King Saud University

College of Medicine

2nd Year, Endocrine Block

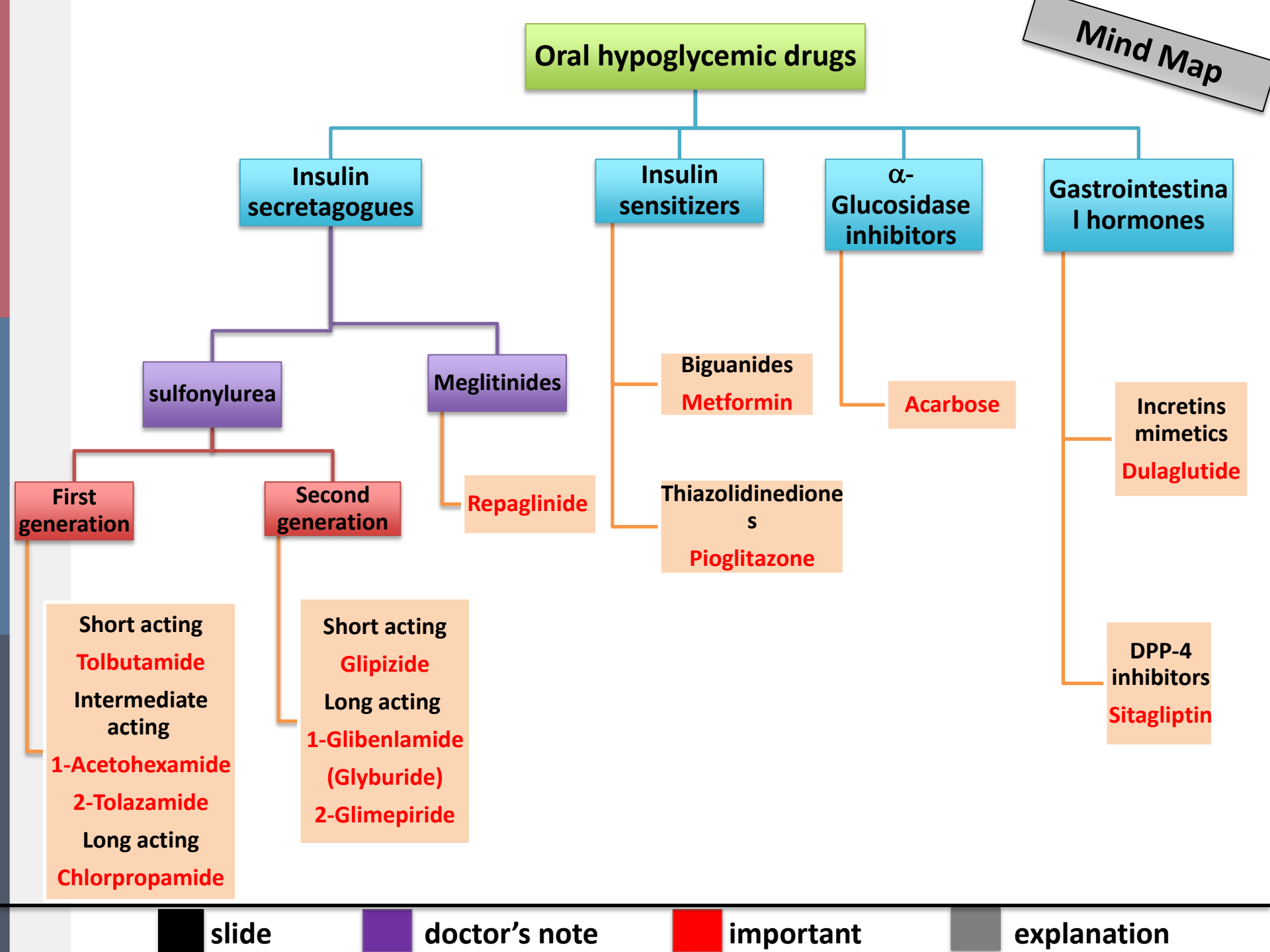
PHARMACOLOGY 433

MED 433 Teams

L8+9-Oral hypoglycemic drugs

Objectives

- ✓ Classify different categories of oral hypoglycemic drugs.
- ✓ Identify mechanism of action, pharmacokinetics and pharmacodynamics of each class of oral hypoglycemic drugs.
- ✓ Identify the clinical uses of oral hypoglycemic drug.
- ✓ Know the side effects, contraindications of each class of oral hypoglycemic drugs.


Mind Map
Oral hypoglycemic drugs
Insulin secretagogues
Insulin sensitizers
α-Glucosidase inhibitors
Gastrointestinal hormones
sulfonylurea
Meglitinides
Biguanides
Metformin
Acarbose
Incretins mimetics
Dulaglutide
First generation
Second generation
Repaglinide
Thiazolidinediones
Pioglitazone
Short acting
Tolbutamide
Intermediate acting
1-Acetohexamide
2-Tolazamide
Long acting
Chlorpropamide
Short acting
Glipizide
Long acting
1-Glibenlamide
(Glyburide)
2-Glimepiride
DPP-4 inhibitors
Sitagliptin
slide
doctor's note
important
explanation

INTRODUCTION

Type 2 Diabetes mellitus

- 80-90% occurrence .
- Over age 35 .
- Pancreatic β-cells are not producing enough insulin (Beta cells still working) .
- Obesity is an important factor.
- Insulin resistance in peripheral tissues.
- Treated by oral hypoglycemic drugs.

Notes:

1-Most of the drugs are taking orally + metabolized in liver & excreted in urine and there is some **EXCPTION**

2- Oral drugs can NOT be given to pregnant women cause it has **high teratogenic effect**

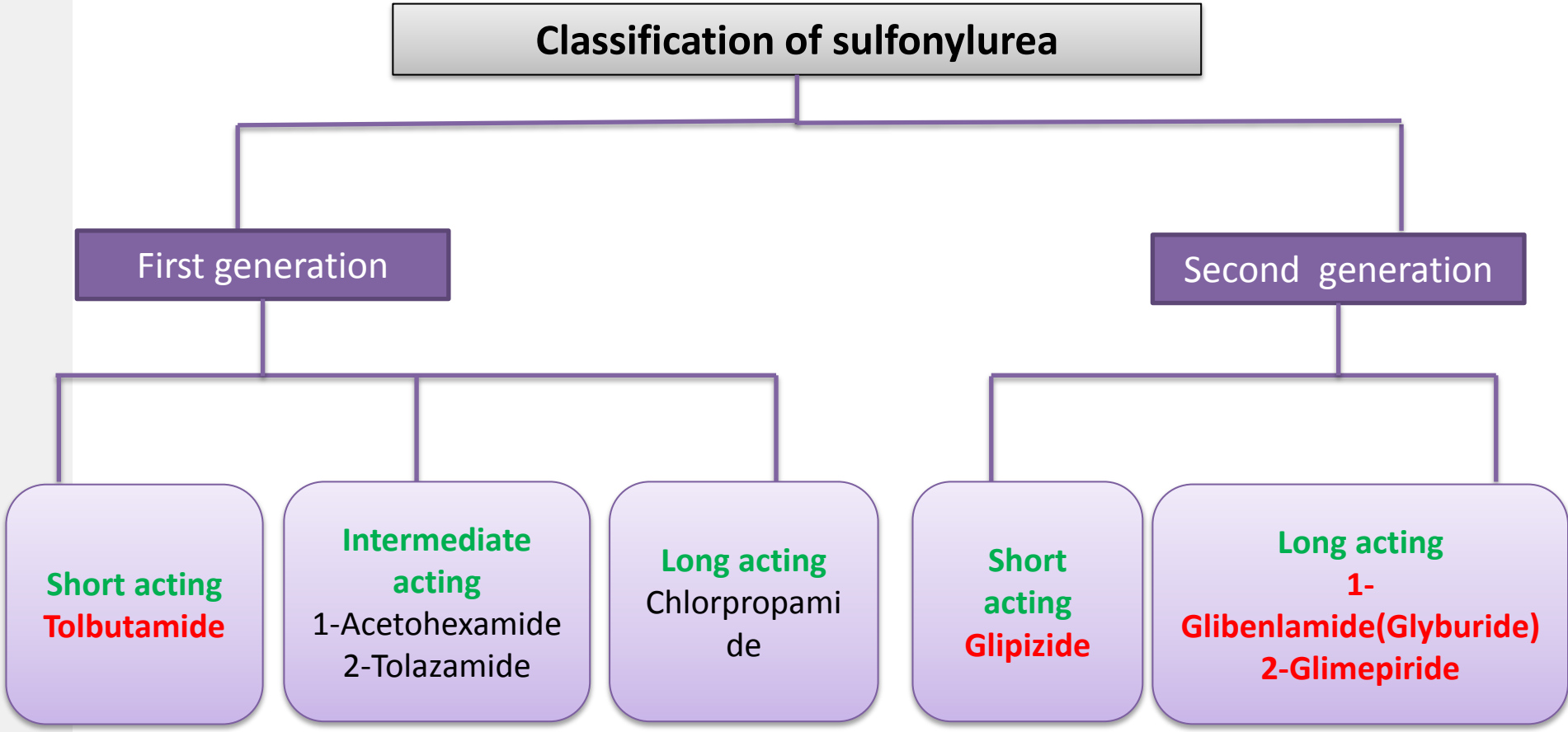
1)Insulin secretagogues

Are drugs which increase the amount of insulin secreted by the pancreas.

Include:

1-Sulfonylurea

2-Meglitinides



1)Sulfonylureas

Mechanism of action	▪ Stimulate insulin release from functioning B cells by blocking of ATP-sensitive K channels → causes depolarization and opening of voltage-dependent calcium channels→causes an increase in intracellular calcium in the beta cells→ stimulates insulin release(Exocytosis).
Pharmacokinetics	▪ Orally, well absorbed. ▪ Reach peak concentration after 2-4 hours. ▪ All are highly bound to plasma protein (drug drug interactions) ▪ Duration of action is variable. ▪ **Second generation has longer duration than first generation.** ▪ Metabolized in liver. ▪ Excreted in urine (not use to elderly and renal disease). ▪ **Cross placenta** → stimulate fetal β cell to release insulin → Fetal hypoglycemic at birth.
Adverse effects	**1)Hyperinsulinemia & Hypoglycemia** • **Less in tolbutamide** • More in long acting sulfonylurea • More in old age , hepatic or renal disease **2)Weight gain** due to increase in appetite 3)Crystalluria(Because it contains sulfa)
Contraindication	▪ Pregnant women because it crosses placenta (It is better to treat her with insulin injection) ▪ Patients allergic to sulfur (Because it contains sulfa)

First generation sulfonylureas

	Short acting	Intermediate acting		Long acting
	Tolbutamide	Acetohexamide	Tolazamide	Chlorpropamide
Absorption	Well	Well	Slow	Slow
Metabolism	Yes	Yes	Yes	Yes
Metabolites	Inactive	Active	Active	Inactive
Duration of action	Short (6-8 hrs)	Intermediate (12-20 hrs)	Intermediate (12-18 hrs)	Long (20-24 hrs)
Excretion	Urine	Urine	Urine	Urine

Tolbutamide:

- **safe for old diabetic patients or patients with renal impairment.**

Second generation sulfonylureas

	Short	Long	
	Glipizide	Glibenclamide	Glimepride
Absorption	Well reduced by food	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites	Inactive	Inactive	Inactive
Duration of action	(10-16 hrs)	(12-24 hrs)	(12-24 hrs)
Doses	Divided doses 30 min before meals	Single dose	Single dose 1 mg
Excretion	Urine	Urine	Urine

Glipizide , Glibenclamide , Glimepride:

- **More potent than first generation**
- **Have longer duration of action**
- **Less frequency of administration**
- **Have fewer adverse effects**
- **Have fewer drug interactions**

2)Meglitinides

Repaglinide :are **rapidly acting** insulin secretagogues.

Mechanism of Action	▪ Insulin secretagogue ▪ Mechanism of action is identical to sulfonylureas.
Pharmacokinetics	▪ Orally, well absorbed. ▪ Very fast onset of action, peak 1 h. ▪ Short duration of action (4 h). ▪ Metabolized in liver and **excreted in bile.** ▪ Taken just before each meal (3 times/day).
Uses	▪ Type II diabetes:monotherapy or in combination with other oral hypoglycemic drugs. ▪ **Safe for Patients allergic to sulfur or sulfonylureas**
Adverse effects	▪ Less incidence than sulfonylureas Hypoglycemia and Weight gain.

2) Insulin sensitizers

Are drugs which increase the sensitivity of target organs to insulin.

Include:

1-Biguanides (Metformin)

2-Thiazolidinediones (Pioglitazone)

1)Metformin (Glucophage)

Mechanism of Action	▪ **Increases peripheral glucose utilization (tissue glycolysis)** ▪ **Reduces insulin resistance.** ▪ **Inhibits hepatic gluconeogenesis.** ▪ **↓LDL &VLDL** ▪ **↑ HDL**
Pharmacokinetics	▪ orally. ▪ NOT bound to serum protein. ▪ NOT metabolized. ▪ t ½ 3 hours. ▪ Excreted unchanged in urine
Uses	▪ **overweight patients with type 2 diabetes** (first-line therapy). ▪ Type II diabetes as monotherapy or in combination.

1)Metformin	
Adverse effects	▪ **GIT disturbances: nausea, vomiting, diarrhea** ▪ **Lactic acidosis. (rare)** ▪ Interference with **vitamin B_{12} absorption** (long term use). ▪ Metallic taste in the mouth
The Advantages	▪ **No risk of hypoglycemia or weight gain** ▪ **Improvement of lipid profile** ▪ **Inexpensive**
Contraindications	▪ **Renal disease.** (cause it excreted in urine) ▪ **Liver disease.** (cause it metabolite in liver) ▪ **Alcoholism.**(can increase lactic acid) ▪ **Cardiopulmonary dysfunction.** ▪ **Pregnancy.**

Note:
To prevent ! we can use metformin in pre diabetic or anyone who are mostly prone to get diabetes

2)Pioglitazone

Mechanism of Action	▪ Activate peroxisome proliferator-activated receptor -γ (PPAR-γ) (nuclear receptors in muscles and adipose tissue). ▪ Increase glucose uptake and utilization in muscle and adipose tissue. ▪ Increase sensitivity of target tissues to insulin.
Pharmacokinetics	▪ Orally (once daily dose). ▪ Highly bound to plasma albumins (99%) ▪ Slow onset of activity (cause it work at level of receptors) ▪ Half life 3-4 h ▪ Metabolized in liver & Excreted in urine 64% & bile
Uses	▪ Type II diabetes with insulin resistance. ▪ Used either alone or combined with sulfonylurea, biguanides or insulin. ▪ No risk of hypoglycemia when used alone
Adverse effects	▪ Hepatotoxicity (liver function tests for 1st year of therapy) ▪ Fluid retention (Edema). ▪ Congestive heart failure ▪ Mild weight gain.(due to fluid retention) ▪ Failure of estrogen-containing oral contraceptives

slide | doctor's note | important | explanation

3)Last group (we can say it is “add on therapy” group)

Include

1-Alpha glucosidase inhibitors (Acarbose & Miglitol)

2-Gastrointestinal hormones:

2-1Incretins (GLP-1) mimetics (Dulaglutide, Liraglutide, Albiglutide, Exenatide)

2=2Dipeptidyl peptidase-4 (DPP-4) inhibitors (Sitagliptin, vildagliptin)

1)α-Glucosidase inhibitors

E.G **Acarbose**	**1-** Given orally **2-**is not absorbed. **3-**Excreted in feces **4-**Taken just before meals. **5-**No hypoglycemia if used alone.
Mechanism of Action	▪ Reversible inhibitors of intestinal α-glucosidases in intestinal brush border that are responsible for carbohydrate digestion. ▪ decrease carbohydrate digestion and glucose absorption in small intestine (**lower postprandial glucose level**).
Uses	▪ are effective alone in the earliest stages of **impaired glucose tolerance** ▪ **are not recommended alone as therapy for moderate to severe hyperglycemia** ▪ **are most useful in combination** with other oral hypoglycemic drugs or with insulin.
Adverse effects	▪ **GIT side effects:** Flatulence, diarrhea, abdominal pain, bloating
Contraindications	▪ **irritable bowel syndrome** ▪ **Inflammatory bowel disorders** ▪ **Intestinal obstruction.**

2)Gastrointestinal hormones

2-1- Incretins (GLP-1) mimetics (glucagon-like peptide-1)

e.g. Dulaglutide

Definition	MOA	Rout of adminstration	Uses	ADRs
Incretins are hormones secreted from intestine in response to food, carried through circulation to beta cells	Stimulate insulin secretion & decrease glucagon secretion then decrease blood glucose **Inactivated by** **(dipeptidyl peptidase-4 (DPP-4).**	given s.c. Once a week	Therapy of patients with type 2 diabetes who are not controlled with oral medicine	Nausea – vomiting (most common). -Abdominal pain -decreased appetite & fatigue

2-2- Dipeptidyl peptidase-4 inhibitor (DPP- 4 inhibitors)

e.g. Sitagliptin

MOA	Rout of adminstration	uses	ADRs
Inhibit DPP-4 enzyme thus increase incretin hormone (GLP-1).	Orally Given once daily	Type II DM as an adjunct to diet & exercise as a monotherapy or in combinantidiabetic ation with other drugs	Nausea abdominal pain, diarrhea

For your knowledge

Hyperglycemic patient first advices him to change his diet and exercises more

If glucose level still high we give him Insulin sensitizers

If it doesn't work we give him insulin secretagogues in combination with insulin sensitizers

Glucose level still high we give him the last group of drugs in combination with the drugs above .

* Insulin therapy is the last option if the patient not responding to the first therapy

SUMMARY

Class	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas Tolbutamide	Stimulates insulin secretion	Pancreatic beta cells	• Effective • Inexpensive	• Hypoglycemia • Weight gain
Meglitinides repaglinide		Pancreatic beta cells	Sulfa free	•Hypoglycemia •Weight gain
Biguanides Metformin	Decreases insulin resistance	Liver	• mild weight loss • No hypoglycemia	• GIT symptoms, • Lactic acidosis • Metallic taste
Thiazolidinediones pioglitazone		Fat, muscle	No hypoglycemia	Hepatoxicity Edema, mild weight gain
α-Glucosidase inhibitors Acarbose	Inhibits α-glucosidase	GI tract	Low risk	•GI symptoms, flatulence
Incretins mimetics Dulaglutide	Increase incretin	GI tract	Once/week, s.c.	Nausea & vomiting
DPP-4 inhibitors Sitagliptin	Inhibit incretin breakdown	GI tract		Nausea & abdominal pain

Quiz yourself

Q1: female, 62 years old, diabetic with renal impairment, which hypoglycemic drug safe in her condition?
A-tolbutamide
B-glipizide
C-Glyburide
D-metformin

Q2: male, 54 years old, diabetic, yesterday he was unwell, he felt thirst and he has palpitation, tremors, hallucination end with coma, which drug can cause these symptoms?
A-acrabose
B-pioglitazone
C-glipizide
D-metformin

Q3: male, 43 years old, he begin with hypoglycemic drugs, suddenly he has swelling of her face, mouth, tongue and sever hypotension, which drug can cause these symptoms?
A-repaglinide
B-dulaglutide
C-glyburide
D-acrabose

Q4: which one of the following hypoglycemic drugs can decrease LDL and increase HDL?
A-metformin
B-glipizide
C-Glyburide
d-repaglinide

Q5: female, 36 years old, obese with developing T2DM, which one of the following drugs is better for her condition?
A-metformin
b-repaglinide
C-Glyburide
d-glipizide

Q6: female, 32 years old, diabetic, she take oral contraceptive, which hypoglycemic drug she should avoid?
A-tolbutamide
B-pioglitazone
C-Glyburide
D-dulaglutide

Q7: all of these hypoglycemic drugs used orally except?
A-sitagliptin
B-miglitol
c-pioglitazone
D-dulaglutide

Answers: Q1: a Q2: c Q3: c Q4: a Q5: a Q6: b Q7: d

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We hope that we made this lecture easier for you
Good Luck !