less expensive than regular (note differences between rapid & regular)
  - Patient ed
    - 30-45 minutes before meals
    - Meals on regular schedule
    - Insulin injection technique
    - Hypoglycemia management
    - Monitoring pre-breakfast and pre-supper

- Follow-up
  - One week for insulin adjustments & inspection of injection site, face to face
INSULIN AGENTS

- NPH/Regular mixture (70%/30%)
  - Humulin 70/30; Novolin 70/30
- NPH/Regular mixture (50%/50%)
  - Humulin 50/50
- Protamine susp/Lispro (75%/25%)
  - Humalog Mix 75/25
- Protamine susp/Aspart
  - Novolog Mix 70/30; Novolog 50/50
1 week from last visit

Assess your patient

- Prebreakfast average: 221 mg/dL
- Presupper average: 267 mg/dL
- No hypoglycemia
- Injection site normal

Plan

- Increase prebreakfast by 6 units; increase presupper by 6 units
MANAGEMENT OF HYPOGLYCEMIA

- Blood glucose < 70 mg/dL
- Blurred vision, sweaty palms, generalized sweating, tremulous, numbness
- “Rule of 15”
- 15 g rapid CHO; repeat in 15 min if <60 mg/dL or if symptomatic; follow with complex CHO/protein snack
  - 10-15 g CHO
    - ½ c (4 oz) OJ or regular soda; 1/3 c apple juice; ¼ c grape juice; 2 tsp sugar or 2 cubes; 5-6 Lifesavers; 2-4 glucose tablets; 2 Tbsp raisins; 1 Juicy Juice box
  - Unconscious: 1 mg SC, IM, or IV of Glucagon
HYPOGLYCEMIA

- Consider following changes if recurring:
  - Decreasing dose of causative oral agent or insulin
  - Add snack before activities and during times of high risk
  - Schedule activities for times when hypoglycemic risk is lower

- Recurring hypoglycemia should not be tolerated, especially with oral agents
  - Make changes to prevent
RESOURCES

- [www.diabetes.org](http://www.diabetes.org)
  - ADA
- [www.aadenet.org](http://www.aadenet.org)
  - American Association of Diabetes Educators
- [www.niddk.nih.gov](http://www.niddk.nih.gov)
  - Nat’l Institute of Diabetes & Digestive & Kidney Diseases
- [www.cdc.gov/diabetes](http://www.cdc.gov/diabetes)
- [www.ncbde.org](http://www.ncbde.org)
  - National Certification Board for Diabetes Educators
- [www.ndep.nih.gov](http://www.ndep.nih.gov)
  - National Diabetes Education Program