Oral and Injectable Medication Options for Diabetes Treatment

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Learning Objectives
- Identify the various classifications of oral and injectable medication currently used in the treatment of diabetes mellitus
- Describe the mechanism of action, pharmacokinetics, dosing, adverse effects and drug interactions of each class of diabetes medications

Pathophysiology
Diabetes Mellitus:
Metabolic disorder characterized by hyperglycemia
- Impaired pancreatic insulin secretion
- Increased hepatic glucose production
- Decreased peripheral glucose uptake
Major Pathophysiologic Defects in Type 2 Diabetes1,2

- Glucagon (alpha cell) dysfunction
- Insulin resistance
- Glucose uptake
- Hyperglycemia
- Hepatic glucose output


Diabetes Treatment
- Meal planning
- Physical Activity
- Self Monitoring of Blood Glucose
- Education
- Oral Medications
- Insulin
- Other injectable medications

Oral medications for diabetes treatment
- Insulin secretagogues
  - Action on pancreatic beta cells
- Insulin sensitizers
  - Improve target cell response to the liver and peripheral tissues
- Alpha-glucosidase inhibitors
  - Slow digestion of carbohydrates
- DPP-4 inhibitors
  - Enhance incretin system
Insulin Secretagogues

Sulfonylureas
Mechanism of Action (MOA): Stimulate insulin secretion from pancreatic beta cells, reduces glucose output from liver, improves insulin sensitivity in periphery

Second Generation Sulfonylureas
- Glyburide (Micronase, Diabeta)
- Glyburide Micronized (Glynase PresTab)
- Glipizide (Glucotrol, Glucotrol XL)
- Glimepiride (Amaryl)

Sulfonylureas

- Kinetics
  - Onset: <60 minutes
  - Peak: 2-4 hours
  - Duration: 12-24 hrs.
- Adverse effects
  - Hypoglycemia
  - Photosensitivity
  - Dizziness
  - Thrombocytopenia
  - Gastrointestinal Disturbances
  - Allergic skin reactions
  - Disulfiram-type reaction

Sulfonylureas

- Drug Interactions
  - Increased Hypoglycemia
    - Anticoagulants
    - Salicylates
    - Sulfonamides
    - MAO Inhibitors
    - Tricyclic antidepressants
    - Azole antifungals
  - Decreased Action
    - Beta Blockers, Diuretics, Ca²⁺ Blockers
    - Corticosteroids, Estrogens, Thyroid Hormones
    - Sympathomimetics, Phenothiazines
    - Isoniazid, Phenytoin, Nicotinic Acid
Sulfonylureas

Precautions
Caution in elderly
Severe allergy to sulfonamides

Administration
Once daily-Twice daily dosing

Insulin Secretagogues

Meglitinides
MOA: Stimulate insulin release from pancreas

Products:
Repaglinide (Prandin)
Nateglinide (Starlix)

Meglitinides

- Kinetics
  - Onset: <30 minutes
  - Duration: 2-3 hrs
- Dosing: With meals

- Adverse effects
  - Hypoglycemia (Repaglinide)
  - Headache
  - Upper respiratory infection
  - Dizziness
  - Diarrhea
Meglitinides- Drug Interactions (CYP3A4, CYP2C9)

- Increased effect
  - Azole Antifungals
  - NSAIDs, Salicylates
  - Sulfonamides
  - Thyroid Hormones
  - Oral Contraceptives

- Decreased effect
  - Rifampin
  - Barbiturates
  - Carbamazepine

Insulin Sensitizers

**Biguanide**

- Drug of choice for Type 2 diabetes

**MOA:**
- Decreases hepatic glucose production
- Decreases intestinal absorption of glucose
- Increases peripheral glucose uptake and utilization

**Biguanide Products:**
- Metformin (Glucophage, Glucophage XR, Riomet)

**Kinetics:**
- Half-life: 4-6 hrs
- Duration: 6-24 hours
- Excreted unchanged in urine

**Dosage:** Once daily- Three times daily

**Adverse effects:**
- Diarrhea
- Nausea, vomiting
- Heartburn
- Flatulence, Abdominal bloating
- Metallic taste
- Anorexia
Biguanide

**Drug Interactions:** (Increased effects)
- Cationic drugs (e.g. Digoxin, Amiloride, Morphine, Procainamide, Quinidine)
- Cimetidine
- Iodinated Contrast Material
- Alcohol
- Nifedipine

**Contraindications:**
- Renal disease (Cr >1.5 mg/dl Men, >1.4 mg/dl Women)
- CHF requiring pharmacologic treatment
- Radiologic studies involving use of iodinated material
- Acute or chronic metabolic acidosis

Insulin Sensitizers

**Thiazolidinediones**
- MOA:
  - Improve insulin sensitivity
  - Enhance glucose uptake in muscle and adipose tissue
  - Inhibit gluconeogenesis

- Products:
  - Rosiglitazone (Avandia)
  - Pioglitazone (Actos)

- Delayed onset of action (up to 12 weeks)
- Metabolized to active and inactive metabolites
Thiazolidinediones

**Precautions:**
- **CARDIAC:** Black box warning for increase in myocardial ischemic events
- **Hepatotoxicity:**
  - Monitor LFTs at start of therapy
  - Monitor LFTs periodically thereafter
  - Do not initiate if ALT >2.5x ULN
- Adverse effects: Edema, weight gain, change in lipids, upper respiratory infection

**Dosing:**
- Pioglitazone: Once daily
- Rosiglitazone: Once or twice daily

**Drug Interactions**
- Increased effect: gemfibrozil, ritonavir
- TZDs may increase effect of: amiodarone, amphetamines, SSRIs, certain beta blockers
- Decreased effect: Carbamazepine, phenobarbital, phenytoin rifampin

Alpha-Glucosidase Inhibitors

**MOA:**
- Delay absorption of carbohydrates
- Inhibit metabolism of sucrose to glucose and fructose

**Products:**
- Acarbose (Precose)
- Miglitol (Glyset)

**Kinetics:**
- Onset: Immediate
- Half-life: 2 hours
- Duration: up to 6 hours (Acarbose)

**Metabolism**
- Acarbose: GI tract
- Miglitol: Not metabolized

Alpha-Glucosidase Inhibitors

**Side Effects:**
- Flatulence
- Abdominal pain
- Diarrhea

**Lab disturbance:**
- Elevated AST, ALT (Acarbose)

**Drug Interactions**
- Decreased effect:
  - Digestive enzymes
  - Intestinal absorbents

- May decrease Digoxin, Glyburide, Propranolol and Ranitidine concentrations
**Alpha-Glucosidase Inhibitors**

**Contraindications**
- Inflammatory Bowel Disease
- Colonic Ulceration
- Intestinal Obstruction
- Chronic Intestinal Diseases

Monitoring: LFTs every 3 months (Acarbose)

Dosing: Three times daily with first bite of each meal

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**DPP-4 Inhibitors**

- New drug class affecting Dipeptidyl peptidase (DPP-4)
- Sitagliptin (Januvia)
- Enhances the incretin system
- Increases insulin release, reduces glucagon

- Dosed once daily
- Available in combination with metformin (Janumet)
- Drug interaction: May increase concentration of digoxin
- Adverse effects:
  - Headache
  - Upper respiratory infection
  - Nasopharyngitis

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**Combination Products**

- Glyburide/Metformin (Glucovance)
- Glipizide/Metformin (Metaglip)
- Rosiglitazone/Metformin (Avandamet)
- Pioglitazone/Metformin (Actoplus Met)
- Rosiglitazone/Glimepiride (Avandaryl)
- Pioglitazone/Glimepiride (Duetact)
Insulin

- Very Rapid Acting
- Rapid/Short Acting
- Intermediate Acting
- Long Acting

Very Rapid Acting (Analogs)
- Differ from human insulin by 1 amino acid in B-chain
  - Insulin Aspart (Novolog)
  - Insulin Lispro (Humalog)
  - Insulin Glulisine (Apidra)
- Onset: <15 minutes
- Peak: 40 min-1.5 hours
- Duration: 3-5 hours
- Clear appearance
# Insulin

## Rapid/Short Acting
- **Regular**
  - Onset: 0.5-1 hr
  - Peak: 2-3 hours
  - Duration: 3-8 hours
  - Available 100 units/ml, 500 units/ml

## Intermediate Acting
- **NPH (Isophane Insulin Suspension)**
  - Onset: 2-4 hrs,
  - Peak: 4-10 hrs,
  - Duration: 10-18 hrs
  - Cloudy appearance

## Insulin-Lang Acting
- **Insulin Glargine** (Lantus)
  - Onset: 2-4 hrs
  - No pronounced peak
  - Duration: 24 hrs
  - Clear acidic solution

- **Insulin Detemir** (Levemir)
  - Onset: 3-4 hrs
  - Peak: 6-8 hrs
  - Duration: dose dependent 6-23 hrs
  - Clear solution

## Insulin Mixtures
- 70% NPH/ 30% Regular (*Humulin 70/30, Novolin 70/30*)
- 75% Lispro protamine/ 25% Lispro (*Humalog 75/25 insulin*)
- 70% Aspart protamine/ 30% Aspart (*Novolog 70/30 insulin*)
- 50% NPH/ 50% Regular (*Humulin 50/50 insulin*)
- 50% Lispro protamine/50% Lispro (*Humalog 50/50 insulin*)
New Injectable Products

- **Exenatide (Byetta)**
  - Incretin system
  - Increases insulin secretion
  - Slows gastric emptying
  - Increases beta cell growth
  - Twice a day injection within 1 hour of meals
  - Indicated for Type 2 Diabetes
  - Available as prefilled pen for 5 mcg or 10 mcg dose

- **Adverse Effects**
  - Hypoglycemia
  - Nausea, vomiting, diarrhea
  - Dysgeusia-impaired taste
  - May affect extent of absorption of oral medications
  - Oral medications should taken 1 hour before injection

- **Twice a day injection within 1 hour of meals**

New Injectable Products

- **Pramlintide (Symlin)**
  - Amylin analog
  - Prolongs gastric emptying time
  - Reduces postprandial glucagon secretion
  - Reduces caloric intake through centrally mediated appetite suppression
  - Injection administered three times a day with meals
  - Dose in mcg (given in insulin syringe)
  - Indicated for type 1 diabetes and type 2 diabetes on insulin therapy
  - Adverse effects
    - Nausea, vomiting, anorexia
    - Hypoglycemia

- **Pramlintide dosing**
  - **Type 1**
    - Initial dose: 15 mcg (2.5 units) before each meal
    - Target dose: 30-60 mcg before each meal
    - Insulin dose is reduced by 50% to avoid hypoglycemia when initiating pramlintide
  - **Type 2**
    - Initial dose: 60 mcg (10 units) before each meal
    - May increase to 120 mcg
    - Pramlintide may delay absorption of other medications
Initiating treatment

- Type and duration of diabetes
- Current blood glucose and A1c measurement
- Concurrent disease state
- Cost/Insurance formulary
- Allergies or past intolerances of medication
- Barriers to adherence

Monitoring

- Blood glucose, A1c
- Blood pressure and lipids
- Electrolytes
- Renal and liver function
- Signs/symptoms of complications
- Adverse effects of medication
- Adherence