Extra-summaries for Oral Hypoglycemics lecture (8 & 9)

« لو أن الناس كلما استصعبوا أمرًا تركوه؛ ما قام للناس دنيا ولا دين! »

عمر بن عبدالعزيز

Drugs used in diabetes mellitus

Insulin and other injectable drugs

- Human **insulin** is made by recombinant DNA technology. For routine use, it is given subcutaneously (by intravenous infusion in emergencies).
- Different formulations of insulin differ in their duration of action:
  - fast- and short-acting soluble insulin: peak action after subcutaneous dose 2–4 h and duration 6–8 h; it is the only formulation that can be given intravenously
  - intermediate-acting insulin (e.g. isophane insulin)
  - long-acting forms (e.g. insulin zinc suspension).
- The main unwanted effect is hypoglycaemia.
- Altering the amino acid sequence ('designer' insulins, e.g. **lispro** and **glargine**) can usefully alter insulin kinetics.
- Insulins are used for all type 1 diabetic patients and approximately one-third of patients with type 2 diabetes.
- **Exenatide** is an incretin mimetic which is injected twice daily in some type 2 diabetic patients inadequately controlled by oral drugs. Unlike insulin it causes weight loss.

Oral hypoglycaemic drugs

- These are used in type 2 diabetes.
- Biguanides (e.g. **metformin**):
  - have complex peripheral actions in the presence of residual insulin, increasing glucose uptake in striated muscle and inhibiting hepatic glucose output and intestinal glucose absorption
  - cause anorexia and encourage weight loss
  - can be combined with sulfonylureas.
- Sulfonylureas and other drugs that stimulate insulin secretion (e.g. **tolbutamide**, **glibenclamide**, **nateglinide**):
  - can cause hypoglycaemia (which stimulates appetite and leads to weight gain)
  - are effective only if B cells are functional
  - block ATP-sensitive potassium channels in B cells
  - are well tolerated but promote weight gain.
- Thiazolidinediones (e.g. **pioglitazone**):
  - increase insulin sensitivity and lower blood glucose in type 2 diabetes
  - can cause weight gain and oedema
  - increase osteoporotic fractures
  - are peroxisome proliferator-activated receptor-γ (a nuclear receptor) agonists.
- Gliptins (e.g. **sitagliptin**):
  - potentiate endogenous incretins by blocking DPP-4
  - are added to other orally active drugs to improve control in patients with type 2 diabetes
  - are well tolerated and weight neutral.
- α-Glucosidase inhibitor, **acarbose**:
  - reduces carbohydrate absorption
  - causes flatulence and diarrhoea.

Clinical uses of oral hypoglycaemic drugs

- *Type 2 diabetes mellitus*, to reduce symptoms from hyperglycaemia (e.g. thirst, excessive urination). ('Tight' control of blood glucose has only a small effect on vascular complications in this setting.)
- **Metformin** is preferred for obese patients unless contraindicated by factors that predispose to lactic acidosis (renal or liver failure, heart failure, hypoxaemia).
- **Acarbose** (α-glucosidase inhibitor) reduces carbohydrate absorption; it causes flatulence and diarrhoea.
- Drugs that act on the sulfonylurea receptor (e.g. **tolbutamide**, **glibenclamide**) are well tolerated but often promote weight gain.
- Glitazones (e.g. **pioglitazone**) improve control (reduce haemoglobin A_{1C}) but increase weight, cause fluid retention and increase risk of fractures.
- Gliptins (e.g. **sitagliptin**) improve control, are well tolerated and weight neutral, but long-term experience is lacking.

DRUG CLASS	MECHANISM OF ACTION	EFFECT ON PLASMA INSULIN	RISK OF HYPO-GLYCEMIA	COMMENTS
First-generation sulfonylureas ***Tolbutamide***	Stimulates insulin secretion	↑	Yes	Well-established history of effectiveness. Weight gain can occur.
Second-generation sulfonylureas ***Glipizide*** ***Glyburide*** ***Glimepiride***	Stimulates insulin secretion	↑	Yes	Well-established history of effectiveness. Weight gain can occur.
Glinides ***Nateglinide*** ***Repaglinide***	Stimulates insulin secretion	↑	Yes (rarely)	Short action with less hypoglycemia either at night or with missed meal. Post-prandial effect.
Biguanides ***Metformin***	Decreases endogenous hepatic production of glucose	↓	No	Preferred agent for type 2 diabetes. Well-established history of effectiveness. Weight loss may occur. Monitor renal function.
Thiazolidinediones (glitazones) ***Pioglitazone*** ***Rosiglitazone***	Binds to peroxisome proliferator–activated receptor-γ in muscle, fat and liver to decrease insulin resistance.	↓↓	No	Effective in highly insulin-resistant patients. Once-daily dosing for *pioglitazone*. Monitor liver function.
α-Glucosidase inhibitors ***Acarbose*** ***Miglitol***	Decreases glucose absorption	⟺	No	Taken with meals. Adverse gastro-intestinal effects.
DPP-IV inhibitors ***Sitagliptin*** ***Saxagliptin***	Increases glucose-dependent insulin release; decreases secretion of glucagon	↑	No	Once-daily dosing. May be taken with or without food. Well tolerated.
Incretin mimetics ***Exenatide*** ***Liraglutide***	Increases glucose-dependent insulin release; decreases secretion of glucagon; slows gastric emptying; increases satiety.	↑	No	Because of its short duration of action, *exenatide* should be injected twice daily within 60 minutes prior to morning and evening meals *Liraglutide* is has a long half-life, allowing for once-daily dosing without regard to meals.

Figure 24.13
Summary of oral agents used to treat diabetes. ⟺ = little or no change. DDP-IV = dipeptidyl peptidase-IV.

SUMMARY Drugs Used for Diabetes

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
INSULINS				
• Rapid-acting: Lispro, aspart, glulisine • Short-acting: Regular • Intermediate-acting: NPH • Long-acting: Detemir, glargine	Activate insulin receptor	Reduce circulating glucose • promote glucose transport and oxidation; glycogen, lipid, protein synthesis; and regulation of gene expression	Type 1 and type 2 diabetes	Parenteral (SC or IV) • duration varies (see text) • *Toxicity:* Hypoglycemia, weight gain, lipodystrophy (rare)
SULFONYLUREAS				
• Glipizide • Glyburide • Glimepiride	Insulin secretagogues: Close K^+ channels in beta cells • increase insulin release	In patients with functioning beta cells, reduce circulating glucose • increase glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Orally active • duration 10–24 h • *Toxicity:* Hypoglycemia, weight gain
• *Tolazamide, tolbutamide, chlorpropamide: Older sulfonylureas, lower potency, greater toxicity; rarely used*				
GLITINIDES				
• Repaglinide	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduces circulating glucose • increases glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Oral • very fast onset of action • duration 5–8 h • *Toxicity:* Hypoglycemia
• Nateglinide	Insulin secretagogue: Similar to sulfonylureas with some overlap in binding sites	In patients with functioning beta cells, reduces circulating glucose • increases glycogen, fat, and protein formation • gene regulation	Type 2 diabetes	Oral • very fast onset and short duration (< 4 h) • *Toxicity:* Hypoglycemia
BIGUANIDES				
• Metformin	Obscure: Reduced hepatic and renal gluconeogenesis	Decreased endogenous glucose production	Type 2 diabetes	Oral • maximal plasma concentration in 2–3 h • *Toxicity:* Gastrointestinal symptoms, lactic acidosis (rare) • cannot use if impaired renal/hepatic function • congestive heart failure (CHF), hypoxic/acidotic states, alcoholism
ALPHA-GLUCOSIDASE INHIBITORS				
• Acarbose, miglitol	Inhibit intestinal α-glucosidases	Reduce conversion of starch and disaccharides to monosaccharides • reduce postprandial hyperglycemia	Type 2 diabetes	Oral • rapid onset • *Toxicity:* Gastrointestinal symptoms • cannot use if impaired renal/hepatic function, intestinal disorders

(*continued*)

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
THIAZOLIDINEDIONES				
• Pioglitazone	Regulates gene expression by binding to PPAR-γ and PPAR-α	Reduces insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • *Toxicity:* Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease
• Rosiglitazone	Regulates gene expression by binding to PPAR-γ	Reduces insulin resistance	Type 2 diabetes	Oral • long-acting (> 24 h) • *Toxicity:* Fluid retention, edema, anemia, weight gain, macular edema, bone fractures in women • cannot use if CHF, hepatic disease • may worsen heart disease
GLUCAGON-LIKE POLYPEPTIDE-1 (GLP-1) RECEPTOR AGONISTS				
• Exenatide	Analog of GLP-1: Binds to GLP-1 receptors	Reduces post-meal glucose excursions: Increases glucose-mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Parenteral (SC) • half-life ~2.4 h • *Toxicity:* Nausea, headache, vomiting, anorexia, mild weight loss, pancreatitis
• *Liraglutide: Similar to exenatide; duration up to 24 h; immune reactions, possible thyroid carcinoma risk*				
DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS				
• Sitagliptin	DPP-4 inhibitor: Blocks degradation of GLP-1, raises circulating GLP-1 levels	Reduces post-meal glucose excursions: Increases glucose-mediated insulin release, lowers glucagon levels, slows gastric emptying, decreases appetite	Type 2 diabetes	Oral • half-life ~12 h • 24-h duration of action • *Toxicity:* Rhinitis, upper respiratory infections, headaches, pancreatitis, rare allergic reactions
• *Saxagliptin, linagliptin: Similar to sitagliptin; longer duration of action*				
AMYLIN ANALOG				
• Pramlintide	Analog of amylin: Binds to amylin receptors	Reduces post-meal glucose excursions: Lowers glucagon levels, slows gastric emptying, decreases appetite	Type 1 and type 2 diabetes	Parenteral (SC) • rapid onset • half-life ~ 48 min • *Toxicity:* Nausea, anorexia, hypoglycemia, headache
BILE ACID SEQUESTRANT				
Colesevelam hydrochloride	Bile acid binder	Lowers glucose through unknown mechanisms	Type 2 diabetes	Oral • 24-h duration of action • *Toxicity:* Constipation, indigestion, flatulence

Thank you for checking our team!

Pharmacology 435

@ pharmacology435

Sources:

1. Pharmacology (Lippincotts Illustrated Reviews Series), chapter 24, 5th edition.
2. Basic & Clinical Pharmacology by Katzung, chapter 41,12th edition.
3. Rang & Dale's pharmacology, chapter 30, 7th edition.