Pharmaceutical Management of Diabetes Mellitus
Diabetes Mellitus (cont’d)

• **Signs and symptoms**
  - Elevated fasting blood glucose (higher than 126 mg/dL) or a hemoglobin A1C (A1C) level greater than or equal to 6.5%
  - Polyuria
  - Polydipsia
  - Polyphagia
  - Glycosuria
  - Unexplained weight loss
  - Fatigue
  - Blurred vision
Type 1 Diabetes Mellitus

- Lack of insulin production or production of defective insulin
- Affected patients need exogenous insulin
- Fewer than 10% of all diabetes cases are type 1
- Complications
  - Diabetic ketoacidosis (DKA)
  - Hyperosmolar nonketotic syndrome
Type 2 Diabetes Mellitus

- Most common type: 90% of all cases
- **Caused by:**
  - Insulin deficiency and
  - Insulin resistance
    - Reduced number of insulin receptors
    - Insulin receptors less responsive
  - Liver making more sugar
  - Missing hormone GLP-1
Several comorbid conditions
- Obesity
- Coronary heart disease
- Dyslipidemia
- Hypertension
- Microalbuminemia (protein in the urine)
- Increased risk for thrombotic events

These comorbidities are collectively referred to as 
metabolic syndrome or insulin-resistance syndrome or syndrome X
Screening for DM

- **Prediabetes**
  - **Categories of increased risk for diabetes**
    - Hemoglobin A1C of 5.7% to 6.4%
    - Fasting plasma glucose (FPG) levels higher than or equal to 100 mg/dL but less than 126 mg/dL
    - Impaired glucose tolerance test (oral glucose challenge)

- **Screening recommended every 3 years for all patients 45 years and older**
Treatment for DM

- **Type 1**
  - Insulin therapy

- **Type 2**
  - Lifestyle changes
  - Oral drug therapy
  - Injectable (non-insulin) therapy
  - Insulin therapy
Oral Antidiabetic Drugs

- Used for type 2 diabetes
- Lifestyle modifications
  - Diet, exercise, smoking cessation, weight loss
- Oral antidiabetic drugs may not be effective unless the patient also makes behavioral or lifestyle changes
Biguanides

- **Mode of Action**
  - Decrease production of glucose by the liver
  - Decrease intestinal absorption of glucose
  - Increase uptake of glucose by tissues
  - Do not increase insulin secretion from the pancreas

- **Side Effects**
  - Primarily affects GI tract: abdominal bloating, nausea, cramping, diarrhea, feeling of fullness
  - May cause metallic taste, reduced vitamin $B_{12}$ levels
  - Lactic acidosis is rare but lethal if it occurs
  - Does not cause hypoglycemia
Sulfanylureas

- **Second generation**: glimepiride (Amaryl), glipizide (Glucotrol), glyburide (DiaBeta, Micronase)

- **Mode of Action**
  - Stimulate insulin secretion from the beta cells of the pancreas, thus increasing insulin levels
  - Beta cell function must be present
  - Improve sensitivity to insulin in tissues
  - Result in lower blood glucose levels

- **Side Effects**
  - Hypoglycemia, nausea,
  - Epigastric fullness, heartburn
Glinides

- repaglinide (Prandin), nateglinide (Starlix)
- **Mode of Action**
  - Action similar to sulfonylureas
  - Increase insulin secretion from the pancreas
- **Side Effects**
  - HA, hypoglycemic effects, dizziness, wt gain, joint pain, upper respiratory infection or flulike symptoms
**Thiazolidinediones (glitazones)**

- pioglitazone (Actos)
- rosiglitazone (Avandia)
  - Only available through specialized manufacturer programs

**Mode of Action**
- Decrease insulin resistance
- “Insulin sensitizing drugs”
- Increase glucose uptake and use in skeletal muscle
- Inhibit glucose and triglyceride production in the liver

**Side Effect**
- Moderate wt gain, edema, mild anemia
- Hepatic toxicity—monitor alanine aminotransferase (ALT) levels
Alpha Glucosidase Inhibitors

• Acarbose (precose), miglitol (Glyset)

• **Mode of Action**
  - Reversibly inhibit the enzyme alpha-glucosidase in the small intestine
  - Result in delayed absorption of glucose
  - Must be taken with meals to prevent excessive postprandial blood glucose elevations (with the “first bite” of a meal)

• **Side Effects**
  - Flatulence, diarrhea, abdominal pain
  - Do not cause hypoglycemia, hyperinsulinemia, or wt gain
Dipeptidyl peptidase-IV (DPP-IV) inhibitors

- sitagliptin (Januvia)
- saxagliptin (Onglyza)
- linagliptin (Tradjenta)

**Mode of Action**
- Delay breakdown of incretin hormones by inhibiting the enzyme DPP-IV
- ↑ insulin synthesis, ↓ glucagon secretion
- ↓ fasting and postprandial glucose concentrations

**Side Effects**
- URI, HA, and diarrhea
- Hypoglycemia can occur and is more common if used in conjunction with a sulfonylurea
Incretin Mimetics

- exenatide (Byetta)
- liraglutide (Victoza)
- Byduran
- Trulicity

**Mode of Action**
- Mimics the incretin hormones
- Enhances glucose-driven insulin secretion from beta cells of the pancreas

**Side Effects**
- Nausea, vomiting, and diarrhea
- Rare cases of hemorrhagic or necrotizing pancreatitis
- Weight loss
Amylin Agonists

pramlintide (Symlin)

- **Mode of Action**
  - Mimics the natural neuroendocrine hormone amylin, synthetic analog
  - Slows gastric emptying
  - Suppresses glucagon secretion, ↓ hepatic glu output
  - Contribute to post-prandial glucose control
  - Centrally modulates appetite and satiety
  - Used when adequate glucose control is not achieved
  - SQ injection

- **Side Effects**
  - Nausea, vomiting, anorexia, headache
Na-glu co-transporter 2 (SGLT2) inhibitor

Ivokana Canagliflozin

• **Mode of Action**
  - 100 mg/d prior to first meal
  - SGLT2 in proximal renal tubules is responsible for majority of reabsorption of filtered glu from the tubular lumen. is an inhibitor of SGLT2.
  - By inhibiting SGLT2, ↓ of reabsorption of filtered glu, ↓ renal threshold for glu, ↑ urinary glucose excretion.

• **Side Effects**
  - UTI, hypokalemia
Hypoglycemia Symptoms

- **Early**
  - Confusion, irritability, tremor, sweating
- **Late**
  - Hypothermia, seizures
  - Coma and death will occur if not treated
Glucose-Elevating Drugs

- Oral forms of concentrated glucose
  - Buccal tablets, semisolid gel
- 50% dextrose in water ($D_{50}W$)
- Glucagon
Diabetes Management Algorithm

1. **Type 2 Diabetes**
   - **Success**: Diet and Physical Activity
   - **Failure**: Overweight/Obese
     - **Success**: Metformin ± Acarbose ± TZDs
     - **Failure**: Non-Obese
       - **Success**: Metformin ± Acarbose ± TZDs ± Insulin Secretagogues
     - **Failure**: Metformin ± Insulin Secretagogues ± TZDs ± Acarbose
   - **Success**: Insulin ± Insulin Sensitisers

*Combination ODA therapy should be considered at the outset in patients with HbA₁c > 10%*

- Start medication at presentation if:
  - Symptomatic
  - HbA₁c > 8%
  - FPG ≥ 11.1 mmol/L
  - RPG > 14.0 mmol/L

- Diet, physical activity and compliance must be emphasized at all levels
- Initiate screening for complications
## Oral Hypoglycaemic Medications

### Agents & Actions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Glucophage®</td>
<td>Inhibit glucose production by the liver</td>
</tr>
<tr>
<td>Sulfonylureas (second-gen)</td>
<td>Glimepiride</td>
<td>Amaryl®, Glucotrol®, Diabeta®, Glynase PresTab®, Micronase®</td>
<td>Increase insulin secretion by pancreatic beta cells</td>
</tr>
<tr>
<td></td>
<td>Glipizide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glyburide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meglitinides</td>
<td>Repaglinide</td>
<td>Prandin®, Starlix®</td>
<td>Increase insulin secretion by pancreatic beta cells</td>
</tr>
<tr>
<td></td>
<td>Nateglinide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones (TZDs)</td>
<td>Pioglitazone</td>
<td>Actos®, Avandia®</td>
<td>Increase glucose uptake by skeletal muscle</td>
</tr>
<tr>
<td></td>
<td>Rosiglitazone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose</td>
<td>Precose®, Glyset®</td>
<td>Inhibit carbohydrate absorption in the small intestine</td>
</tr>
<tr>
<td></td>
<td>Miglitol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>