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Review Article

Pharmacotherapeutic Agents in Diabetes Mellitus: A Narrative Review

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ABSTRACT

Diabetes is a growing public health concern in India and globally. Transition in lifestyle, urbanization have led to soaring of diabetes cases in recent years. International Diabetes Federation estimates that in 2050, around 853 million people will be living with diabetes worldwide. Proper diagnosis and early intervention is essential to prevent irreversible complications of this chronic metabolic disease. A good understanding of the pharmacotherapeutic agents available to treat diabetes will enable clinicians and health care providers in treating diabetes optimally. Research in the field of diabetes has evolved providing many new drugs with promising outcomes. This narrative review explores the pharmacological basis and the clinical importance of medications used in clinical practice.

Keywords: Biguanides, Diabetes mellitus, Pharmacotherapy, Type 2 diabetes.

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INTRODUCTION

Diabetes is a metabolic syndrome characterized by chronic hyperglycemia associated with disturbances in carbohydrates, protein and fat metabolism. Diabetes mellitus is broadly divided into 2 types-Type 1 and type 2 diabetes.

The major contributors to the rise in type 2 diabetes in recent years include urbanization, sedentary lifestyle, obesity and aging population.

Two major pathophysiological mechanisms contribute to the development of diabetes. Insulin resistance or decrease in insulin sensitivity and inadequate secretion or absence of insulin secretion.

The development of insulin resistance results in impaired uptake of glucose by peripheral tissues like skeletal muscle. The ensuing hyperglycemia increases the demand for insulin synthesis. This continues until pancreatic beta cell activity can no longer adequately meet the insulin demand created by insulin resistance resulting in hyperglycemia. Lifestyle modification with decreased calorie requirement remains the first line management in conjunction with pharmacological agents in people with type 2 diabetes (Muralidharan, 2024).

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By contrast, in type 1 diabetes there is complete absence of insulin secretion. Autoimmune destruction of pancreatic beta cells is the likely cause, and the patient has to rely on exogenous insulin throughout their lifetime.

Epidemiology

The prevalence of diabetes has seen a sharp rise in recent years. The ICMR-INDIAB study a largest national survey aimed to assess the prevalence of metabolic syndrome and NCD's in India revealed a prevalence rate of 11.4% which is 101 million people across all 31 states and union territories (Anjana *et al.*, 2025).

Existing evidence from epidemiological studies identifies India in the second place with largest number of people with diabetes in the world.

The International Diabetes Federation-Diabetes *Atlas* 2025 reports that 590 million people worldwide have diabetes which is around 11.1% of the adult population aging between 20 and 79 years. By 2050, IDF projections show that 853 million people will be living with diabetes globally (International Diabetes Federation, 2025).

Diabetes is diagnosed if any one of the following criteria is fulfilled.

fasting plasma glucose >/=126 mg/100 mL or

HbA_{1C} >/=6.5% or

2-hr glucose during 75 g oral glucose tolerance testing >/=200 mg/100 mL.

Current ADA guidelines emphasize that in addition to lowering blood glucose levels, other benefits including cardiovascular protection, renal protection and so on must be considered before selecting, initiating and intensifying the therapeutic regimen to achieve optimized therapeutic outcomes and advocate a "Comprehensive Diabetes Care" addressing the symptoms of hyperglycemia, co morbidities and screening or treating complications.

Pharmacologic agents for the treatment of diabetes

- Older Medications,
- Oral Hypoglycemic Agents,
- Role of Insulin Secretagogues,

Drugs falling under the insulin secretagogues can be further subdivided into "sulfonylureas" and "nonsulfonyl urea" secretagogues,

- Sulfonylureas.

Mechanism of Action

Sulfonylureas act by binding to SUR-1 subtype of potassium sensitive ATP channels and lead to channel closure followed by potassium retention within the cell. This results in depolarization and depolarization sensitive potassium channels open enabling influx of extracellular calcium into the cell resulting in the fusion of vesicle and cell membrane followed by the release of insulin (DeMarsilis *et al*., 2022).

Clinical Pearls

Hypoglycemia and weight gain are the most worrisome side effects associated with this class. These drugs are classified as "potentially inappropriate" medication for adults according to Beer's criteria due to the heightened risk of hypoglycemia in this population. Gliclazide, glipizide and glimipiride are the sought after agents in adjunct to metformin monotherapy or diet and lifestyle changes by clinicians in clinical practice. Decades of use, low cost, wide availability and fast glycemic response can be attributed to their widespread use. FDC's of sulfonylurea and metformin is widely used to reduce the pill burden and improve compliance (DeMarsilis *et al*., 2022; Piper *et al*., 2019).

Meglitinides

These agents are nonsulfonylureas and act in a way similar to sulfonylureas. Meglitinides are considered effective in controlling post prandial glucose excursions.

They are short-acting and are prescribed 15-30 min prior meals. Advantages of meglitinide is that they do not cause "late onset" hypoglycemia due to their short duration of action (Piper *et al*., 2019).

Biguanide

Metformin is the only biguanide currently available and most commonly used agent to treat type 2 diabetes and is proposed as the first line treatment for type 2 diabetes mellitus.

Mechanism of Action

This can be attributed to its multifaceted effects. In addition to inhibiting hepatic gluconeogenesis it increases cellular AMP kinase activity which enhances the peripheral uptake of glucose into muscle and fat cells and improves glucose and fat metabolism thereby increasing insulin sensitivity. Metformin is an ideal drug for overweight and obese patients (Ahmad and Haque, 2024).

Decades of clinical experience, cost-effectiveness and favorable side effect profile are the reasons for using metformin as a first line therapy among majority of patients diagnosed with diabetes.

Clinical Pearls

Most of the side effects of metformin are gastrointestinal related and can be managed by decreasing the dose. Nausea, diarrhea are common and subside with decreasing the dose and with continued use.

Metformin is also known to lower vitamin B12 levels. Chronic use of metformin deserves a vitamin B 12 monitoring.

Renal impairment with eGFR between 30 and 45 mL/min/1.73 m^2 necessitates cautious use and the dose is restricted to 1,000 mg/day. Its use is contraindicated in patients with eGFR <30 mL/min/1.73 m^2 and in critically ill patients with sepsis, dehydration and acute heart failure.

Otherwise, metformin is a versatile drug.

Thiazolidinediones

Thiazolidinediones are insulin sensitizers. Rosiglitazone and pioglitazone fall under this class.

Mechanism of Action

Thiazolidinediones act on the PPAR-Gamma receptors. By binding to these intranuclear receptors these agents regulate genes related to glucose and lipid metabolism. These drugs have primary effect on the adipose tissue where they promote fatty-acid uptake and storage with a consequent decrease in accumulation in the liver, muscle and pancreas. PPAR-Gamma agonists also increase adiponectin a protein derived from adipocytes with insulin sensitizing properties secretion and GLUT-4 expression in muscle and adipose tissue facilitating glucose uptake in muscles (Doupis *et al*., 2021; Galicia-Garcia *et al*., 2020).

Clinical Pearls

Major side effect include fluid retention seen in 3-7.5% of patients. TZDs are contraindicated in patients with a known history of

heart failure or diastolic dysfunction and in symptomatic heart failure.

Other contraindications include active or history of fracture or high risk of fracture, liver transaminases >2.5 times the upper limit normal, active or history of bladder cancer and pregnancy.

α-Glucosidase Inhibitors

This class includes drugs like acarbose, voglibose and miglitol. All drugs are available only as oral formulations.

Mechanism of Action

These oral drugs are reversible inhibitors of enzyme alpha-glucosidase present in the small intestinal brush border cells leading to a decrease in the absorption of complex polysaccharides.

Clinical Pearls

These drugs are generally prescribed in combination with other oral hypoglycemic agents. AGI's are contraindicated in patients with chronic intestinal diseases like inflammatory diseases, colonic ulceration, gastroparesis and in patients predisposed to intestinal obstruction.

DPP-4 Inhibitors

Mechanism of Action

DPP-4 inhibitors work by blocking the enzyme DPP-4, which breaks down incretins like GIP, GLP-1. By inhibiting DPP-4, these medications increase the levels of active GLP −1 which stimulates insulin release and inhibits glucagon secretion, ultimately leading to lower blood glucose levels.

DPP-4 inhibitors prefer sulfonylureas as adjunct to metformin as they do not cause weight gain or hypoglycemia and have similar efficacy.

Clinical Pearls

DPP-4 inhibitors are renoprotective. Linagliptin, which undergoes hepatobiliary excretion through feces can be used in patients with renal insufficiency and in patients with End Stage Renal Disease.

Other agents of this class including sitagliptin, vildagliptin and saxagliptin require dose adjustment in patients with renal impairment.

NEWER Medications GLP 1 Receptor Agonists

New class of medications under "incretin based therapies."

Liraglutide, dulaglutide, semaglutide and tirzepatide fall under this class. Tirzepatide is the recent new drug and has been launched under the trade name Mounjaro since March 2025 in India (Mounjaro). Though these drugs are costlier, weight loss is the advantage that seeks the attention of Indian population. According to the current data on prevalence of obesity the proportion of obese Indians has risen from 25% in 2,013-40% in 2023 necessitating the need for effective weight loss drugs. These agents are in the race to transform obesity management in India accompanied with management of type 2 diabetes (Bhupathiraju and Hu, 2016).

Mechanism of Action

GLP-1 agonists stimulates insulin secretion in glucose dependent way, suppresses glucagon secretion and slows gastric emptying and reduces appetite. Central hypothalamic and gastrointestinal mechanisms contribute to the benefit of weight loss. Short-acting agents like exenatide improve postprandial hyperglycemia and long-acting drugs like liraglutide and semaglutide improve basal hyperglycemia.

Clinical Pearls

GLP-1 agonists has been evaluated as monotherapy in addition to diet and exercise but also together with OHAs and basal insulin.

Lead-2 trial (liraglutide Effect and action in Diabetes) has demonstrated that once daily liraglutide injection achieved better weight loss, less hypoglycemic episodes and good glycemic control compared with glimipiride, when both were added to metformin (DeMarsilis *et al*., 2022).

Dulaglutide is given once weekly starting at a dose of 0.75 mg subcutaneous to a maximum dose of 4.5 mg subcutaneous with higher doses showing significant reductions in HbA_{1C} and body weight.

Unlike other agents semaglutide is available in both oral and subcutaneous formulations. Oral preparations are available in 3, 7 and 14 mg tablets. Oral tablets are started at a dose of 3 mg and the dose is gradually titrated to a maximum dose of 14 mg day^{-1} at monthly intervals.

Contraindications to their use includes pregnancy, personal or family history of multiple endocrine neoplasia type 2 A and 2B, Medullary thyroid cancer and pancreatitis.

SGLT 2 Inhibitors or "the gliflozins"

SGLT 2 receptors present on the luminal membrane of Proximal Convoluted Tubule of nephrons play a pivotal role in glucose homeostasis by accounting for nearly 97% of glucose reabsorption.

Mechanism of Action

SGLT 2 inhibitors block SGLT 2 receptors, lower the renal threshold for glycosuria, and decrease renal glucose reabsorption.

Clinical Pearls

SGLT 2 inhibitors have demonstrated a wide range of effects on biochemical and hemodynamic pathways, accounting for their

beneficial cardiovascular and renal outcomes. They are the fourth pillar in GDMT for heart failure with reduced ejection fraction.

These agents show a HbA_{1C} reduction of 0.7%.

Common adverse reactions related to these drugs are hypoglycemia, urosepsis/pyelonephritis, genital mycotic infections and bladder outlet obstruction.

Gliflozins are preferred agents in presence of heart failure with or without diabetes mellitus.

Glimins

Imeglimin, prototype of the novel class of antidiabetic agents "Glimins" was approved for use in India in October 2022.

Mechanism of Action

It works by targeting the 3 main pathways leading to type 2 diabetes. These agents inhibit hepatic glucose production by down regulating PEPCK and glucose-6-phosphatase in hepatocytes via mitochondrial dependent pathway.

Secondly, by increasing GLUT-4 expression and regulation of insulin substrate phosphorylation it stimulates glucose uptake by skeletal muscles (Hallakou-Bozec *et al*., 2021).

Clinical Pearls

With moderate oral absorption and rapid attainment of blood levels the drug is safe to use in patients with hepatic impairment.

It may be considered as an alternative to metformin in view of intolerable gastrointestinal side effects. A 8 weeks, Phase IIa study, comparing the effectiveness and safety of metformin and imeglimin has concluded that both have similar efficacy on controlling blood sugar levels and gastrointestinal side effects are less comparatively to metformin.

Insulin Therapy

The ultimate pharmacotherapy in the management of diabetes is the administration of physiological agent in modified form which is insulin.

Mechanism of Action

Insulin increases skeletal muscle and fat uptake of peripheral tissues, stimulates lipogenesis and protein synthesis and also inhibits proteolysis, lipolysis, hepatic glycogenolysis and gluconeogenesis.

Insulin therapy can be categorized into 2:

• Basal Insulin Therapy.• Bolus Insulin Therapy.Basal Insulin Therapy

In "Basal insulin regime" intermediate and long-acting insulins are administered. Intermediate acting insulins like NPH Insulin has a duration of action 10-16 hr and are given twice daily.

Long-acting insulins include Insulin glargine (100 IU/mL, 300 IU/mL), insulin degludec (100 IU/mL, 200 IU/mL).

Basal insulin provides constant background insulin, working akin to natural pancreas, regulates hepatic glucose production and fasting blood glucose levels.

Advantage of basal insulin therapy is that with flatter pharmacokinetics and prolonged duration of action, they are dosed once daily with reduced injections per day and reduced nocturnal hypoglycemic event (DeMarsilis *et al*., 2022).

Basal and Rapid-Acting Insulin

Regular insulin developed by rDNA technology has a faster onset of action with 1-2 hr and the action lasts for 3-5 hr. Regular insulin is given 30 min before meals. Premixed preparations of basal and prandial insulin are available and are widely used. Examples include NPL 50%/50 and 75%/75%, NPA 75%/20%. Premixed insulin is administered twice daily in the morning and evening. Commonly 2/3 of the dose is given in the morning, before food and 1/3 of the dose is given before dinner.

In patients with severe diabetes mellitus (HbA_{1C} >8%), premixed insulin provides superior glycemic control over basal insulin replacement.

Bolus Insulin Therapy

Bolus insulin therapy involves the administration of regular human insulin according to blood glucose levels 3 times a day which is before breakfast, lunch and dinner with or without long-acting insulin.

Common ADRs of Insulin Therapy

Common ADRs include hypoglycemia, weight gain, fluid retention, local injection site reactions like lipodystrophy and hypokalemia.

Pharmacotherapy of diabetes mellitus has evolved over the past decade. Many new drugs have entered the therapeutic arena of diabetes mellitus. Selecting appropriate agents based on patient specific characteristics, ensuring proper administration and compliance to medications among patients, regular self-monitoring of glucose comprehensively will lead to quality care and cure of diabetes.

CONCLUSION

This review describes in detail unique aspects of various pharmacological agents used in the management of diabetes mellitus. The clinical importance of the medications is analyzed giving a comprehensive outlook on anti-diabetic agents used currently in clinical settings. This review helps to optimize treatment in patients with this chronic disease.

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ABBREVIATIONS

ADA: American Diabetes Association; **ADR:** Adverse Drug Reaction; **AGI:** Alpha-Glucosidase Inhibitor; **AMP:** Adenosine Monophosphate; **ATP:** Adenosine Triphosphate; **DPP-4:** Dipeptidyl Peptidase-4; **eGFR:** Estimated Glomerular Filtration Rate; **FDC:** Fixed Dose Combination; **GDMT**: Guideline-Directed Medical Therapy; **GIP:** Glucose-Dependent Insulinotropic Polypeptide; **GLP-1:** Glucagon-Like Peptide-1; **GLUT-4:** Glucose Transporter Type 4; **HbA_{1C}:** Glycated Hemoglobin; **HR:** Hour; **ICMR**: Indian Council of Medical Research; **IDF:** International Diabetes Federation; **IU:** International Unit; **MEN:** Multiple Endocrine Neoplasia; **NCD:** Non-Communicable Disease; **NPH:** Neutral Protamine Hagedorn; **OHA:** Oral Hypoglycemic Agent; **PPAR:** Peroxisome Proliferator-Activated Receptor; **rDNA:** Recombinant Deoxyribonucleic Acid; **SGLT-2:** Sodium-Glucose Cotransporter-2; **SUR-1:** Sulfonylurea Receptor-1; **TZD:** Thiazolidinedione.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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