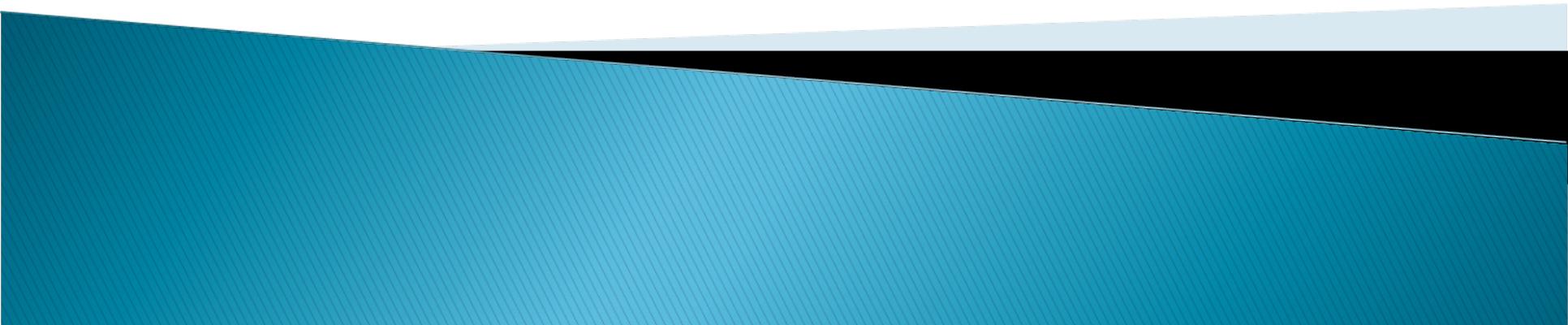


Antiglycemic Therapy in the Age of Comparative Effectiveness: Is Newer Better?



Objectives

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

Treatment

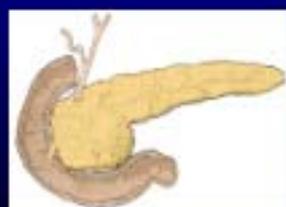
- ▶ Exercise
- ▶ Weight loss
- ▶ Education



Therapy for Type 2 Diabetes: Sites of Action

Pancreas

Impaired Insulin Secretion = Insulin Deficiency

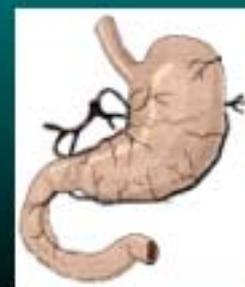


↑ Sulfonylurea
↑ Repaglinide/Nateglinide
Exogenous Insulin Rx

Gut

Carbohydrate Metabolism

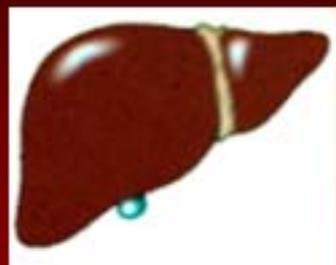
↓ Acarbose
↓ Miglitol



Hyperglycemia

Liver

↑ Hepatic Glucose Production

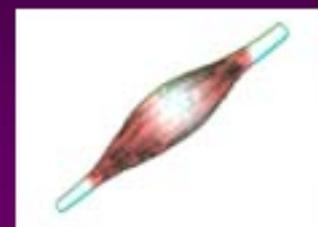


↓ Metformin

Muscle

↓ Glucose Uptake = Insulin Resistance

↑ Rosiglitazone
↑ Pioglitazone



Sulfonylureas(1950's)

- ▶ 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
- 

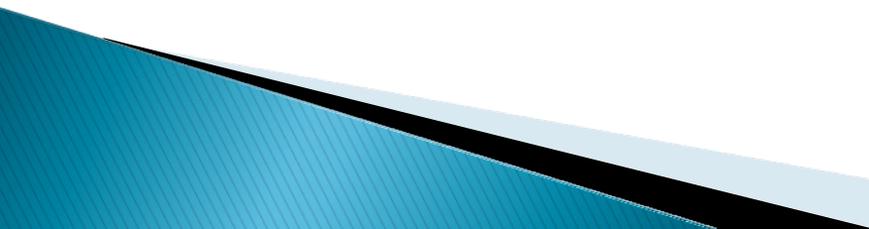
Biguanides(1995)

- ▶ 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

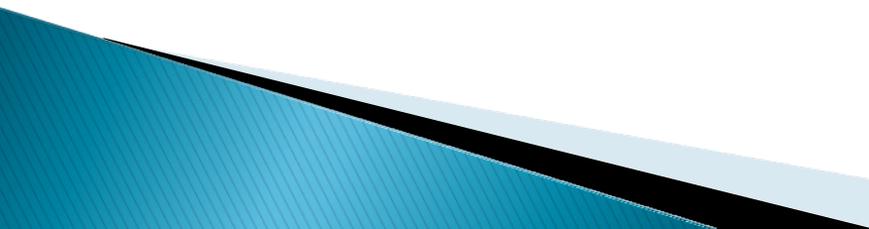
Biguanides

- ▶ 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

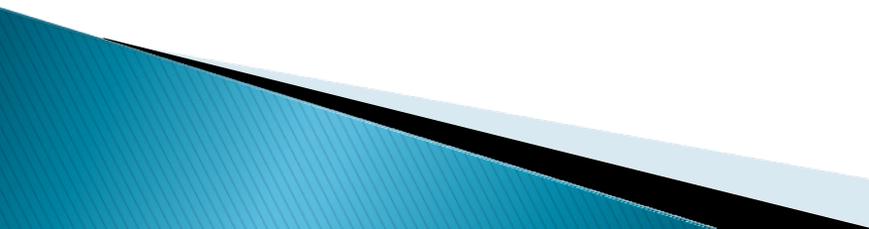
Meglitinides(1998)

- ▶ 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 PPAR γ (peroxisome proliferator-activated receptor gamma)
 - PPAR γ upon activation ultimately alters transcription of genes regulating CHO and lipid metabolism

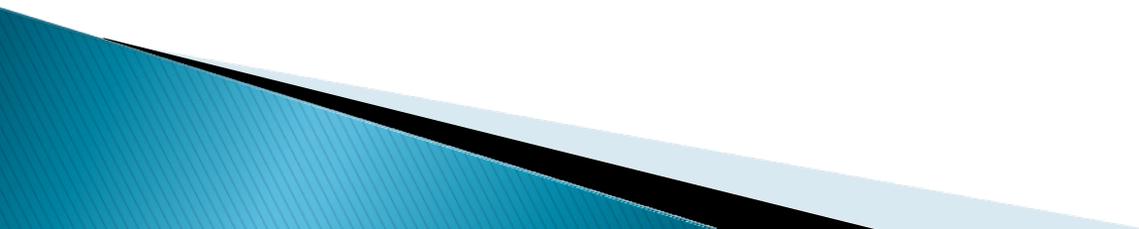
Thiazolidinediones (TZD-1997)

- ▶ 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
- 

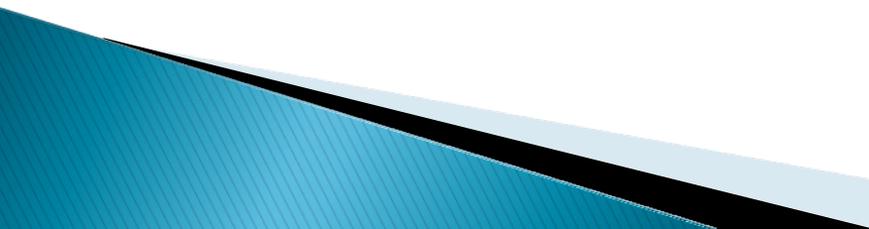
Thiazolidinediones (TZD)

- ▶ 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

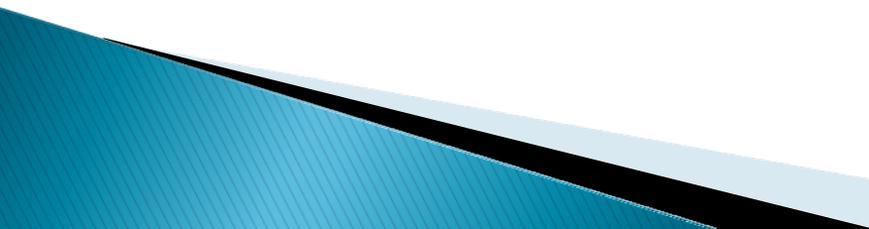
Alpha-Glucosidase Inhibitors(1996)

- ▶ 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[®] (Pramlinitide) – 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

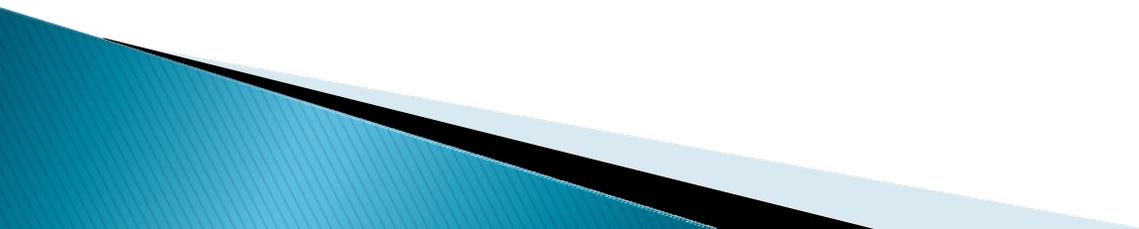
Can be used with metformin or SU

Decrease preprandial insulin by 50% while adding Symlin[®]

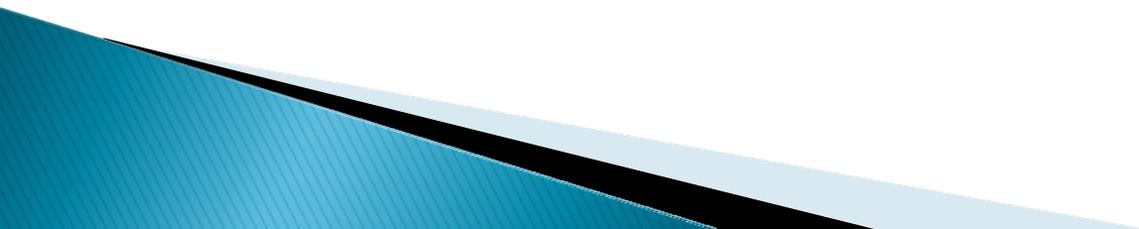
Side effects– nausea, vomiting, anorexia, headache, hypoglycemia

Contraindicated in patients with gastroparesis

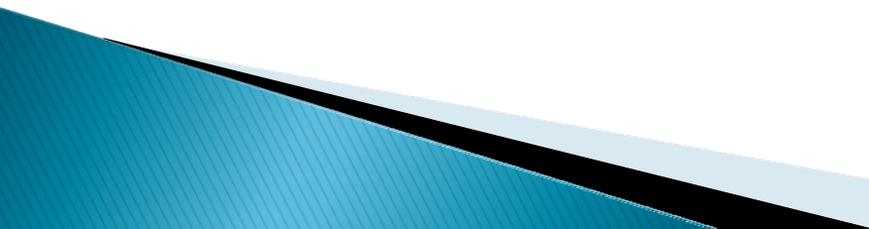
Exendin-4 (2005)

- ▶ 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
- 

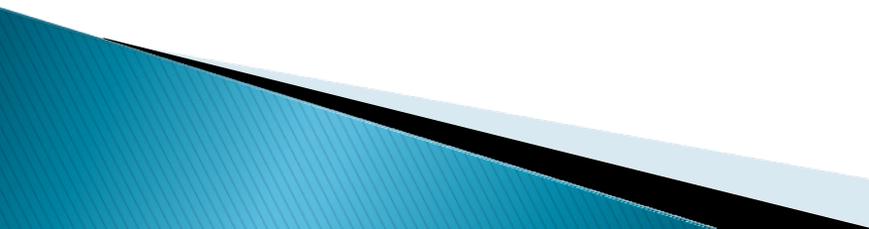
Byetta®

- ▶ Approved for use with Type 2 DM on metformin, sulfonylurea, or TZD
 - ▶ SQ injection given within one hour before eating, start with 5micrograms bid and increase to 10micrograms over one month
 - ▶ Not to be given if ESRD or severe GI disease
 - ▶ Side effects–nausea, weight loss
- 

Byetta®

- ▶ 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/1 mg, 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)

DM treatment

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

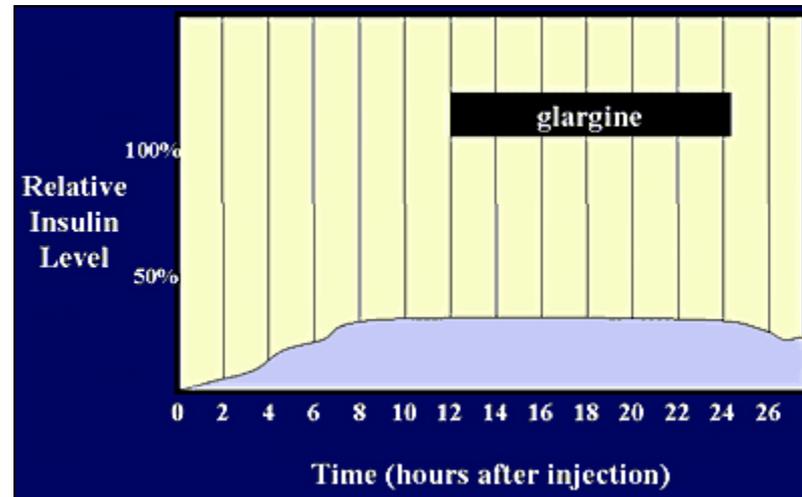
DM 2 Treatment

- ▶ 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

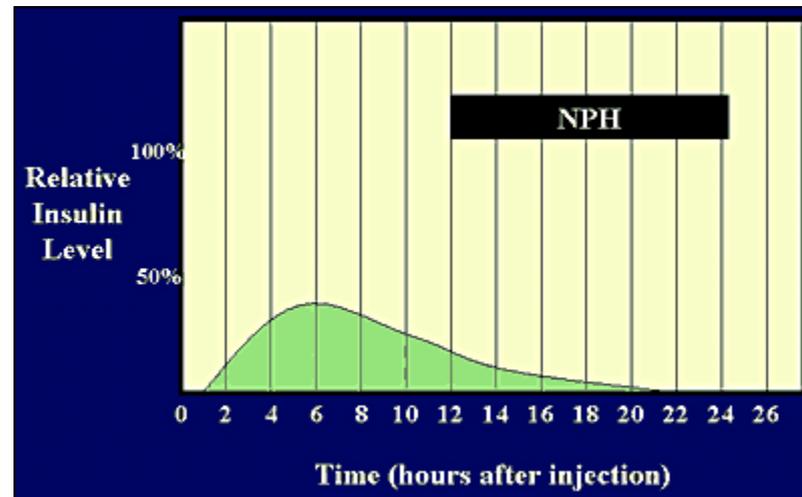
DM 2 Treatment– Insulin

- ▶ 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)
- ▶ Humalog[®] –(Lispro–1996) now have NovoLog[®](Aspart–2000) and Glulisine (Apidra[®]–2004)
- ▶ Glargine (Lantus[®]–1999) Detemir (Levemir[®]–2006)
- ▶ Novolog Mix 70/30–(2001)

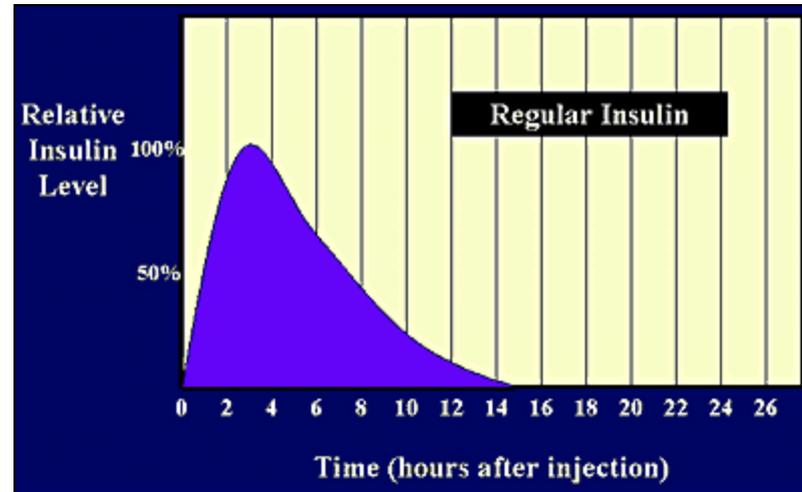
DM 2 Treatment- Insulin



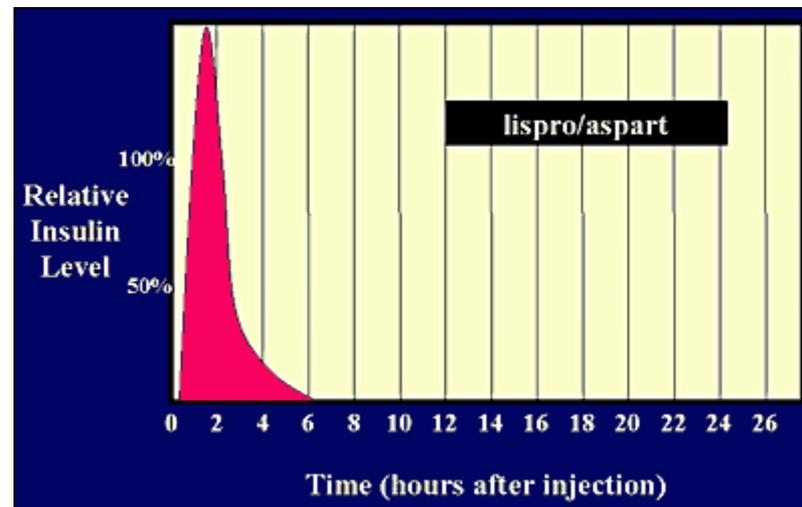
DM 2 Treatment- Insulin



DM 2 Treatment- Insulin



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–morbidity 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

DM 2 Treatment– Insulin

- ▶ 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

Insulin Tx

- ▶ If the patient will comply with multiple daily injections of insulin...
 - Lantus[®] or Levemir[®] or NPH at bedtime (roughly $\frac{1}{2}$ the total daily dose of insulin)
 - Aspart (NovoLog[®]), Lispro(Humalog[®]) or Glulisine (Apidra[®]) or regular pre-meal (added up for the other $\frac{1}{2}$ of the total daily dose)

Insulin TX

- ▶ 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

Insulin Adjustments

- ▶ 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

Insulin Adjustments

- ▶ 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 1 ml syringe or 0.2ml
- ▶ We write “100 units of U-500 insulin which is equal to 20 units in a 0.5ml syringe”

U-500

- ▶ 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– $\frac{2}{3}$ of total daily dose in AM and $\frac{1}{3}$ of total daily dose in PM
 - AM– $\frac{2}{3}$ NPH and $\frac{1}{3}$ regular
 - PM– $\frac{1}{2}$ NPH and $\frac{1}{2}$ Regular (best if Regular is taken with supper and NPH at bedtime)
 - Example– total daily dose of 36 units ($\frac{2}{3} = 24$ units and $\frac{1}{3} = 12$ units)
 - AM– 16 units NPH and 8 units Regular
 - PM– 6 units NPH and 6 units Regular

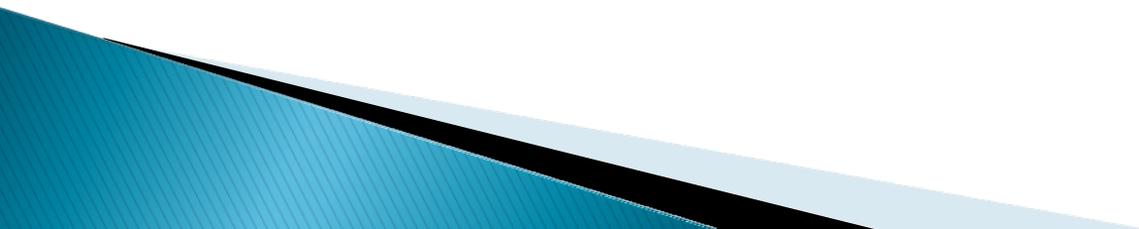
Prevention

- ▶ 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