Drugs used in DM type 2

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

No objectives

Dr. Fouda Video

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Type 2 Diabetes Mellitus (DM)

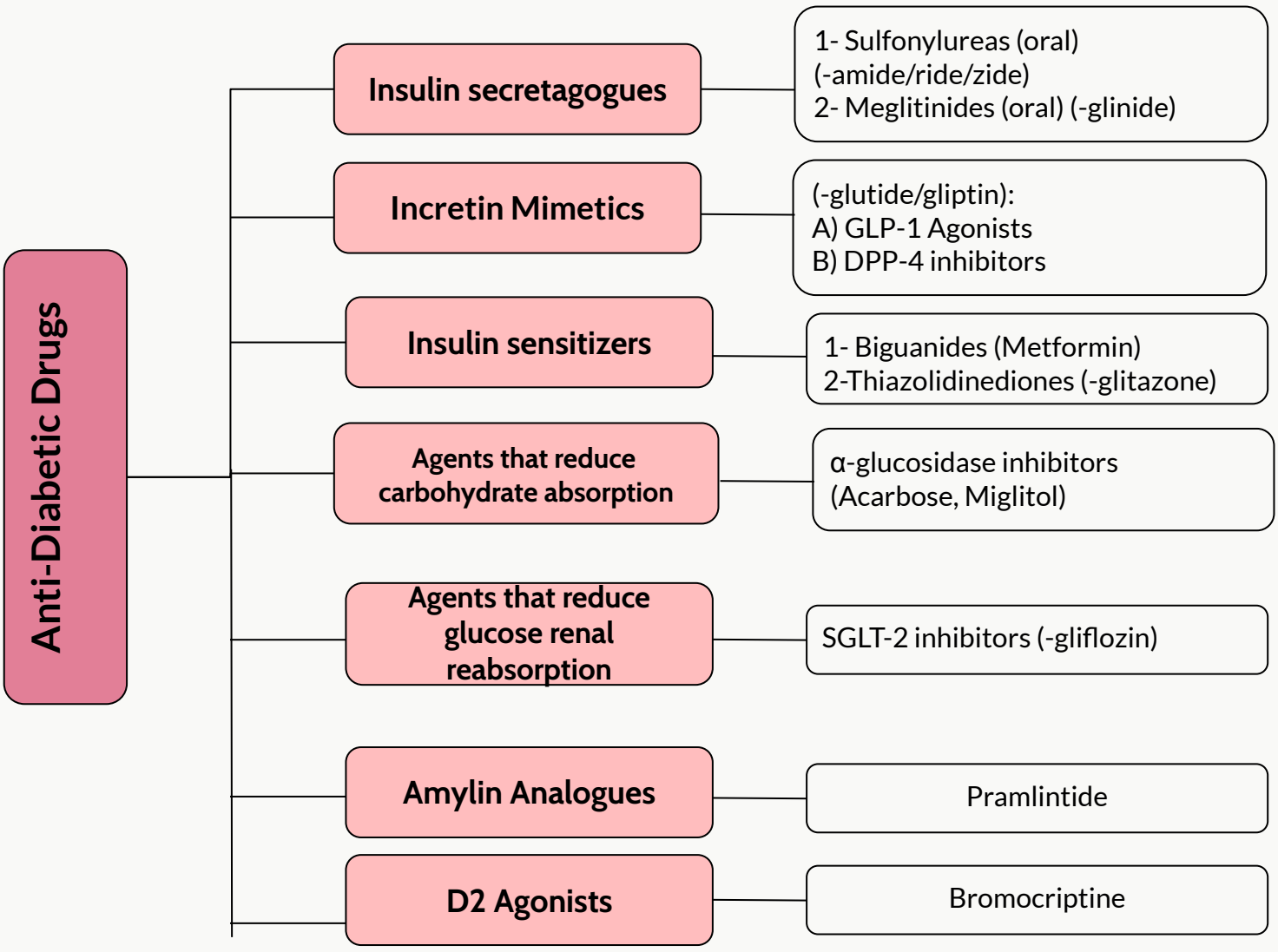
- 90 - 95 % occurrence
- Over age 35

Causes:

- Obesity is an important factor.
- Abnormal insulin secretion.
- Resistance to insulin action in target tissues associated with decreased number of insulin receptors. (sensitivity)

Treatment of Type 2 DM

- Proper Dietary Management (First Line)
- Caloric restriction and weight loss are important in obese diabetic patients
- Increase physical activity
- Antidiabetic drugs (used if lifestyle changes are not effective, first-line therapy is metformin)



Oral Antidiabetic Drugs

1. Insulin Release (Secretagogues)

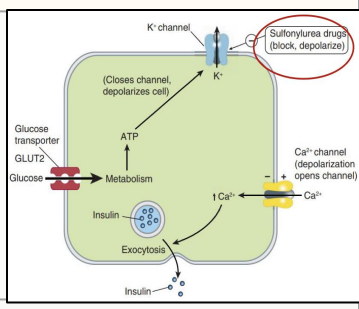
Drugs which increase the amount of insulin secreted by the pancreas
- Their action depends upon functioning pancreatic β-cells so not used in T1DM
- include: **1. Sulfonylureas 2. Meglitinides**

A) Sulfonylureas

	First generation		Second generation	
Drugs	**Short acting**	**Long acting**	**Short acting**	**Long acting**
	Tolbutamide	**Acetohexamide** **Tolazamide** **Chlorpropamide**	**Gliclazide** **Glipizide**	**Glyburide (glibenclamide)** (هو الوحيد اللي ممكن يستخدم في سكر الحمل) **Glimepiride**

M.O.A

they **stimulate insulin release from functioning β cells by**
1- blocking of ATP-sensitive K channels which causes depolarization and
2- opening of voltage- dependent calcium channels, which causes
3- an increase in intracellular calcium in the β cells, which
4- stimulates insulin release.



P.K

- Orally, well absorbed.
- Reach peak concentration after 2-4 hr.
- All are highly bound to plasma proteins. (Risk of drug interactions like salicylates/ Compete for binding sites) will increase the effect of sulfonylurea
- Duration of action is variable. Second generation has longer duration than first generation.
- Metabolized in liver
- Excreted in urine (their action is increased in elderly and renal disease).
- Cross placenta and enters breast milk, stimulate fetal β-cells to release insulin → fetal hypoglycemia at birth

Advantages of second generation:
- More potent than first generation.
- Longer duration of action.
- Less frequency of administration. (high frequency in elderly and children)
- Fewer adverse effects & drug interactions.

Uses

Treatment of Type 2 diabetes monotherapy or in combination with other antidiabetic drugs

ADRs

1. Hyperinsulinemia & Hypoglycemia: that is why it's not the first line, Unlike metformin
   - More common in long acting sulfonylureas; particularly (glyburide, glimepiride)
   - More in old age, hepatic or renal diseases. (avoid long acting and give short acting instead)
2. Weight gain due to increase in appetite
3. Allergic rashes can occur, and bone marrow toxicity

Contraindications? Pregnancy, renal disease, Liver disease

Oral Antidiabetic Drugs

1. Insulin Release (Secretagogues)

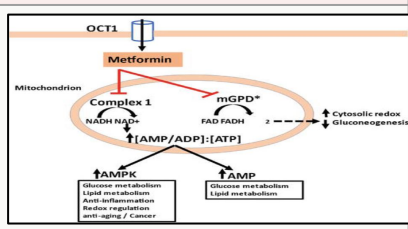
B) Meglitinides

Drugs	**Repaglinide & Nateglinide**
M.O.A	• Rapidly acting insulin secretagogues. • Mechanism of action is identical to sulfonylureas (stimulate insulin release by blocking ATP-sensitive K+ channels)
P.K	• Orally, well absorbed. • Very fast onset of action, peak 1 h. • Short duration of action (4 h). • Taken just before each meal (3 times/day). • Control postprandial glucose & the dose should be skipped if the meal is missed. • Metabolized in liver and excreted in bile.
Uses	• Type 2 diabetes: monotherapy or in combination with other oral hypoglycemic drugs. • As alternative to sulfonylureas (SU) in patients allergic to them (SU).
ADRs	- **Less incidence than sulfonylureas:** • Hypoglycemia. • Weight gain.

2. Insulin sensitizers

A) Biguanides

Drugs	**Metformin**
M.O.A (Important)	• It has specific action on mitochondrial respiration that reduce intracellular ATP and activation of AMP-dependent kinase(AMPK) leading to reduced insulin resistance (reduce intracellular ATP) • Increase sensitivity of liver, muscle & adipose tissues to insulin. • Increase peripheral glucose utilization (tissue glycolysis). • Inhibits hepatic glucose production (gluconeogenesis). • Impairs glucose absorption from GIT. • Improve lipid profile:↓LDL,↓VLDL ,↑HDL (DM patients have abnormal lipid profile) • Stimulation of hepatic fatty acid oxidation



Oral Antidiabetic Drugs

2. Insulin sensitizers

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

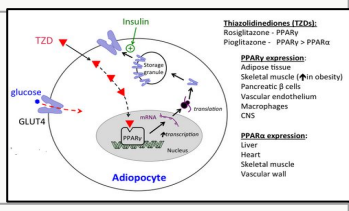
A) Biguanides

Drugs	Metformin
P.K	• Given orally • Not bound to serum protein • t 1/2: 3 hours • Not metabolized, excreted unchanged in urine it is hydrophilic
Uses	• first-line therapy In patients with type 2 diabetes who are obese, because it promotes modest weight reduction. • Type 2 diabetes as monotherapy(prediabetes) or in combination • Infertility in women with polycystic ovarian syndrome (off labelled use means not the main use which the drug approved for)
Advantages	• No risk of hypoglycemia. "doesn't increase insulin release" • No weight gain. • Prominent lipid-lowering activity. • Inexpensive • Hypoglycaemia during Biguanide therapy is rare. Therefore it is termed (euglycemic agents)
ADRs	• GIT disturbances: - Metallic taste in the mouth, nauses, vomiting, diarrhea . - Metformin should be taken with meals and should be started at a low dose to avoid intestinal side effects then increase gradually (meals are protective) • Lactic acidosis (very rare): Serious lactic acid accumulation (pH around 7.2) usually occurs only in the presence of predisposing conditions: - Renal insufficiency(e.g. IV contrast) - Severe liver disease - Alcohol abuse - Heart failure - Pulmonary insufficiency - Cardiogenic or septic shock hypoxia=tissue injury=lactic acid accumulation • In long term use: Interference with vitamin B12 absorption
C.I	• Renal disease • Liver disease • Alcoholism • Cardiopulmonary dysfunction • Pregnancy (can be used, but in pregnancy insulin is your first choice)

Oral Antidiabetic Drugs

2. Insulin sensitizers

B) Thiazolidinediones (glitazones)

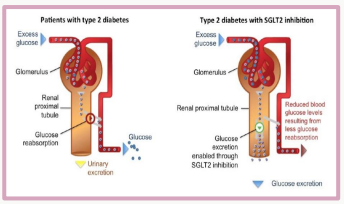
Drugs	Pioglitazone, Rosiglitazone
M.O.A	Activate peroxisome proliferator-activated receptor-γ (PPAR-γ) (nuclear receptor) → ↑ sensitivity of target tissues to insulin → ↑ glucose uptake and utilization in muscle and adipose tissue. nuclear receptor —>enhance transcription—>mRNA —> Translation —>(GLUT4) muscle\adipose
P.K	• Orally (once daily dose). • Highly bound to plasma albumins (99%) • Slow onset of activity, Half life 3-4 h. • Metabolized in the liver,Excreted in bile and urine 
Uses	• Type 2 diabetes with insulin resistance. • Used either alone or in combination with sulfonylurea, biguanides or insulin
ADRs	• Hepatotoxicity (liver function tests for 1st year of therapy) • Fluid retention (Edema) (PPAR-γ receptors are also present in the kidneys→ ↑reabsorption of Na → edema and vasodilation → may lead to heart failure) • Congestive heart failure • Mild weight gain Enhance fat storage • Failure of estrogen-containing oral contraceptives (DDI)
Advantage	No risk of hypoglycaemia when used alone (doesn't affect insulin)

3. α-Glucosidase inhibitors

Drugs	Acarbose	Miglitol
M.O.A	• Reversible inhibitors of intestinal α-glucosidases in intestinal brush border cells that are responsible for carbohydrate digestion. • ↓ carbohydrate digestion and glucose absorption in small intestine (lower postprandial glucose level).	
P.K	• Given orally, Not absorbed • Taken before meals, Excreted in feces • No hypoglycemia if used alone	
Uses	• Effective alone in the earliest stages of impaired glucose tolerance • Not recommended alone as therapy for moderate to severe hyperglycemia • Most useful in combination with other oral hypoglycemic drugs or with insulin.	
ADRs	• GIT: Flatulence, bloating, diarrhea, abdominal pain. Acarbose	
C.I	• Irritable bowel syndrome (IBS). • Inflammatory bowel disorders (IBD). • Intestinal obstruction.	

Oral Antidiabetic Drugs

4. glucose transporter inhibitor

Drugs	Canagliflozin, Dapagliflozin, Empagliflozin
M.O.A	• Glucose is freely filtered by the renal glomeruli and is reabsorbed in the proximal tubules by the action of sodium-glucose transporters (SGLTs). • **The SGLT2 inhibitors act by promoting glucose excretion into the urine,** thereby reducing the concentration of circulating glucose. The resulting glycosuria is associated with an osmotic diuresis and salt excretion. 
P.K	• Orally absorbed • Half life: 10-14 h
Uses	• Type 2 diabetes. • Have potentially beneficial effect on weight-blood pressure-cardiovascular outcome Decrease fluid retention
ADRs	• Urinary and genital tract infections • Polyuria and thirst • Itching in genital area (pruritus) • osmotic diuresis and constipation

5. D2-agonist

Drug	Bromocriptine
M.O.A	Lowers glucose through unknown mechanism inhibit the hypothalamus axis that increase glucagon which result in inhibition of glucagon release
P.K	• Oral drug • Duration of action up to 24h
ADRs	• Nausea and vomiting • Headache • Dizziness

Incretin mimetics & related drugs (Parenteral)

Definition

- Incretins are GI hormones secreted intestine in response to food (not secreted as long as we are not eating) even before blood glucose level becomes elevation..
- Carried through circulation to pancreatic β cells.

Include

1- GLP-1 (Glucagon-Like Peptide-1)

2- GIP (Gastric Inhibitory Peptide)

- **GLP-1** is secreted by L cells which are more widely distributed in the gut, including in the ileum and colon
- **GIP** is stored in and secreted by enteroendocrine K cells in the duodenum and proximal jejunum.

Both of these hormones are released by food ingestion and provide:

- Stimulating insulin secretion and reduce glucagon secretion.
- Slowing the rate of absorption of digested food by reducing gastric emptying.
- They are also implicated in control of food intake via appetite and satiety.
- The actions of GIP and GLP-1 are terminated Rapidly by dipeptidyl peptidase-4 (DPP-4).

Parenteral Antidiabetic Drugs

1. Incretin mimetics & related drugs

A) Glucagon-like peptide-1 (GLP-1) agonists

The GLP-1 sequences are modified to protect against the action of DPP-4.

Drugs	Dulaglutide	Liraglutide The only drug from this group that approved for weight loss	Exenatide
Overview	-	- **Victoza®**: is the lower dose for diabetes. S.C once daily - **Saxenda®**: is the higher dose for obesity. S.C once daily - As a treatment for adults who are obese or overweight with at least one weight related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia).	- **Byetta®**: immediate-release given S.C. twice daily - **Bydureon®**: extended-release given once weekly

M.O.A

- This class binds to GLP-1 receptors & stimulates insulin secretion from β cells.
  - Binding of agonists to the GLP-1 receptor activates the cAMP-PKA pathway. This alters the activity of several ion channels
  - In β cells, the end result of these actions is increased insulin biosynthesis and exocytosis in a glucose-dependent manner

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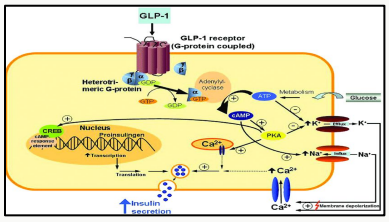
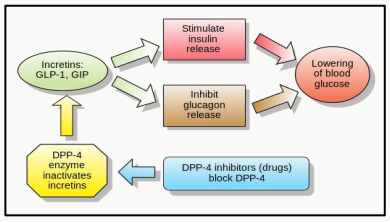
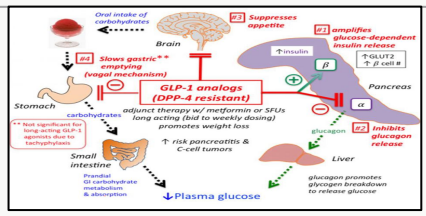
- It also reduces glucagon secretion by inhibiting alpha cells of the pancreas.
- Activation of GLP-1 receptors in the CNS accounts for decreasing appetite and gastric emptying, Thus inhibits body weight gain.





ADRs

- Nausea, vomiting and diarrhea (most common)
- Hypoglycemia when combined with Sulfonylureas or insulin
- Pancreatitis (rare).



Drug

Semaglutide (First oral GLP-1)

Uses

- **Ozempic ®:** (S.C once weekly): the injectable version was approved in December 2017
  - used for the treatment of type 2 diabetes and as anti-obesity medication for long-term weight management. may cause suicidal ideation and GI side effects

- **Rybelsus ®**(Orally once daily): was the first and only oral GLP-1 approved by US FDA to for type 2 diabetes treatment (Sep. 2019).

Parenteral Antidiabetic Drugs

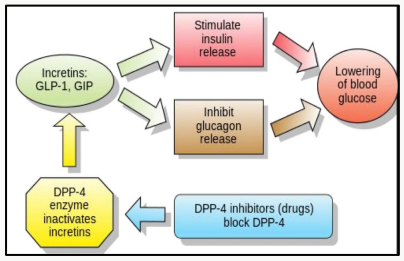
1. Incretin mimetics & related drugs

B. Gastric inhibitory polypeptide analogues

Drug	Tirzepatide (Mounjaro ®)
M.O.A	• It is dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist. • Tirzepatide has a greater affinity to GIP receptors than to GLP-1 receptors
Use	• It was approved for medical use in the United States in May 2022 • It is the first-in-class medication. It is used for the treatment of type 2 diabetes and obesity. S.C once weekly
ADRs	Nausea, diarrhea and vomiting
Advantages	• These medications aid in weight loss, reduce the risk of hypoglycaemia. • Contribute to cardiorenal protective effects. • Providing good glycemic control.

C. Dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitors)

e.g. Sitagliptin, vildagliptin

Drug	Sitagliptin (Januvia®)
M.O.A	• Inhibit DPP-4 enzyme and leads to an increase in incretin hormones (GLP-1)level. • This results in an increase in insulin secretion & decrease in glucagon secretion. • Slows gastric emptying, decreases appetite. 
P.K	Given orally/once daily.
Uses	Type 2 DM as an adjunct to diet & exercise as a monotherapy or In combination with other antidiabetic drugs.
ADRs	• Nausea, abdominal pain, diarrhea. • Nasopharyngitis. • Headache. • Pancreatitis, rare allergic reaction. • ↑ Upper respiratory tract infections.

Parenteral Antidiabetic Drugs

2- Amylin analogues

Drug	Pramlintide
Overview	• Islet amyloid polypeptide (amylin) • is produced in the pancreatic β cell and secreted with insulin
M.O.A	• Pramlintide likely acts through the amylin receptor in specific regions of the hindbrain. • Activation of the amylin receptor reduces glucagon secretion, delays gastric emptying, and fosters a feeling of satiety.
P.K	• synthetic form of amylin with several amino acid modifications to improve bioavailability. • administered as a S.C. prior to meals • Metabolism and clearance are primarily renal.
Uses	• Pramlintide is approved for treatment of types 1 and 2 diabetes as an adjunct inpatients who take insulin with meals. • Pramlintide is a pregnancy category C drug.
ADRs	The most common adverse effects are nausea and hypoglycemia especially with insulin.

Summary From the slides

Class	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas Gliclzide	Stimulates insulin secretion	Pancreatic beta cells	• Effective • Inexpensive	• Hypoglycemia • Weight (Wt) gain
Meglitinides Repaglinide			Sulfa free	•Hypoglycemia •Wt 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 wt gain
Incretins mimetics Dulaglutide	Increase incretin	GI tract	Once/week, s.c.	Nausea & vomiting
DPP-4 inhibitors Sitagliptin	Inhibit incretin breakdown	GI tract	orally	Nausea & abdominal pain
α-Glucosidase inhibitors Acarbose	Inhibits α-glucosidase	GI tract	Low risk	•GI symptoms, flatulence
SGLT-2 inhibitors Dapagliflozin	Inhibit renal SGLT-2	Kidney	Orally Reduced Na (CV benefits)	Genital yeast/UTI Increased urination

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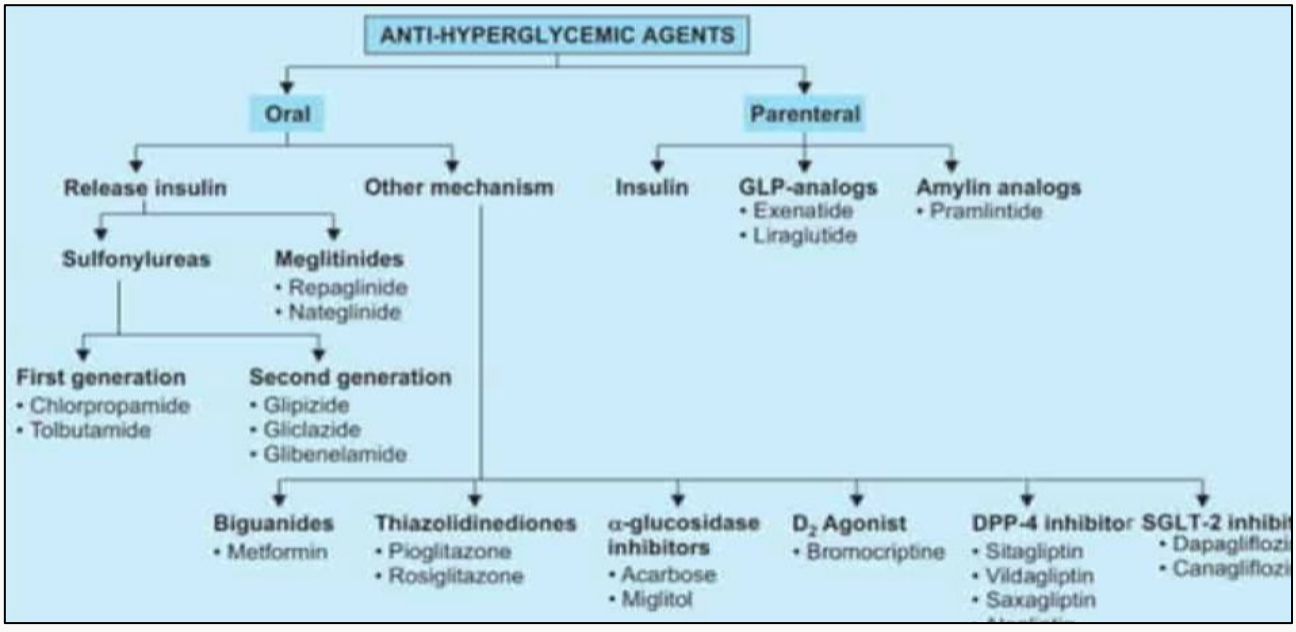

MCQ

Q1 Which of the following drugs should be avoided in renal failure?

A. Liraglutide	B. Acarbose	C. Glyburide	D. Repaglinide

Q2 Which of the following is an incretin mimetic?

A. Glucophage	B. Glitazone	C. Acarbose	D. Liraglutide

Q3 What is the mechanism of action of sitagliptin?

A. Block ATP-sensitive K channels	B. inhibits alpha glucosides	C. Activates PPAR gamma	D. Inhibits DPP-4

Q4 Which one of these drugs is contraindicated in patients allergic to sulfur?

A. Isophane	B. Metformin	C. Repaglinide	D. Tolbutamide

Q5 A patient with DM is being treated with thiazolidinediones. The drug also caused a decrease in lipids because of its action on which of the following?

A. Carnitine palmitoyl transferase	B. Leptin	C. PPAR-gamma	D. Ghrelin

Q6 Which of the following group of drugs is classified as an insulin sensitizer?

A. Biguanides, such as metformin	B. Meglitinides	C. sulfonylurea drugs	D. None of the above

1:C ,2:D ,3:D ,4:D ,5:C ,6:A

SAQ

1 **Name GLP-1 agonists and specify their route of administration**

Liraglutide (S.C), Dulaglutide (S.C), Exenatide (S.C)

2 **What is the mechanism of action of Metformin**

Decrease hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity of liver, muscle and adipose tissue and increases peripheral glucose uptake and utilization

3 **What are some precautions when taking Sulfonylureas?**

Pregnancy, allergies, elderly, liver and kidney diseases

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