Pharmacotherapy of Diabetes Mellitus
KHOI NGUYEN LAM

<table>
<tr><td></td><td>TYPE 1</td><td colspan="3">TYPE 2</td></tr>
<tr><td>Epidemiology</td><td>- 10% of DM
- <1% of population</td><td colspan="3">- 90% of DM
- 8.7% of population > 20 yoa</td></tr>
<tr><td>Disease State Definition</td><td>Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.

Beta cell destruction (immune mediated or idiopathic) → complete insulin deficiency

GESTATIONAL :: glucose intolerance while pregnant (NOT pregnant woman with DM)</td><td colspan="3">body is insulin RESISTANT (w/or w/o insulin deficient

screening every 3 years > 45 yoa</td></tr>
<tr><td>Patho-physiology</td><td>- Autoimmune destruction of the beta cells of the pancreas (immunity against islet and beta cells)</td><td colspan="3">- Abnormalities that result in the resistance to insulin action (ie apple built frame)</td></tr>
<tr><td>Clinical Presentation</td><td colspan="4">- Classical (polyuria, polydipsia, unexplained wt loss)
- Hyperglycemia (polyuria, polydipsia, wt loss, polyphagia, blurred vision)
- Complications
o Vascular Diseases
▪ Macrovascular
• accelerated coronary atherosclerosis
• cerebrovascular atherosclerosis
• peripheral vascular disease
• MI
• stroke
▪ Microvascular
• Retinopathy
• Nephropathy
o Neuropathic Conditions
▪ Sensorimotor neuropathy
o Autonomic neuropathy
▪ Gastroparesis
▪ diabetic diarrhea
▪ neurogenic bladder
▪ impotence in men
▪ impaired cardiovascular reflexes
o Mixed Vascular and Neuropathic Disease
▪ Leg ulcers, foot ulcers</td></tr>
<tr><td>Risk Factors</td><td colspan="2">- certain HLA types
- Islet cell antibodies present
- idiopathic</td><td colspan="2">- Family Hx
- Metabolic syndrome
o >40” XY; >35” XX
o TG > 150
o HDL < 40 XY; <50 XX
o BP > 130/>85
o FBG > 110</td></tr>
<tr><td rowspan="4">Diagnosis (FPG is preferred because of ease and cost)</td><td>Stage</td><td>Fasting Plasma Glucose (FPG)</td><td>Casual Plasma Glucose</td><td>Oral Glucose Tolerance</td></tr>
<tr><td>Diabetes</td><td>≥ 126</td><td>Sx + ≥ 200</td><td>2hr plasma ≥ 200</td></tr>
<tr><td>Impaired Glucose Homeostasis</td><td>110 – 126</td><td>-</td><td>140-200</td></tr>
<tr><td>Normal</td><td>≤ 110</td><td>-</td><td>< 140</td></tr>
</table>

<table>
<tr><td>Desired Therapeutic Outcomes*

*Reference of Guidelines Used</td><td colspan="3">- tight control decreases progression of complications by 70% (Diabetes Control and Complications Trial, United Kingdom Prospective Diabetes Study)
- (xxx) American College of Endocrinology and the American Association of Clinical Endocrinologists 2001

<table><tr><td></td><td>Goal</td><td>Normal</td></tr><tr><td>PrePrandial</td><td>90 – 130 (< 110)</td><td>< 110</td></tr><tr><td>PostPrandial</td><td>< 180 (< 140)</td><td>< 140</td></tr><tr><td>HS glucose</td><td>110 – 150</td><td>< 120</td></tr><tr><td>A1c</td><td>< 7% (< 6.5%)</td><td>4-6%</td></tr><tr><td>Blood Pressure</td><td>< 130/80</td><td></td></tr><tr><td>LDL</td><td>< 100</td><td></td></tr><tr><td>TG</td><td>< 150</td><td></td></tr><tr><td>HDL</td><td>> 40 XY
> 50 XX</td><td></td></tr></table></td></tr>
<tr><td>Treatment Options**

(Non-drug and Drug Therapy – include all therapeutic classes/agents available and preferences per treatment guidelines)

**See Treatment Options Table</td><td>Insulin, Diet + exercise</td><td colspan="2">Diet + exercise, oral agents, insulin

Exercise (150min/wk moderate intensity aerobic physical activity, 90min/wk vigourous aerobic exercise)

Drugs:
- Secretagogues
- Sulfonylureas (Glipizide, Glyburide, Glimepiride)
- Meglitinides (Repaglinide, Nateglinide)
- Biguanide (Metformin)
- α – Glucosidase Inhibitors (Acarbose, Miglitol)
- Thiazolidinedione (Pioglitazone, Rosiglitazone)
- Incretin Mimetics (Exenatide)
- Amylin Anaglog (Pramlintide)
- Insulin (Aspart, Lispro, Glulisine, Glargine, Detemir, NPH)</td></tr>
<tr><td>Monitoring

(Efficacy and Toxicity Parameters)</td><td></td><td colspan="2"></td></tr>
</table>

	FPG	A1c	Wt	Lipids	GI	CV effects	Hypo-glycemia	Liver enzymes	Scr	URTI	Anemia	Derma
Secretagogues	X	X			X	X	X			X		
Sulfonylureas	X	X			X		X	X	X			X
Meglitinides												
Biguanide	X	X	X	X	X						X	
A-glucosidase Inh	X	X			X			X				
Thiazoidinedione	X	X	X			X		X		X	X	
Incretin Mimetic	X	X	X		X							
Amylin Analog	X	X			X		X					
Insulin	X	X	X				X					

Pharmacological Treatment Options for DM (type 2)

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	SULFONYLUREAS	MEGLITINIDES	BIGUANIDE
Product Availability Generic (Brand)	• Glyburide (Diabeta, Micronase) • Glyburide mcironized (Glynase) • Glipizide (Glucotrol) • Glipizide ER (Glucotrol XL) • Glimepiride (Amaryl) • Acetohexamide • Chlorpropamide (Diabinese) • Tolazamide (Tolinase) • Tolbutamide (Tol-Tab)	• Repaglinide (Prandin) • Nateglinide (Starlix)	• Metformin (Glucophage) • Metformin SR (Glucophage XR)
Mechanism of Action	• Stimulate release of insulin from pancreatic beta cells • Enhance beta cell sensitivity to glucose • Normalized increased hepatic glucose production	• Take with meal • Similar to S/U but only stimulates pancreas to release insulin when glucose is high • Binding site on beta cells • Quick onset • Short DOA • Skip dose if skip meal	• Decreased hepatic glucose production • Increase skeletal muscle glucose uptake • Decrease intestinal absorption of glucose • Does not stimulate insulin secretion
EFFICACY **(Indication/Use, Clinical Data Support)**	• Type 2 diabetes who had failed diet and exercise therapy, provided they have some degree of pancreatic Fx • Reduce FPG 60-70 mg/dl • Reduce A1c 2% • (glipizide, intermediate acting, good in postprandial) • (Glyburide, longer acting, more hypoglycemia, good in fasting glucose)	• Type 2 DM • NOT Type 1 • Sulfa allergy • Hypoglycemia on low doses of S/U	• Decreases FBG 20-30% (about 60 mg/dl) • Additive with OSA • No wt gain, • Wt loss • Advantageous lipid profile • Type 2 DM • Children >10 yoa
SAFETY			
Interactions	• Acarbose (alpha glucosidace Inh) – not glimepiride • FQ • Bosentan	• Gemfibrozil • Itraconazole	• Drugs containing iodine • FQ
Pre-cautions	• Hypoglycemic unawareness • Renal/hepatic insufficiency	• Adrenal or pituitary insufficiency (more susceptible to hypoglycemia) • Elderly, debilitated or malnourished (more susceptible to hypoglycemia) • Hepatic impairment • Renal impairment • Stress due to infection, fever, trauma, surgery • Don't use with or in place of Secretagogue (Starlix) •	• Excessive EtOH incr LA • Elderly incr risk of LA • Hepatic dx incr risk of LA
Contra-Indications	• Sulfa allergy	• Type 1 DM •	• CrCl > 1.5 XY • CrCl > 1.4 XX • CHF on pharmacology • Increased risk lactic acidosis • Excessive EtOh • >80 yoa • acetazolamide

	SULFONYLUREAS	MEGLITINIDES	BIGUANIDE
AE	• GI • Derm Rxn • Alcohol intolerance (chlorpropamide) • Hyponatremia or SIADH • Hepatotoxicity • Hypothyroidism • Hypoglycemia • Wt gain	• Similar to S/U with higher CV and less hypoglycemia • Upper Resp tract inf • GI • UTI • Arthralgia	• Black Box: Lactic Acidosis • GI • Neurologic asthenia • anorexia
Preg Cat	• Glyburide (B) • Glipizide (C) • Glimepiride (C) • Acetohexamide • Chlorpropamide (C) • Tolazamide (C) • Tolbutamide (C)	• Repaglinide (C) • Nateglinide (C)	• Metformin (B)
Dosage & Administration **(Include renal and/or hepatic adjustments)**	• QD Give with breakfast or first main meal • Could be given BID • ER given QAM • Glipizide taken 30mins before breakfast, BiD if >15mg/d	• Given within 15-30 minutes of each meal • Skipped if meal skipped •	• BiD-TiD dosing • Geriatric conservative dosing •
Monitoring Efficacy/ Toxicity	• FBG • A1c • hypoglycemia	• FBG • A1c • hypoglycemia	• FBG, A1c • LDL, HDL, TG • Metformin plasma levels (> 5ug/mL) • CrCl (Renal insufficiency) • Vit B12 (megaloblastic anemia) • LFTs (Liver Fx)
Patient Education		• careful about hypoglycemic unawareness • EtOH use changes hyper/hypo	
Cost (1-month)	• Glyburide ($32.00) • $21.00 (Glynase) • Glipizide ($17.00) • Glipizide ER ($24.00) • Glimepiride ($12.00)	• $91.00 (Prandin) • $115.00 (Starlix)	• Metformin ($40.00) • Metformin SR ($44.60)
References (Guidelines, Drug Info Sources)	• DiPiro, J. Pharmacotherapy, A Pathophysiologic Approach. 6th Ed. 2005. • Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2006. URL: http://www.clinicalpharmacology.com. Updated February 2006. • PDR® Electronic Library™ [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated January 2006. • Diabetes Care. 2006 Jan; 29 Suppl 1:S1-2		

Pharmacological Treatment Options for DM (type 2)

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	A-GLUCOSIDASE INH	THIAZOLIDINEDIONE	INCRETINE MIMETIC	AMYLIN ANALOG
Product Generic (Brand)	• Acarbose (Precose) • Miglitol (Glyset) • Voglibose (Bansen) under review	• Rosiglitazone (Avandia) • Pioglitazone (Actos)	• Exenatide (Byetta)	• Pramlintide (Symlin)
Mechanism of Action	• Blocks the breakdown of complex carbohydrates in intestines • Decr Post-Prandial • Drug not absorbed – works in intestine	• Improves the action of liver, muscles and fat tissues as an insulin sensitizer • Active PPAMR gamma nuclear receptor • Increase glucose uptake in skeletal muscle • Lowers hepatic glucose output	• Mimics the enhancement of glucose-dependent insulin secretion • Binds to BLP-1 • Slows gastric emptying • Reduces food intake • Suppresses glucagons secretion	• Mimetic of Amylin, co-excreted with insulin from pancreas. •
EFFICACY **(Indication/Use, Clinical Data Support)**	• Type 2 DM • Post prandial hyperglycemia	• DM Type 2 w/ failed conventional oral therapy	• DM type 2 • Conjunction with metformin, S/U,	• Suppresses inappropriately high postprandial glucagons secretion • Slows gastric emptying • Enhances satiety • Good in Type 1 and Type DM
SAFETY				
Interactions	• FQ •	• Increased risk of CHF w/ insulin • Bosentan decr plasma concentration • Liver dysfx • Oral contraceptives w/pio (decr AUC) • Progestins incr insulin tolerance	• None severe	• Antimuscarinics • Cisapride • Diphenoxylate • Erythromycin • Loperamide • Metoclopramide • Octreotide • Opiate agonists • Tegaserod • TCA • Severe hypoglycemia with insulin (black box)
Pre-cautions	• SCr > 2mg/dL	•	• Caution to use with other antidiabetics because not enough data • End stage renal (CrCl <30) • Not recommended for GI diseseas • Hypoglycemia with S/U	• Therapy only if A1c < 9% • Need good compliance on insulin therapy • Not on GI stimulant drug • NO pediatrics • Caution with other antidiabetics causes severe hypoglycemia • NEVER mix with insulin

	A-GLUCOSIDASE INH	THIAZOLIDINEDIONE	INCRETINE MIMETIC	AMYLIN ANALOG
Contra-Indications	• Cirrhosis (Acarbose) • Colon ulceration • Too much intestinal gas • Malabsorption problems • Inflammatory bowel disease • Bowel obstruction	• Type 1 – only work in the presence of insulin • Ketoacidosis • CHF III & IV • Abnormal LFT	• Type 1 DM • Colitis • Cresol hypersensitivity • Crohn's dx • Diabetic ketoacidosis • Gstroparesis • GI bleeding, dx, obstruction • Hypoglycemia • Illeus • IBD • Pseudomembranous colitis • Renal failure • Ulcerative colitis	• Gastroparesis • Hypoglycemia unawareness • Cresol hypersensitivity
AE	• GI (ab pain, flatulence) • Decr Fe • Increase liver enzymes • Renal impairment (Miglitol)	• Edema (wt gain) • Back pain • Anemia • Myalgias • Upper resp inf • Hepatotoxicity (rare) • CHF • Ovulation in premenopausal XX who are anovulation from insulin resistance	• N/V/D	• N/V • hypoglycemia
Preg Cat	• Acarbose (B) • Miglitol (B)	• Rosiglitazone (C) • Pioglitazone (C)	• Exenatide (C)	• Cat C
Dosage & Administration **(Include renal and/or hepatic adjustments)**	• TiD • Take with first bite of each main meal	• QD or BiD • Hepatic dosing may be necessary but recommendations are available • d/c Rosi if ALT > 2.5	• SQ BiD • W/in 60mins before meals • Need to have CrCl > 30 • May need to decr dose of S/U	• SQ TiD • Reduce insulin dose initially • Give before meal of >250 Kcal or >30 carbs
Monitoring Efficacy/ Toxicity	• FGB, A1c, • <u>BP</u> • SCr • LFT (3m) Acarbose)	• FGB • <u>A1c</u> • Liver enzymes (2m) • Jaundice	• FBG • A1c	• FBG • A1c
Patient Education	• Rescue meds need to be DEXTROSE and not glucose • Must take with first bite	• Taken w/o regards to meals • Look out for edema and difficulty breathing • Need to be on birth control pills if anovulation because of insulin resistant	• Given BEFORE meals not with meals • Refrigerate • Protect from light • Discard after 30days	
Cost (1-month)	• $61 (Precose) • $62 (Glyset)	• $226.17 (Avandia) • $217.67 (Actos)	• AWP $183.75 (5ug BID prior to meals)	• AWP $95.40 (5mL)
References (Guidelines, Drug Info Sources)	• DiPiro, J. Pharmacotherapy, A Pathophysiologic Approach. 6th Ed. 2005. • Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2006. URL: http://www.clinicalpharmacology.com. Updated February 2006. • PDR® Electronic Library™ [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated January 2006. • Diabetes Care. 2006 Jan; 29 Suppl 1:S1-2			

Pharmacological Treatment Options for DM (type 2)

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	INUSLIN RA	INSULIN SA	INSULIN IA	INSULIN LA
Product Availability Generic (Brand)	• Lispro (Humalog) • Aspart (Novolog) • Glulisine (Apidra)	• Regular (Humulin R, Novolin R)	• NPH (Humulin N, Novolin N) • Lente (Novolin L)	• Glargine (Lantus) • Detemir (Levemir)
Mechanism of Action	• Limits hyperglycemia after meals • Binds to insulin receptors on muscle cells to help facilitate absorption of glucose into cell cytoplasm	• Limits hyperglycemia after meals • Binds to insulin receptors on muscle cells to help facilitate absorption of glucose into cell cytoplasm	• Suppresses glucose production between meals and overnight •	• Suppresses glucose production between meals and overnight •
EFFICACY **(Indication/Use, Clinical Data Support)**	• Type 1 DM • Type 2 DM (adjunct to oral medication) • Special inpatient circumstances	• Type 1 DM • Type 2 DM (adjunct to oral medication) • Special inpatient circumstances	• Type 1 DM • Type 2 DM (adjunct to oral medication) • Special inpatient circumstances	• Type 1 DM • Type 2 DM (adjunct to oral medication) • Special inpatient circumstances
SAFETY				
AE	• Hypoglycemia • Wt gain • Hypokalemia • lipohypertropy	• Hypoglycemia • Wt gain • Hypokalemia • Lipohypertropy	• Hypoglycemia • Wt gain • Hypokalemia • Lipohypertropy	• Hypoglycemia • Wt gain • Hypokalemia • lipohypertropy
Interactions	• Thiazolidinediones → Incr risk of HF/edema	• Thiazolidinediones → Incr risk of HF/edema	• Thiazolidinediones → Incr risk of HF/edema	• Thiazolidinediones → Incr risk of HF/edema
Pre-cautions	• Taking any number of medications that may lower or increase glycemic control • NO IV dosing	• Taking any number of medications that may lower or increase glycemic control • IV OK	• Taking any number of medications that may lower or increase glycemic control	• Taking any number of medications that may lower or increase glycemic control
ContraIndic	• m-cresol hypersensitivity • Do not give if hypoglycemic	• m-cresol hypersensitivity • Do not give if hypoglycemic	• m-cresol hypersensitivity • Do not give if hypoglycemic	• m-cresol hypersensitivity • Do not give if hypoglycemic • IV therapy •
Preg Cat	• Cat B (Lispro) • Cat C (Aspart) • Cat C (Glulisine) •	• Cat B	• Cat C	• Cat C
Dosage & Administration	• Individualized • 5-10 mins prior to meals	• Individualized • 5-10 mins prior to meals or HS	• Individualized • 5-10 mins prior to meals or HS	• Individualized • QD • Decrease dose if switch from NPH to prevent hypoglycemia •
Renal Dosing	• None	• None	• None	• None
Hepatic Dos	• Yes, but no guidelines so must individualize	• Yes, but no guidelines so must individualize	• Yes, but no guidelines so must individualize	• Yes, but no guidelines so must individualize •

Student Name, PharmD Candidate 2007
University of Maryland School of Pharmacy

	INUSLIN RA	INSULIN SA	INSULIN IA	INSULIN LA
Monitoring **(Efficacy and Toxicity Parameters)**	• FPG • A1c • S/Sx of hypoglycemia • Wt gain • Hypokalemia • lipohypertropy	• FPG • A1c • S/Sx of hypoglycemia • Wt gain • Hypokalemia • lipohypertropy	• FPG • A1c • S/Sx of hypoglycemia • Wt gain • Hypokalemia • lipohypertropy	• FPG • A1c • S/Sx of hypoglycemia • Wt gain • Hypokalemia • Lipohypertropy
Patient Education	• Warm and mix up insulin by rolling the vial between your hand. • Inject subcutaneously in abdomen and 2" apart each time • It is important to eat within 15 minutes after injection • Do not miss a dose, if you do, do not double the next dose • Some drugs may hide the effects of hypoglycemia and you will need to monitor glucose more closely (BB, clonidine, gaunethidine, reserpine) •	• Warm and mix up insulin by rolling the vial between your hand. • Inject subcutaneously in abdomen and 2" apart each time • It is important to eat within 15 minutes after injection • Do not miss a dose, if you do, do not double the next dose • Some drugs may hide the effects of hypoglycemia and you will need to monitor glucose more closely (BB, clonidine, gaunethidine, reserpine) •	• Warm and mix up insulin by rolling the vial between your hand. • Inject subcutaneously in abdomen and 2" apart each time • It is important to eat within 15 minutes after injection • Do not miss a dose, if you do, do not double the next dose • Some drugs may hide the effects of hypoglycemia and you will need to monitor glucose more closely (BB, clonidine, gaunethidine, reserpine) •	• Warm and mix up insulin by rolling the vial between your hand. • Inject subcutaneously in abdomen and 2" apart each time • It is important to eat within 15 minutes after injection • Do not miss a dose, if you do, do not double the next dose • Some drugs may hide the effects of hypoglycemia and you will need to monitor glucose more closely (BB, clonidine, gaunethidine, reserpine) • CANNOT MIX
Cost (1-month)	• $278.00 (Humalog 100U) • $145.00 (Novolog 100U) • Glulisine (Apidra)	• Regular (Humulin R, Novolin R)	• NPH (Humulin N, Novolin N) • Lente (Novolin L)	• $133.00 (Lantus 100U) • $215.00 (Levemir)
References (Guidelines, Drug Info Sources)	• DiPiro, J. Pharmacotherapy, A Pathophysiologic Approach. 6th Ed. 2005. • Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2006. URL: http://www.clinicalpharmacology.com. Updated February 2006. • PDR® Electronic Library™ [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated January 2006. • Diabetes Care. 2006 Jan; 29 Suppl 1:S1-2			