Antiglycemic Therapy in the Age of Comparative Effectiveness: Is Newer Better?
Objectives

- Review FDA approved Diabetic medications
- Discuss treatment options for Type 2 diabetes
Treatment

- Exercise
- Weight loss
- Education
Therapy for Type 2 Diabetes: Sites of Action

Pancreas
Impaired Insulin Secretion = Insulin Deficiency
- ↑ Sulfonylurea
- ↑ Repaglinide/Nateglinide
- Exogenous Insulin Rx

Gut
Carbohydrate Metabolism
- ↓ Acarbose
- ↓ Miglitol

Liver
Hepatic Glucose Production
- ↓ Metformin

Muscle
Glucose Uptake = Insulin Resistance
- ↑ Rosiglitazone
- ↑ Pioglitazone
Interact with ATP-sensitive potassium channels in the beta cell membrane to increase secretion of insulin (secretagogues)

- First generation – have fallen out of favor
  - acetohexamide (Dymelor®)
  - chlorpropramide (Diabinese®)
  - tolazamide (Tolinase®)
  - tolbutamide (Orinase®)
- Second generation –
  - Glimepiride (Amaryl® – 1 to 4 milligrams once a day), Glipizide (Glucotrol® or Glucotrol XL® – 5 to 20 milligrams once a day or divided),
  - Glyburide
    - (Diabeta®, Micronase® – 1.25 to 20 milligrams daily, Glynase® – 3 to 12 milligrams once a day or divided)
Sulfonylureas

- Side effects – hypoglycemia and weight gain
- Can be used with metformin, alpha glucosidase inhibitors, TZD’s, insulin
- Average HbA1C reduction – 1.0 to 2.0
- Metabolized hepatically and cleared renally
- Fast onset – 1–2 weeks
Biguanides (1995)

- Decrease hepatic glucose production
- Decrease insulin resistance
- Lower triglycerides, LDL, and total cholesterol, may slightly increase HDL
- Can lead to modest weight loss
- Most common side effects— GI side effects (abdominal pain and diarrhea), lactic acidosis
- Can interfere with B12 absorption but very rarely is associated with anemia
Biguanides

- Metformin (Glucophage®) – 500 to 2550 milligrams in divided doses or Glucophage XR® in 1500milligrams to 2000milligrams once a day
  - Contraindicated in
    - females with creatinine of 1.4 or greater,
    - males with creatinine of 1.5 or greater,
    - in either males or females with creatinine clearance less than 60
    - in patients with CHF, liver failure, alcohol abuse, history of metabolic acidosis
  - Should be discontinued
    - the day before patients undergo contrast studies and should not be restarted for 48 hours after the study
    - Should be discontinued in hospitalized patients
  - Consider stopping in patients > 70 and certainly > 80 years old
Biguanides

- Can be used with sulfonylureas, TZD’s, insulin and alpha glucosidase inhibitors

- Expected HbA1C reduction – 1.0 to 2.0
Meglitinides (1998)

- Also bind to ATP-sensitive potassium channels on beta cells and increase insulin release (non sulfonylurea secretagogues)

- Repaglinide (Prandin®) – 0.5 milligrams to 4 milligrams tid with meals

- Nateglinide (Starlix®) – 60 to 120 milligrams tid with meals

- Rapid absorption and peak within 30 to 60 minutes after eating and return to baseline prior to next meal
Meglitinides (1998)

- More expensive than sulfonylurea secretagogues
- Can cause hypoglycemia and weight gain
- Can be used with metformin or TZD
- Average HbA1C reduction – 0.5 to 1.5
Thiazolidinediones (TZD–1997)

- Decrease insulin resistance
  - bind to PPARγ (peroxisome proliferator–activated receptor gamma)
  - PPARγ upon activation ultimately alters transcription of genes regulating CHO and lipid metabolism
Thiazolidinediones (TZD–1997)

- Pioglitazone (Actos®– 15 to 45 milligrams once a day)
- Rosiglitazone (Avandia®– 2 to 8 milligrams once a day or divided)
- Side effects– weight gain, edema
- Increase HDL, decrease triglycerides (may slightly increase LDL)
- Expected reduction in HbA1C–1.0–2.0
- Slow onset– 2–3 months
Thiazolidinediones (TZD)

- Can cause anemia and hepatotoxicity
- Contraindicated in class III and IV CHF, CAD and liver disease
- Check LFTs at baseline and then periodically
- Discontinue if ALT > 3 times the ULN (upper limit of normal)
- Approved for use with metformin, sulfonylureas, and glinides
- Avandia–per PI, increased risk of MI has been observed, coadministration with insulin is not recommended
Alpha–Glucosidase Inhibitors (1996)

- Acarbose (Precose®)– 50 to 100 milligrams tid with meals
- Miglitol (Glyset®)– 50 to 100 milligrams tid with meals
- Interfere with the hydrolysis of carbohydrates and delay absorption of glucose and other oligosaccharides or disaccharides
- Side effect– diarrhea, abdominal pain, flatulence
- Contraindications– cirrhosis/liver dysfunction, chronic intestinal diseases
Alpha-Glucosidase Inhibitors (1996)

- Acarbose—possible increase in liver associated enzymes
- Monotherapy or with sulfonylurea, metformin, TZD (thiazolidinedione) or insulin
- Typical HbA1C reduction (0.5–0.8), reduce FBG up to 15mg/dl, reduce PPBG up to 50mg/dl
Amylin (2005)

- Polypeptide co-secreted with insulin
- Symlin® (Pramlintide) – analog of amylin with 3AA substitutions
- Decreases post-prandial hyperglycemia
- Decreases gastric emptying, decreases appetite
- Decreases glucagon secretion
- Adjunct for patients using mealtime insulin and have failed to achieve glucose control
Amylin

- Pramlintide acetate (Symlin®)– synthetic analog of human amylin
- Approved for use with Type 1 or Type 2 DM
- SQ injection– Type 1: start with 15 microgram before meals, titrated up by 15 microgram intervals to max of 60 micrograms
  
  Type 2: start with 60 micrograms before meals and increase to 120 micrograms at max
Amylin

Can be used with metformin or SU

Decrease preprandial insulin by 50% while adding Symlin®

Side effects—nausea, vomiting, anorexia, headache, hypoglycemia

Contraindicated in patients with gastroparesis
Exendin-4 (2005)

- Exenatide (Byetta®)– incretin mimetic and synthetic exendin-4 (hormone in saliva of Gila monster)– similar to GLP-1 (glucagon like peptide)

- GLP-1 stimulates insulin secretion without hypoglycemia (upregulates beta cells) and causes delay in gastric emptying and inhibits glucagon secretion
Approved for use with Type 2 DM on metformin, sulfonylurea, or TZD

SQ injection given within one hour before eating, start with 5 micrograms bid and increase to 10 micrograms over one month

Not to be given if ESRD or severe GI disease

Side effects—nausea, weight loss
Reduces HbA1c ~1

Acute pancreatitis risk: counsel patients regarding symptoms of pancreatitis and stop the drug if pancreatitis occurs

Do not use in patients with a history of pancreatitis
DPP-4 Inhibitor (2006)

- Sitagliptan (Januvia®)–inhibits DPP-IV which is an enzyme responsible for breaking down GLP-1

- 100mg, 50mg and 25mg tablets

- CrCl >50 use 100mg, CrCl 30–50 use 50mg, CrCl <30 use 25mg
Januvia®

- FDA approved with metformin, sulfonylureas and TZD’s (specifically Actos on the PI)

- Per PI, has not been studied with insulin

- DM 2 only

- Can cause runny nose, sore throat, headache, or hypersensitivity reaction including anaphylaxis, angioedema, and Stevens Johnson syndrome)
Fixed Combinations

- **Glucovance®** (glyburide plus metformin- 1.25/250, 2.5/500, 5/500)
- **Metaglip ®**(glipizide plus metformin–2.5/250, 2.5/500, 5/500)
- **Avandamet®** (avandia® plus metformin– 1/500, 2/500, 4/500, 2/1000, 4/1000)
- **Duetact®** (actos® plus glimepiride)–30mg/2mg, 30mg/4mg
- **Avandaryl®** (avandia® plus glimepiride)– 4mg/1mg, 4mg/2mg, 4mg/4mg
- **Actoplusmet®** (actos® plus metformin)–15mg/500mg, 15mg/850mg
- **Janumet®** (januvia® plus metformin) 50mg/500mg, 50mg/1000mg
- **Prandimet®** (Prandin® plus metformin) 1mg/500mg, 2mg/500mg
DM 2 Treatment

- Type 2 with new onset and fasting glucose >250, random glucose >300 or HgA1c >10 often have islet cell stunning
  - need insulin for two to three months

  - will probably adjust to oral medications after the two to three month period

  - Follow newly diagnosed diabetics and diabetics who are uncontrolled closely and frequently (weekly or more often if severe elevations of blood glucose are present)
In selecting medications, consideration must be given to:

- efficacy
- contraindications
- drug interactions
- side effects
- cost
- patient preferences
DM 2 Treatment

- Start with Lifestyle changes and education
- start on Metformin 500mg bid with meals and increase to 1000mg bid with meals
- If goal not met, add sulfonylurea or a basal insulin
- Can consider using TZD’s, alpha glucosidase inhibitors, meglitinides, DPP–4 inhibitors or GLP–1 agonists for those patients intolerant of metformin or sulfonylurea or in patients with contraindications to metformin or sulfonylureas
DM 2 Treatment– Insulin

- Insulin– discovered in 1922– Nobel prize to Banting and Macleod in 1923
- Protamine Zinc Insulin– 1930’s
- Neutral Protamine Hagedorn (NPH)–1940’s
- Lente Insulin– 1950’s
- Recombinant DNA Insulin–1978 (no more stockpiles of animal pancreases)
- Novolog Mix 70/30–(2001)
DM 2 Treatment—Insulin

[Graph showing relative insulin levels over time for glargine injection]
DM 2 Treatment – Insulin

![Graph showing insulin levels over time]

- **Relative Insulin Level**
- **Time (hours after injection)**
- **NPH**
DM 2 Treatment—Insulin
DM 2 Treatment – Insulin
Insulin dosages must be individualized according to:

- Type of diabetes
- Age
- Weight (presence or absence of obesity)
- Co-morbid conditions
- Concomitant medications
- Patients ability to perform SMBG and inject the insulin
- Complexity of the management strategy (e.g. number of injections and CHO counting)
- Risks of hypoglycemia
- Magnitude and pattern of hyperglycemia
Consider insulin when:
- Significant hyperglycemia—fasting glucose $>250$, random glucose $>300$ and/or HbA1c $>10$
- Hyperglycemia despite maximal oral medications
- Acute injury, stress, infection, surgery
- Pregnancy
DM 2 Treatment– Insulin

- When adding insulin, start with PM dose with Lantus® or Levemir® or NPH at 5 to 10 units (0.1 to 0.2U/kg/day)
- Increase every two to five days until target of <120mg/dl is met (fasting)
- Once fasting glucose is at or lower than 120mg/dl, consider adding rapid acting insulin (Novolog®, Humalog® or Apidra®) to help with high postprandial glucoses (If cost/formulary considerations are paramount, regular insulin can be used)
DM 2 Treatment – Insulin

- Daily insulin dose is 0.5 to 1 U/kg/day (higher depending on insulin resistance)
- Basal bolus with Lantus® or Levemir® or NPH
  - Lantus® or Levemir® or NPH 50% of total at bedtime
  - Novolog®/Humalog®/Apidra® (or regular insulin) 50% of total divided tid with meals
  - Total of 4 injections per day – Lantus® or Levemir® or NPH plus short acting insulin with meals
If the patient will comply with multiple daily injections of insulin...
- Lantus® or Levemir® or NPH at bedtime (roughly ½ the total daily dose of insulin)
- Aspart (NovoLog®), Lispro(Humalog®) or Glulisine (Apidra®) or regular pre-meal (added up for the other ½ of the total daily dose)
If the patient will not give multiple injections, and clearly needs some pre–meal insulin…
  ◦ Pre–mixed insulin is reasonable approach
  ◦ e.g., 70/30 insulin before breakfast and dinner
Make adjustments based on FS data

- Take weekly averages of pre-breakfast, pre-lunch, pre-supper, and bedtime FS measurements

- Adjust appropriate insulin dose based on where “high” FS averages are occurring
  - If highs are everywhere, then increase all dosages

- Patients can also self-titrate their insulin dosages themselves based on their own observations
Common mistake – pts are often “over-basaled” and “under-bolused”
  ◦ e.g., Glargine (Lantus®) 60 units, Aspart (NovoLog®) 5 units pre-meal
  ◦ Leads to hypoglycemia if patient misses a meal
  ◦ The Glargine (Lantus®) dose should be roughly equivalent to the sum of the pre-meal insulins
  ◦ Would be appropriate to change this patient’s insulin regimen to Glargine (Lantus®) 30–40 units, and Aspart (NovoLog®) 10–15 units pre-meal
U–500 (1952)

- Consider when total insulin need is >200 units per day

- U–500 = 500 units per ml

- 100 units of U–500 is 1/5 of a 1ml syringe or 0.2ml

- We write “100 units of U–500 insulin which is equal to 20 units in a 0.5ml syringe”
Use bid for total daily doses <300 units (50–60% am and 40–50% pm)

Use tid for total daily doses 300–600 units

Consider QID for total daily doses >600 units
DM 2 Treatment– Insulin

- NPH regimen– 2/3 of total daily dose in AM and 1/3 of total daily dose in PM
  - AM– 2/3 NPH and 1/3 regular
  - PM– 1/2 NPH and 1/2 Regular (best if Regular is taken with supper and NPH at bedtime)
  - Example– total daily dose of 36 units (2/3 = 24 units and 1/3 = 12 units
    - AM– 16 units NPH and 8 units Regular
    - PM– 6 units NPH and 6 units Regular
Prevention

- Diet
- Exercise
- Education
So is newer better?
Sometimes “yes” and sometimes “no”

- Newer
  - Extend the armamentarium
  - Provide other options
  - Address newer concepts like β-cell preservation
  - Remain relatively expensive
  - Long term safety and efficacy data uncertain
So is newer better?
Sometimes “yes” and sometimes “no”

- In selecting medications, consideration must be given to:
  - efficacy
  - contraindications
  - drug interactions
  - side effects
  - cost
  - patient preferences