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Introduction

- Type 2 diabetes must be managed in the context of the metabolic syndrome.
- At the time of diagnosis, many people with Type 2 diabetes already have evidence of macrovascular and microvascular disease

Biguanides

- Metformin
- Immediate-release and the extended-release
- MECHANISM OF ACTION
- First-line therapy:
- Reduction in all-cause mortality and vascular complications independent of glycemic control
- Modestly lowers total cholesterol and triglycerides ,Improve HDL-C levels
- Mean weight loss of 0.5 to 3.8 kg can occur in adults receiving metformin immediate-release tablets as monotherapy

ADVERSE EFFECTS

- Gastrointestinal Effects
- Diarrhea and other GI disturbances such as nausea, abdominal discomfort, metallic taste, flatulence and anorexia
- Lactic Acidosis

CONTRAINDICATIONS AND PRECAUTIONS

- Patients with renal impairment, liver disease, or other states predisposing them to hypoxia, acute or chronic metabolic acidosis, DKA, or a history of lactic acidosis should be excluded from therapy

- Not recommended in ≥1.4 mg/dL for women or ≥1.5 mg/dL for men

DRUG INTERACTIONS

- Alcohol
- Vitamin B12
- Topiramate
- Parenteral contrast use iodinated materials

EFFICACY

- As monotherapy, metformin can be expected to reduce the A1C by 1.3% to 2.0% and the FPG by 50 to 70 mg/dL.
- **Polymorphisms**

- For patients unable to achieve goals of therapy with metformin alone within 3 months of initiating therapy, addition of insulin or another agent should be considered

Nonsulfonylurea Insulin Secretagogues (Glinides)

- Repaglinide (Prandin)
- Nateglinide (Starlix)

- MECHANISM OF ACTION
- Rapid onset and shorter duration of action

Nonsulfonylurea Insulin Secretagogues (Glinides)

- ADVERSE EFFECTS
- Hypoglycemia
- Weight gain
- Elevated hepatic enzymes
- Hypersensitivity reactions

CONTRAINDICATIONS AND PRECAUTIONS

- Not be used in Type 1 diabetes
- With caution in patients with liver dysfunction.
- Contraindicated in patients with DKA.
- Repaglinide clearance is reduced in patients with severe renal insufficiency, but may still be used safely at a reduced dose.

DRUG INTERACTIONS

- Gemfibrozil should be avoided in combination with repaglinide owing to the risk of hypoglycemia.
- Concomitant use of Clopidogrel may result in increased serum concentrations of repaglinide; therefore, dose reduction of repaglinide may be required
- Cyclosporine inhibits the metabolism of repaglinide causing increased serum concentrations of repaglinide

EFFICACY

- As monotherapy, the mean decrease in FPG, postprandial glucose, and the A1C values were 61 mg/dL, 104 mg/dL, and 1.7%, respectively.

DOSAGE AND CLINICAL USE

- In Type 2 diabetes as monotherapy or in combination with metformin or a TZD

- As the initial treatment ,in patients who are naïve to oral antidiabetic therapy or in patients with A1C values less than 8%, the recommended starting dose is 0.5 mg 15 to 30 minutes prior to eating up to 4 times a day

- When used in patients who have failed sulfonylureas or in those with A1C values greater than 8%, the initial dose is 1 to 2 mg with each meal up to 4 times a day.

DOSAGE AND CLINICAL USE

- Maximum of 4 mg/dose or 16 mg/day
- Repaglinide should be initiated at a 0.5-mg dose in patients with severe renal dysfunction
- Should be titrated cautiously in patients with liver dysfunction

Sulfonylureas

- Until metformin and other antidiabetic agents became available in the United States, sulfonylureas were the first-line pharmacologic treatment for people with Type 2 diabetes first-generation
- First-generation
- Second-generation (Glipizide ,glyburide and Glimepiride)
- **MECHANISM OF ACTION**

ADVERSE EFFECTS

- Hypoglycemia (particularly for those that are long-acting)
- Weight gain (~2 kg)
- GI symptoms (nausea, fullness, bloating that can be relieved if taken with meals)
- Rare blood dyscrasias
- Allergic dermatologic

CONTRAINDICATIONS AND PRECAUTIONS

- Type 1 diabetes;
- Pregnancy or breast-feeding, because these agents (except glyburide) can cross the placental barrier and can be excreted into breast milk;
- Documented hypersensitivity to sulfonylureas;
- Severe hepatic or renal dysfunction;
- Severe, acute intercurrent illness (e.g., infection, MI), surgery, or other stress that can unduly affect BG control, in which case insulin therapy should be used;
- G6PD deficiency—risk for hemolytic anemia if they take chlorpropamide—consider using a nonsulfonylurea medication as an alternative.

Agent/Generic Name (Brand Name)/Mechanism	FDA Indications	A1C Efficacy[a]	Adverse Effects	Comments
Nonsulfonylurea secretagogues (glinides) Repaglinide (Prandin) Nateglinide (Starlix) Stimulates insulin secretion	Monotherapy; combined with metformin or TZD	Monotherapy: ↓ A1C ˜1% (repaglinide) ↓ A1C ˜0.5% (nateglinide) Combination: additional 1% ↓ A1C	Hypoglycemia, weight gain	Take only with meals. If a meal is skipped, skip a dose. Flexible dosing with lifestyle. Safe in renal and liver failure. Rapid onset. Useful to lower PPG
Sulfonylureas Various; see Table 53-26. Stimulates insulin secretion. May decrease hepatic glucose output and enhance peripheral glucose utilization	Monotherapy; combined with metformin; combined with insulin (glimepiride)	Monotherapy: ↓ A1C ˜1% Combination: additional 1% ↓ in A1C	Hypoglycemia, especially long-acting agents; weight gain (5–10 lb); rash, hepatotoxicity, alcohol intolerance, and hyponatremia rare	Very effective agents. Some can be dosed once daily. Rapid onset of effect (1 week)

Thiazolidinediones

- MECHANISM OF ACTION
- Insulin sensitizers

- As with metformin, TZDs have been shown to directly stimulate the AMPK pathway in liver and adipose tissue, resulting in a lowering of glucose and free fatty acids

- Favorable effects on triglycerides, reduction of inflammatory mediators, inhibition of vascular smooth muscle cell proliferation, improved endothelial function, lowering microalbumin excretion, and enhanced fibrinolysis.

ADVERSE EFFECTS

- Hepatotoxicity
- Hematologic Effects
- Weight Gain
- Vascular and Cardiovascular Effects
- Macular edema
- Contraindicated in patients with bladder cancer
- An increased risk of distal limb bone fractures in women receiving TZDs

CONTRAINDICATIONS AND PRECAUTIONS

- Type 1 diabetes
- Patients with type 2 diabetes using insulin: TZDs should be used with caution because of the increased risk of developing edema.
- Preexisting hepatic disease
- Symptomatic or severe (NYHA classes III and IV) HF
- Myocardial ischemia (rosiglitazone only)
- Premenopausal anovulatory women
- History of hypersensitivity to TZDs
- Patients with osteoporosis or at risk for bone fractures
- Drugs metabolized by CYP 3A4
- Patients with a current or previous history of bladder cancer should not use TZDs.
- Macular edema

EFFICACY

- The effects of TZDs on A1C and FPG are intermediate between those of acarbose and the sulfonylureas or metformin
- Effect on the A1C:
- 0.9%–1.3% decrease with a sulfonylurea
- 0.8%–1.0% decrease with metformin
- 0.7%–1.0% decrease with insulin
- Increase HDL-C levels by 10%

DOSAGE AND CLINICAL USE

- For monotherapy or combination therapy with a sulfonylurea, metformin, or insulin, the starting dose for pioglitazone is 15 or 30 mg once daily with or without food.

- The dose can be titrated to a maximum of 45 mg/day

Glucosidase Inhibitors

- Acarbose
- Miglitol
- **MECHANISM OF ACTION**
- **PHARMACOKINETICS**
- Minimally absorbed from the GI tract
- Metabolized by GI amylases
- Peak plasma concentration :1 hour
- Elimination half-life: 2 hours

ADVERSE EFFECTS

- Flatulence
- Diarrhea
- Abdominal pain
- Fermentation of unabsorbed carbohydrate in the small intestine
- Slowly titrating the dose
- Monitoring hepatic transaminases every 3 months for the first year of therapy

CONTRAINDICATIONS AND PRECAUTIONS

- Contraindicated with known hypersensitivity to the medications
- DKA
- Acarbose is contraindicated in patients with cirrhosis
- Gastrointestinal Conditions(malabsorption, inflammatory bowel disease, colonic ulceration or other marked disorders of digestion or absorption, or with intestinal obstruction)
- **Renal Impairment**

EFFICACY

- Lower postprandial plasma glucose concentrations in patients with type 2 diabetes by 25 to 50 mg/dL
- Mean A1C values decline by 0.3% to 0.7%
- No effect on weight or lipid profiles

DOSAGE AND CLINICAL USE

- As add-on therapy in patients who have failed monotherapy or combination therapy with other oral antidiabetic agents
- The recommended initial dose of either drug is up to 25 mg TID, taken at the start of each meal
- The dosage of acarbose can be gradually increased (e.g., 25 mg/meal) every 4 to 8 weeks to a maximum of 50 mg TID for individuals weighing 60 kg or less, or 100 mg TID for individuals weighing more than 60 kg

Incretin-Based Therapies

- Insulinotropic hormones secreted from specialized neuroendocrine cells in the small intestinal mucosa in response to carbohydrate ingestion and absorption
- Glucose-dependent insulinotropic polypeptide (GIP)
- Glucagon-like peptide-1 (GLP-1)

Glucagon-like Peptide-1 Agonists (GLP-1 Mimetics/Analogs)

- Exenatide (twice-daily injection)
- Extended-release exenatide(once weekly injections)
- Albiglutide (once weekly injections)
- Liraglutide (once-daily injection)
- Dulaglutide (once weekly injections)

GLP-1 Mimetics/Analogs

- **MECHANISM OF ACTION**
- Absorption of liraglutide is delayed owing to its self-association in heptameric aggregates within the injection depot that are too large to cross the capillary membranes.
- This delayed absorption is the primary reason for its prolonged action.
- Liraglutide is highly protein bound (>98%)
- Half-life of 13 hours
- Metabolism of liraglutide occurs endogenously in a manner similar to large proteins and there is no specific organ as its route of elimination

ADVERSE EFFECTS

- GI side effects are common and dose-dependent, particularly nausea, vomiting, and diarrhea.
- Hypoglycemic risk can be increased in patients who are also taking an oral insulin secretagogue (e.g., sulfonylurea) or insulin
- Acute pancreatitis

CONTRAINDICATIONS AND PRECAUTIONS

- Contraindicated in patients with known hypersensitivity
- History of pancreatitis
- Severe GI disease
- Personal or family history of medullary thyroid carcinoma (MTC) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2)

DRUG INTERACTIONS

- Hypoglycemia when used with sulfonylureas or insulin.

- With caution in patients taking medications that require rapid GI absorption and are dose dependent on threshold concentrations for efficacy, such as antibiotics and oral contraceptives.

EFFICACY

- Liraglutide monotherapy: ↓ in FBG of 15 to 26 mg/dL and A1C of 0.8% to 1.1%, and weight loss of 2.1 to 2.5 kg.

- As combination therapy, additional A1C lowering of 1% to 1.5% can be expected.

DOSAGE AND CLINICAL USE

- GLP-1 agonists are indicated as add-on agents in patients with Type 2 diabetes who have been unable to reach target goals on monotherapy with metformin or in combination therapy

- The starting dose of liraglutide is 0.6 mg SC once daily for 1 week, may be increased to 1.2 mg daily.
- If the A1C goal is not achieved, further increased to 1.8 mg daily.

Dipeptidyl Peptidase-4 Inhibitors

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

Dipeptidyl Peptidase-4 Inhibitors

- MECHANISM OF ACTION
- DPP-4 inhibitors have minimal-to-no effect on satiety and delaying gastric emptying
- PHARMACOKINETICS
- Sitagliptin
- Linagliptin

ADVERSE EFFECTS

- Because these agents differ significantly in chemical structure from one another, some adverse events may be unique to the individual agent and may not be indicative of a class wide effect
- Sitagliptin: nasopharyngitis, upper respiratory tract infection, hypoglycemia, and headache
- Linagliptin :hypoglycemia, nasopharyngitis, diarrhea, and cough.
- Effect on the immune system, because lymphocytes express DPP-4.
- Increase risk for pancreatitis; however, studies have shown this risk to be low.

CONTRAINDICATIONS AND PRECAUTIONS

- All DPP-4 inhibitors should be avoided in patients with a history of serious hypersensitivity reaction to the drug.

- DRUG INTERACTIONS
- Sitagliptin: digoxin
- Linagliptin: weak-to-moderate inhibitor of CYP3A4 and a P-glycoprotein substrate

EFFICACY

- In monotherapy, sitagliptin lowers fasting glucose by 12 mg/dL and A1C by 0.5% to 0.6%
- Reduce 2-hour postprandial glucose by approximately 45 mg/dL.
- As add-on combination therapy, A1C lowering is greater (0.7%–0.9%).
- Linagliptin, as monotherapy in clinical trials versus placebo, decreased fasting glucose by 13 mg/dL from baseline and decreased A1C by 0.4%.

DOSAGE AND CLINICAL USE

- As add-on therapy
- All are approved for use as monotherapy.
- Sitagliptin : initiated at 100 mg taken once daily with or without food.
- Renal function should be assessed before initiation of this agent.
- In patients with moderate renal insufficiency (CrCl 30– 50 mL/minute), 50 mg once daily, and in severe renal insufficiency (CrCl <30 mL/minute) or for those in end-stage renal failure requiring dialysis, 25 mg once daily.
- Without regard to the timing of hemodialysis.
- Only sitagliptin should be used in patients on peritoneal dialysis

DOSAGE AND CLINICAL USE

- Linagliptin is dosed at 5 mg once daily with or without food.

- No dose adjustment is necessary for patients with renal impairment; however, patients with a CrCl <30 mL/minute may be more prone to hypoglycemia; therefore, dosing adjustments of concomitant antidiabetic medications and frequent monitoring may be necessary

Sodium–Glucose Transporter 2 (SGLT2) Inhibitors

- Reduce BG by decreasing tubular reabsorption of glucose in the kidney
- Highly selective, reversible inhibitors of SGL T2.
- Canagliflozin, Dapagliflozin, and Empagliflozin,
- Their mechanism of action is independent of insulin resistance or β-cell function, these medications can be used in combination with all antidiabetic agent classes
- These agents have added benefits of weight loss, increase in HDL, and decrease in blood pressure;
- However, genital and urinary infections may be an adverse effect of these agents.

ADVERSE EFFECTS

- The most common adverse effects associated with empagliflozin include female genital mycotic infections and urinary tract infections

CONTRAINDICATIONS AND PRECAUTIONS

- Contraindicated in patients with hypersensitivity reactions to the agents and in patients with severe renal impairment, ESRD, and dialysis
- Renal function: prior to the initiation of these agents and periodically during treatment
- Blood pressure
- Hypoglycemia
- LDL
- Ketoacidosis

DRUG INTERACTIONS

- Empagliflozin does not induce or inhibit CYP450 enzymes or UGT1A1;
- Therefore, is not expected to have interactions with concomitantly administered medications at are substrates of the CYP450 pathway or UGT1A1.

EFFICACY

- Empagliflozin monotherapy, in a clinical trial compared to placebo, decreased A1C by 0.7% to 0.8%, decreased FPG by 19 to 25 mg/dL, and decreased body weight by 2.8 to 3.2%

DOSAGE AND CLINICAL USE

- The SGL T2 agents are indicated for use in patients with Type 2 DM as an adjunct to diet and exercise as monotherapy or concomitantly with other antidiabetic agents

- Empagliflozin should be initiated at a dose of 10 mg once daily in the morning, with or without food, and may be increased to 25 mg once daily.
- Do not initiate empagliflozin therapy in patients with an eGFR <45 mL/minute/1.73m2 and discontinue therapy if eGFR persistently falls below 45 mL/minute/1.73 m2