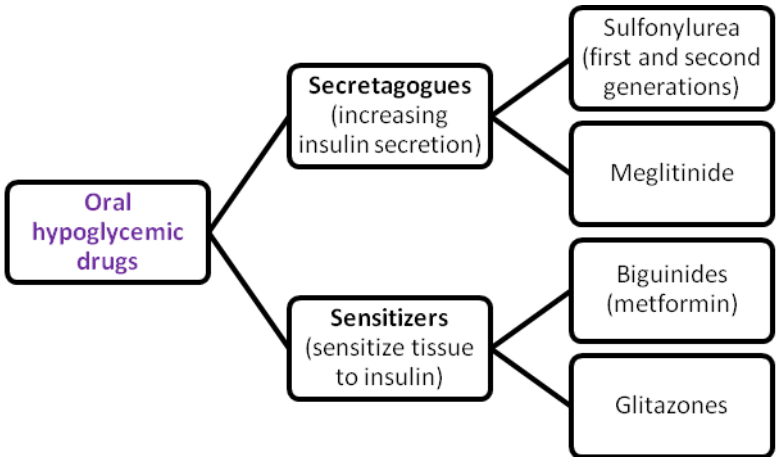
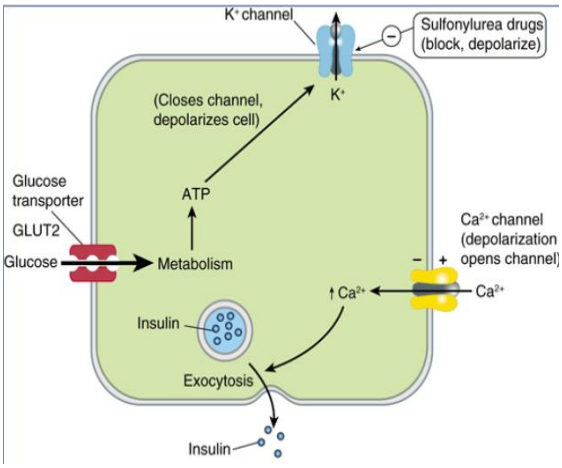
Unit IV – Problem 2 – Pharmacology: Oral Hypoglycemics

- **Targets for oral antidiabetic drugs:**

Pancreas	• Stimulation of insulin secretion. • Inhibition of glucagon secretion.
Liver, muscles and adipose tissues	• Improved insulin receptor sensitivity.
Metabolic pathways	• Suppression of glyconeogenesis. • Stimulation of glycolytic pathway. • Activation of PPAR-γ pathway.
Gastrointestinal tract	• Prolonging gut hormones that regulate gastric emptying and insulin secretion; inhibition of glucose assimilation.
Kidneys	• SGLT2- inhibitors prevent proximal tubular re-absorption of glucose and promote urinary elimination of glucose.



- **Secretagogues:**
  - **Sulfonylurea:**
    - ✓ Example: Glimepiride (Amaryl) which belongs to 2nd generation.
    - ✓ Mechanism of action: blocking K^+-channels in β-cells of islet of Langerhans. Therefore, resulting in depolarization of the cell membrane and opening of voltage-gated Ca^{2+}- channels causing the release of insulin from storage granules via exocytosis.
    - ✓ Adverse reactions: hypoglycemia and weight gain.

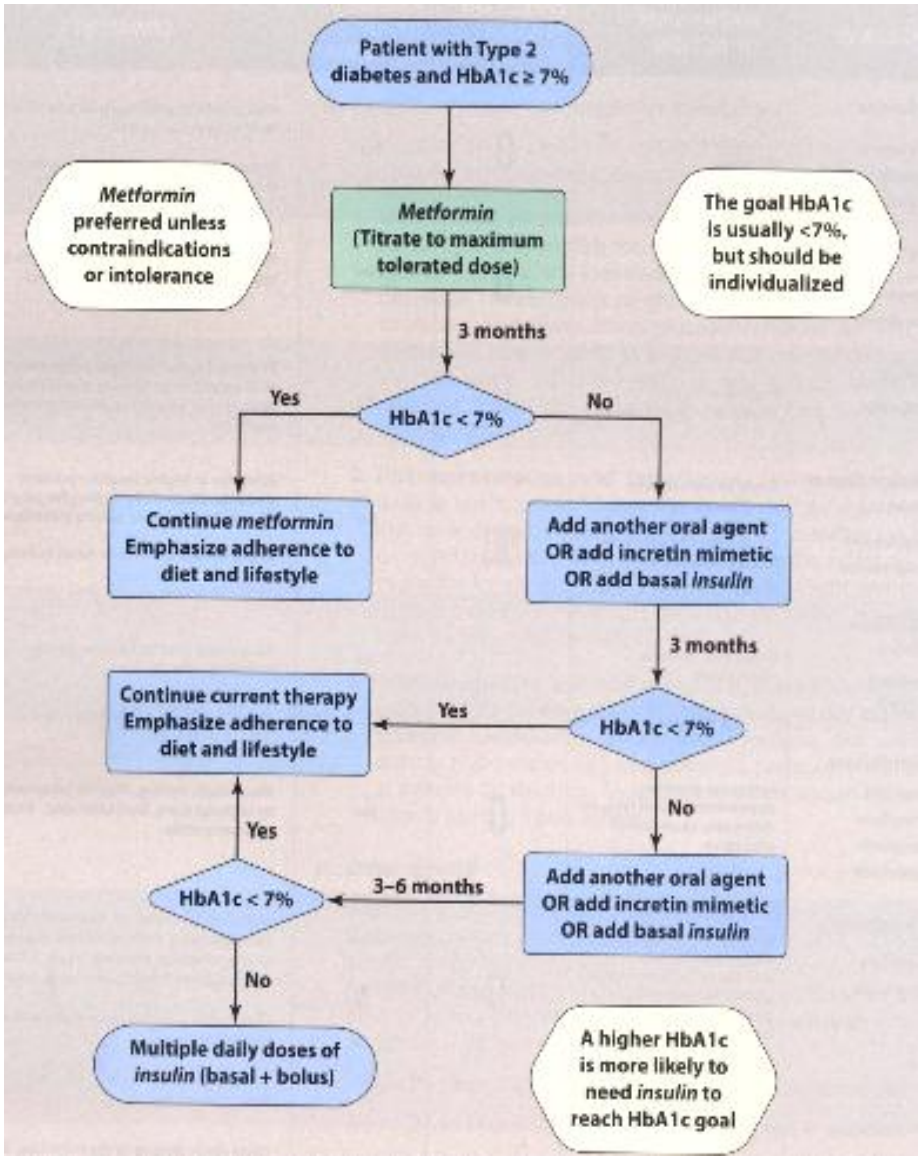


    - ✓ Note: second generation drugs of this class (such as Amaryl) are more potent (given in a low dose) and have a longer duration of action.
  - **Meglitinides:**
    - ✓ Example: rapaglinide.
    - ✓ Mechanism of action: same as salfonylurea.
    - ✓ Advantages: rapid onset + short duration of action.
    - ✓ Adverse reactions: hypoglycemia and weight gain (but less than sulfonylurea).

- **Sensitizers:**
  - **Metformin (trade name: glucophage):**
    - ✓ Mechanism of action: enhancing the activity of AMPK enzyme thus inhibiting liver gluconeogenesis.
    - ✓ Advantages: causing no hypoglycemia (because it is not enhancing insulin release), reducing hyperlipidemia (less coronary artery disease) and leading to weight loss.
    - ✓ Adverse reactions: lactic acidosis (being most important and serious), diarrhea and vitamin B12 deficiency.
  - **Glitazones**:
    - ✓ Example: pioglitazone.
    - ✓ Mechanism of action: binding to PPAR-γ (which is a nuclear receptor) → causing more uptake of glucose by the liver and muscles. They also resuce liver gluconeogenesis.
    - ✓ Advantages: causing no hypoglycemia (because they are not enhancing insulin secretion).
    - ✓ Adverse reactions: lower limb edema and heart failure.
  - **Comparison between metformin and glitazones:**

PARAMETER	METFORMIN	THIAZOLIDINEDIONES
Molecular target	AMPK	PPAR
Main pharmacologic action	Suppression of hepatic glucose production	Enhanced insulin sensitivity
Reduction of HbA_{1c}	1.0-1.25%	0.5-1.4%
Reduction of FFA	Minimal	Moderate
Stimulation of adiponectin	Minimal	Significant
Effect on body weight	Minimal	Increased
Peripheral edema	Minimal	Moderate
Fracture risk	None	Increased
Lactic Acidosis	Rare	None

- **Glucosidase inhibitors:**
  - Examples: acarbose and miglitol
  - Mechanism of action: inhibiting the enzyme α-glucosidase which digest complex sugars to simple sugars. These drugs are weak.
  - Adverse reactions: GIT distress.


Patient with Type 2 diabetes and HbA1c ≥ 7%
Metformin preferred unless contraindications or intolerance
Metformin (Titrate to maximum tolerated dose)
The goal HbA1c is usually <7%, but should be individualized
3 months
Yes
HbA1c < 7%
No
Continue metformin Emphasize adherence to diet and lifestyle
Add another oral agent OR add incretin mimetic OR add basal insulin
3 months
Continue current therapy Emphasize adherence to diet and lifestyle
Yes
HbA1c < 7%
No
Yes
HbA1c < 7%
3–6 months
Add another oral agent OR add incretin mimetic OR add basal insulin
No
Multiple daily doses of insulin (basal + bolus)
A higher HbA1c is more likely to need insulin to reach HbA1c goal